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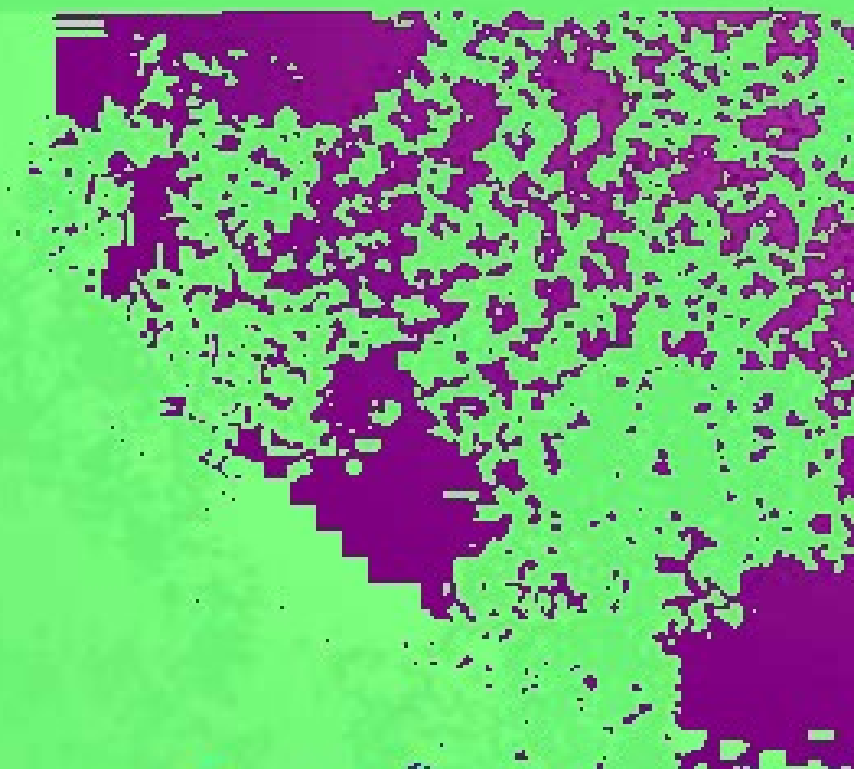

Mieczyslaw Pokorski

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Respiratory Regulation – Clinical Advances

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Preface

The book contains the articles related to the clinical advances in the regulation of the respiratory system. The research presented herein was communicated and discussed at the International Conference 'Advances in Pneumology,' which was held in Bonn, Germany, on June 17–18, 2011. The articles are a selection of peer-reviewed manuscripts to demonstrate the scope of the issues tackled at the conference. The conference is thought as a merger between basic and clinical research concerning respiratory medicine, neural and chemical respiratory regulation, and the mutual relationship between respiration and other neurobiological functions. Clinical pathophysiology of the respiratory system is always at the core of these meetings. The topics included lung function, hypoxic lung pathologies, pharmacotherapy, epidemiology, and cardiovascular-respiratory interactions, particularly during sleep. Other essential topics of interest were infections and inflammatory conditions exemplified by asthma and chronic obstructive pulmonary disease (COPD), respiratory allergy and cough, and also psychosomatic issues which broadened the scope of the conference. In the articles presented in this volume, the cutting-edge knowledge is communicated and discussed by prominent experts in the areas of science outlined above. I want to thank all the speakers at the conference and the authors and reviewers of the articles; their contributions certainly will enhance the value of this volume.

The 'Advances in Pneumology' is an annual conference organized alternately in Poland and Germany. It refers to the long-standing contacts between Polish and German clinicians and researchers in the field of respiration. The contacts have begun decades ago from the common interest in prophylaxis and treatment of respiratory ailments in coal miners and in populations inhabiting the mining regions of both countries. Nowadays, the coal mining is limited, but the diseases and clinical problems persist.

The 2011 conference was the fruit of many collaborative efforts. The Local Organizing Committee was headed by Dr. Rüdiger Siekmeier of the Federal Institute for Drugs and Medical Devices (BfArM) in Bonn, Germany. I am indebted to him for his efforts and to all those who extended a helping hand and advice in the organization, particularly Prof. Dr. med. Kurt Rasche of HELIOS Klinikum Wuppertal Lungenzentrum, Klinik für Pneumologie, Allergologie, Schlaf- und Beatmungsmedizin and Ms. Anke Hastenrath of Wuppertal, and Dr. Tadeusz M. Zielonka of Warsaw Medical University and the Polish Respiratory Society in Warsaw, Poland.

I also want to thank the non-profit research and academic institution which kindly cooperated and supported the organization of the conference and the publication of this book, particularly the Medical Research Center of the Polish Academy of Sciences in Warsaw, the Polish Respiratory Society, and the Rhein-Ruhr-Stiftung in Essen. Finally, I am also grateful to Mr. Max Haring, Ph.D., and Ms. Tanja van Gaans of Springer for their expert management of the production process of this book.

Due to the efforts of all involved in the conference, the participants could not only benefit from scientific knowledge and contacts but also could enjoy the vibrant Bonn's life. It had been decided at the conference that the next conference of this series will be held in the city of Wroclaw in southwest Poland on October 5–6, 2012; details can be accessed at http://www.pneumology.pl.

Warsaw, Poland Mieczyslaw Pokorski

Contents

Chapter 1
Assessment of Airway Hyperresponsiveness: Comparison of Spirometry and Body Plethysmography

F. Nensa, N. Kotschy-Lang, H.-J. Smith, W. Marek, and R. Merget

Abstract While methacholine (MCH) testing is commonly used in the clinical diagnosis of asthma, the detection of airway narrowing often relies on either spirometry or body plethysmography, however comparative studies are rare. In this study we performed MCH testing in 37 patients with variable shortness of breath at work and in 37 patients with no history of airway disease. The inclusion criteria were: no acute respiratory infection within 6 weeks, no severe diseases, normal baseline specific airway resistance (sR_{aw}), normal baseline forced expiratory volume in 1 s (FEV_1), Tiffeneau index >70%, no previous treatment with steroids within 14 days and no short acting bronchodilators within 24 h. Cumulative doses of 0.003, 0.014, 0.059, 0.239 and 0.959 mg MCH were inhaled by a dosimeter method. A FEV_1 decrease of ≥20% from baseline and a 100% increase of sR_{aw} to ≥2.0 kPa/s was defined as end-of-test-criterion. Provocation doses were calculated by interpolation. Performance of lung function parameters was compared using receiver-operating-characteristic (ROC) analysis. ROC analysis resulted in an area under the ROC curve (AUC) of 0.74 for FEV_1 *vs.* 0.82 for sR_{aw}. The corresponding Youden Indices (J) were 0.46 for FEV_1 and 0.57 for sR_{aw}. The Youden Index of sR_{aw} was higher and sensitivity and specificity (73%/84%) were rather well-balanced, in contrast to FEV_1 (54%/92%). In conclusion, in cumulative MCH challenges sR_{aw} was found to be the overall most useful parameter for the detection of bronchial hyperresponsiveness. Body plethysmography yielded a balanced sensitivity-specificity ratio with higher sensitivity than spirometry, but comparable specificity.

Keywords Airway hyperresponsiveness • Asthma • Bronchodilation • Body plethysmography • Methacholine • Spirometry • Airway resistance

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1.1 Introduction

Airway hyperresponsiveness is defined as an exaggerated bronchoconstrictive response to a number of inhaled physical, chemical or pharmacologic stimuli that occurs in patients with asthma, but not or rarely in healthy subjects. As a distinctive characteristic of asthma it regularly appears earlier (at lower doses) and is more intensive in patients with asthma and therefore underlies the rationale for bronchial challenge testing (Crapo et al. 2000; Cockcroft et al. 1977; Juniper et al. 1981). Both the American Thoracic Society (ATS) (Crapo et al. 2000) and the European Respiratory Society (ERS) (Sterk et al. 1993) recommend challenge tests by inhalation of aerosolized methacholine (MCH).

Spirometry being technically simple, cheap and highly reliable is currently the most commonly used method of indirect airway narrowing detection. A fall of the forced expiratory volume in 1 s (FEV_1) of at least 20% from baseline following MCH inhalation is widely used to determine airway hyperresponsiveness. However, FEV_1 largely depends on the subject's cooperation, which especially has to be considered in the context of pediatric examinations and medical opinions. Furthermore, FEV_1 maneuvers require maximal inspiration that has been shown to reduce bronchoconstriction induced by histamine or methacholine (Cockcroft and Davis 2006; Nadel and Tierney 1961). Slats et al. (2007) showed that airways inflammation plays an essential role in the bronchoprotective effects of deep inhalations in healthy subjects and patients with bronchial asthma. Bronchoprotection by deep inhalation may however be of only minor importance in patients with chronic obstructive pulmonary disease (COPD) and increased levels of airway resistance (Slats et al. 2007).

In contrast, body plethysmographic measurements of specific airway resistance (sR_{aw}) are performed under tidal breathing conditions, requiring only a minimum of the subject's cooperation. A ≥100% increase of sR_{aw} from baseline to a minimum absolute value of 2.0 kPa/s is a commonly used threshold to determine airway hyperresponsiveness (Baur et al. 2005; Criée et al. 2011). Comparative studies between spirometry and body plethysmography as effect parameters are rare. Hence both methods were compared in order to evaluate the concordance of spirometry and body plethysmography concerning their clinical value during MCH testing.

1.2 Methods

1.2.1 Subjects

MCH testing was performed in 74 patients (Table 1.1) during their stay at Berufsgenossenschaftliche Klinik für Berufskrankheiten, Falkenstein, Germany. Subjects were assigned to two groups. The asthma group consisted of 37 (20 males) patients who reported variable shortness of breath at work in recent years. Subjects with isocyanate exposure and subjects with COPD-like disease were excluded. The control group consisted of 37 (22 males) patients with unrelated diagnoses that are not known to cause airway hyperresponsiveness, but no history of airway diseases.

All subjects met the following criteria: no acute respiratory infection or exacerbation within the preceding 6 weeks; no severe accompanying diseases; normal baseline sR_{aw} and FEV_1, FEV_1/FVC >70%, no previous treatment with oral or inhaled steroids within 14 days, and no short acting bronchodilators within 24 h before MCH testing. Also patients were asked to refrain from using caffeine containing beverages. A paradoxical increase in FEV_1 >5% of baseline during methacholine testing was regarded as a sign of unstable breathing control and those tests (n = 8) were subsequently excluded from the study for quality assurance. All patients were over 18 years

Table 1.1 Demographic and pulmonary baseline data of subjects included in the study

Group	N (males)	Age (year)	Weight (kg)	Height (cm)	sR_{aw} (kPa/s)	FVC (L)	FEV_1 (L)	FEV_1/FVC (%)
Normal	37 (20)	48 ± 13	78 ± 15	171 ± 9	0.70 ± 0.2	4.1 ± 0.9	3.3 ± 0.8	82 ± 6
Asthmatic	37 (22)	47 ± 14	83 ± 18	170 ± 10	0.85 ± 0.2	4.2 ± 0.9	3.4 ± 0.7	82 ± 5

Table 1.2 Methacholine testing protocol

Step	Concentration	Dose (mg)	Cumulative dose (mg)	Substance	Procedure
B	0.9%	0.072	0.072	Saline	8 breaths
1	3.3 mg/mL	0.003	0.003	Methacholine	1 breath
2	16.5 mg/mL	0.011	0.014	Methacholine	1 breath
3	16.5 mg/mL	0.045	0.059	Methacholine	3 breaths
4	16.5 mg/mL	0.180	0.239	Methacholine	10 breaths
5	16.5 mg/mL	0.720	0.959	Methacholine	16.36 s inspiration

of age (range 22–74, average 47 years) and informed written consent was obtained from each subject. The study protocol was approved by a local Ethics Committee.

1.2.2 Methacholine Testing

An ATS-adapted dosimeter method was used, with minor modifications as described recently (Merget et al. 2009). Briefly, methacholine chloride (Provokit, Lindopharm, Hilden, Germany) was dissolved in sterile water supplied with the product to a concentration of 3.3 mg/mL for the first very low dose provocation step and 16.5 mg/mL for all following steps (Table 1.2). After measuring baseline values and an initial inhalation of aerosolized isotonic saline, MCH was administered in up to five steps (0.003, 0.011, 0.045, 0.180, and 0.720 mg) aerosolized by a MedicAid nebulizer (mass median aerodynamic diameter of particles of 3.2 μm) and dosimetrically applied by the APS provocation system (CareFusion, Höchberg, Germany).

The cumulative inhaled doses after each step of inhalation (0.003, 0.014, 0.059, 0.239, and 0.959 mg MCH) were obtained by taking one breath (3.3 mg/mL) at step one, one breath (16.5 mg/mL) at step two, three breaths (16.5 mg/mL) at step three and ten breaths (16.5 mg/mL) at step four. At step five patients took multiple breaths until a total inspiration time of 16.36 s was accumulated.

1.2.3 Lung Function Measurements

sR_{aw} and intrathoracic gas volume (FRCpleth) were recorded by body plethysmography (MasterScreen, CareFusion, Höchberg, Germany). Spirometry was performed after sR_{aw} tidal breathing analysis and linked to FRCpleth in the sitting position. Body plethysmography and forced spirometric maneuvers were performed at rest and 2 min after inhalation of saline and each MCH dose, with the measurements of sR_{aw}, FRCpleth, and FEV_1.

A fall of FEV_1 ≥20% from baseline together with an sR_{aw} increase of ≥100% from baseline to ≥2 kPa/s or application of the maximum MCH dose was defined as end-of-test-criterion. Because most thresholds in MCH testing are defined relative to the baseline values and therefore the accuracy of these are critical to the whole test, baseline measurements without any prior inhalation were repeated several times. From three spirometric measurements that fulfilled acceptability criteria the best was identified by the maximal sum of FEV_1 and forced vital capacity (FVC). Calculating the median of

five airway resistance and three FRCpleth measurements reduced artifacts in body plethysmographic baseline values. While body plethysmography was performed in an identical way after each intermediate MCH inhalation step, spirometry was done only once. After the end-of-test-criterion was reached measurements were performed as during baseline measurements.

1.2.4 Data Analysis

It was the aim of this study to compare body plethysmographic and spirometric parameters not only regarding the dose response at discrete steps of provocation levels, but to perform statistical data analysis over a continuous dose interval. Using regression analysis of the recorded lung function parameters with the applied MCH doses as the covariates the corresponding MCH provocation doses or concentrations (PD or PC) at arbitrary thresholds could be estimated by interpolation. An interpolated MCH dose that was needed to cause a fall of FEV_1 of 20% (10%) from baseline was called $PD_{20}FEV_1$ ($PD_{10}FEV_1$). $PD_{100}sR_{aw}$ was defined as the interpolated MCH dose needed to cause an increase in sR_{aw} of 100% from baseline, $PD_{+100}sR_{aw}$ with the additional increase of sR_{aw} to ≥2 kPa/s.

Performance of lung function parameters in binary classification of patients into asthmatic and non-asthmatic groups was compared using receiver-operating-characteristic (ROC) analysis taking the MCH dose as the varying discrimination threshold. For comparison of the ROC curves the area-under-the-ROC-curve (AUC), a robust measure for the overall quality of a classifier, was calculated. In contrast to the AUC being a summary statistic for test comparison the maximum test performance was quantified by estimating the Youden Index $J = max(sensitivity + specificity - 1)$ (Schisterman et al. 2005), which also provides a criterion for choosing an 'optimal' threshold value (Greiner et al. 2000).

To investigate the impact of the definition of the reactive thresholds on the tests' ability to discriminate subjects with and without asthma, ROC analysis was performed iteratively over broad intervals of reasonable threshold definitions and summarized by plotting these thresholds against their corresponding AUC values (Fig. 1.2). According to O'Connor et al. (1987), the dynamics of the dose–response curves were summarized by a measure defined as the slope of a line extending from baseline to the last data point obtained from provocation. FEV_1 and sR_{aw} were again compared by ROC analysis using this alternative approach.

All calculations were done using an Oracle© 10 g XE database, custom Java© code (Java Development Kit 1.6) and the R software environment for statistical computing (Ihaka and Gentleman 1996). ROC analysis was facilitated by the ROCR (Sing et al. 2005) package.

1.3 Results

Normal and asthmatic subjects were comparable in terms of demographic and pulmonary baseline characteristics (Table 1.1). Baseline sR_{aw} was significantly ($p<0.05$) higher in the asthmatics group but still within normal limits due to inclusion criteria used.

1.3.1 ROC Analysis

When applying $PD_{20}FEV_1$ for spirometry and $PD_{+100}sR_{aw}$ including an absolute threshold of ≥2.0 kPa/s for body plethysmography (Fig. 1.1), ROC analysis resulted in AUC of 0.74 for FEV_1 *vs.* 0.82 for

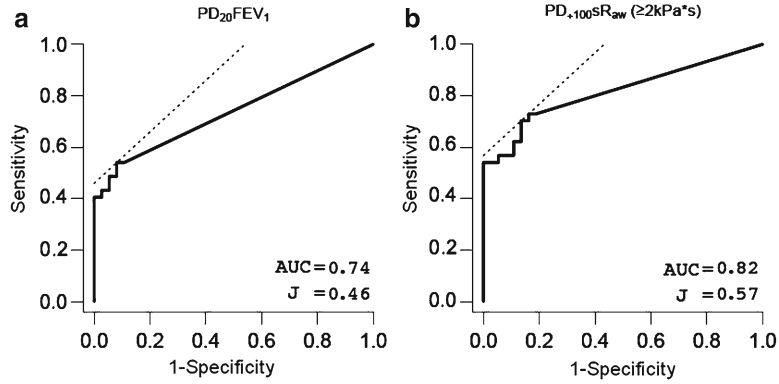

Fig. 1.1 Comparison of FEV_1 and sR_{aw} using ROC analysis. The intersections of the *dashed line* with the ROC curves represent the Youden Indices (J). *AUC* area under the curve

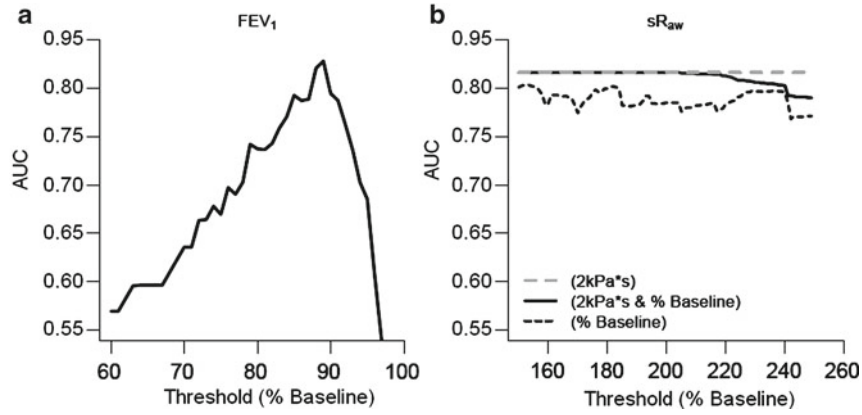

Fig. 1.2 Effect of the definition of reactive thresholds on test performances measured as areas under the curves (*AUC*)

sR_{aw}. The corresponding Youden Indices (J) were 0.46 for FEV_1 and 0.57 for sR_{aw}. The Youden Index in sR_{aw} was not only higher, but sensitivity and specificity (73%/84%) were rather well-balanced, in contrast to FEV_1 (54%/92%).

1.3.2 Threshold Optimization

By iterative threshold variation, FEV_1-based MCH testing was found to perform best at thresholds near 90% ($PD_{10}FEV_1$) of baseline value (Fig. 1.2, left part) being significantly better than that at 80% ($PD_{20}FEV_1$). Evaluating threshold definitions for body plethysmography was more complex because two synergistic thresholds, relative increase (% baseline) and 2.0 kPa/s absolute value, and their logical "AND" combination had to be analyzed. The performance of sR_{aw} based MCH testing was completely determined by the absolute threshold of 2.0 kPa/s. Variation of the relative threshold did not improve the performance of the test but instead resulted in a test performance decline for thresholds ≥200% (Fig. 1.2, right part).

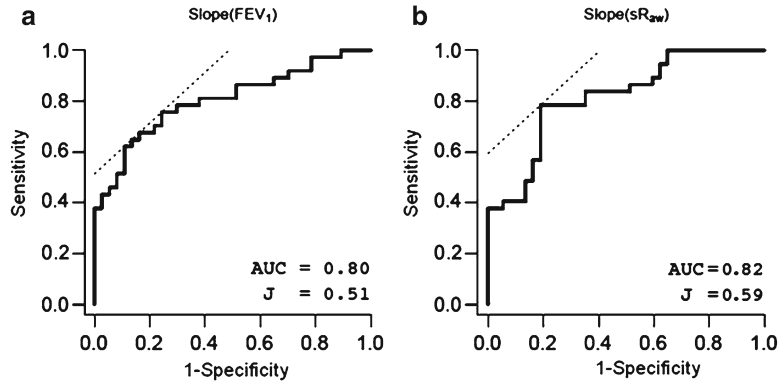

Fig. 1.3 ROC analysis of dose–response curve slopes. The intersections of the *dashed line* with the ROC curves represent the Youden Indices (J). *AUC* area under the curve

1.3.3 Slopes as Alternative Measures

The discrimination between both groups based on slopes of both FEV_1 and sR_{aw} were comparable. ROC analysis of sR_{aw} slopes resulted in a slightly higher AUC (0.82 sR_{aw} *vs.* 0.80 FEV_1) and a higher Youden Index (0.59 sR_{aw} *vs.* 0.51 FEV_1), but FEV_1 slopes produced a more uniform and stable ROC curve with several alternative maxima suitable as Youden Indices (Fig. 1.3). Both parameters provide well balanced sensitivity and specificity ratios (78%/81% sR_{aw} *vs.* 76%/76% FEV_1).

1.4 Discussion

It was the aim of the present study to assess the diagnostic value of spirometry and body plethysmography in MCH testing. We chose a case–control design, which has also been used for the same purpose by Cockcroft and Berscheid (1983) almost 30 years ago. In that study the authors compared $PC_{20}FEV_1$ and $PC_{35}sG_{aw}$ (provocation dose at a 35% fall of specific airway conductance from baseline) in 16 asthmatic and 27 normal subjects. The major result of that study was that $PC_{20}FEV_1$ was about fourfold larger than $PC_{35}sG_{aw}$, but the authors recommended to use FEV_1 because of better separation of both groups. The study was criticized some years later by Popa and Singleton (1988) because of the ceiling method that was used to define the cut-offs. The ceiling method selects the highest provocation dose in the asthmatic group as the cut-off value consequently leading to poor specificity if provocation doses overlap between normal and asthmatic groups, which appears to be the situation in the general population (Cockcroft et al. 1983; Hendrick et al. 1986; Tiffeneau 1957; van der Lende et al. 1973; Woolcock et al. 1987). There was very little overlap between groups in Cockcroft and Berscheid's (1983) study, possibly due to selection of the subjects. In the study by Popa and Singleton (1988), $PD_{20}FEV_1$ was about threefold higher than $PD_{40}sG_{aw}$ and the authors recommended using $PD_{20}FEV_1$ because this parameter produced lower misclassification rates due to lower variability of the endpoint. However, as it was obviously not the primary goal of that study to compare spirometry and body plethysmography and no threshold variations of sG_{aw} besides the $PD_{40}sG_{aw}$ (40% fall without an additional absolute threshold) were considered, this result is threading on thin ice.

Whereas both studies considered only one, Khalid et al. (2009) compared $PC_{20}FEV_1$ with three different body plethysmographic parameter variations (45%, 52%, and 56% fall). That study was

performed retrospectively in subjects with suspected asthma. However, because $PD_{20}FEV_1$ was used as the gold standard for ROC analysis, it could not answer the question whether one method was superior to the other and thus the authors could not explain the high number of subjects with significant responsiveness in sG_{aw} without reaching the spirometric criterion. All available studies had used the spirometric end-of-test-criterion because of the much lower threshold doses of body plethysmography. Although it is a plausible assumption that subjects with a 20% fall of FEV_1 will all show a significant fall in sG_{aw}, this has never been demonstrated by using two combined end-of-test-criteria, i.e., to terminate the test when both end-of-test criteria are reached.

When we designed this study, firstly, we wanted to avoid limitations of earlier studies by comparing spirometry and body plethysmography over continuous threshold intervals. Secondly, our study was designed as a systematic comparison of FEV_1 and sR_{aw} with both spirometric and body plethysmographic parameters as end-of-test criteria without the need for extrapolation to missing values. Third, we wanted to test a second body plethysmographic criterion that is widely used in Germany. As it may not be relevant to produce a relative change within reference limits, it is plausible to add an absolute criterion of a clinically relevant airway obstruction (at a sR_{aw} of about 2 kPa/s subjects experience dyspnea).

It is essential for case control studies to clearly define cases and controls. In this study we used subjects with suspected occupational asthma, i.e., variable shortness of breath at work. This may be considered as a weakness of the present study explaining its relatively low sensitivities (e.g., with the 20% fall of FEV_1 criterion merely 20 asthmatics were considered hyperresponsive). However, low sensitivities within a similar range as in our study were reported in a recent cohort study (Anderson et al. 2009). In order to avoid misclassification in future studies, further information should be included in the case definition.

The main conclusion of our study is that sR_{aw} is the overall most useful parameter for the detection of airway hyperresponsiveness. sR_{aw} yielded a more balanced sensitivity-specificity ratio with higher sensitivity than FEV_1, but comparable specificity. With a threshold at 80% of baseline the FEV_1-based test may not be tuned to produce optimal results. Optimization of reactive thresholds showed a distinct absolute peak near 90% of baseline ($PD_{10}FEV_1$) for FEV_1 that indicates that the often-used $PD_{20}FEV_1$ might not always be ideal, particularly as lower thresholds (closer to baseline) decrease false negative test rates. It must be considered though, that our study group was assembled to meet criteria like normal baseline FEV_1 as well as Tiffeneau index >70%, which subsequently reduced variance in airway obstruction and therefore shifted optimal thresholds closer to the baseline. Furthermore, by not including those patients in the study that showed mild airway obstruction at baseline, and consecutively in most cases a strong airway response to MCH, the sensitivity of both FEV_1 and sR_{aw}, was artificially reduced. FEV_1 tends to be more specific than sensitive and therefore yields more false negative test results, which is not a desirable feature of early screening tests. In fact MCH testing should be adjusted to provide low false negative rates, which of course requires high sensitivities.

Threshold optimization of sR_{aw} showed the test performance to be completely determined by the absolute 2.0 kPa/s threshold, which might as well be attributed to our concrete study group that did not include patients with non-asthmatic obstructive pulmonary diseases. Relative thresholds avoid the misclassification of subjects with those diseases, such as silicosis. These obstructive diseases are characterized by high absolute baseline resistance and therefore might cross the 2.0 kPa/s boundary prematurely without originating in airway hyperresponsiveness.

Apart from describing hyperresponsiveness with static absolute or relative thresholds there are alternative approaches that focus on the dynamics of the dose–response curve. Lötvall et al. (1998) proposed different pathophysiological mechanisms that lead to differently shaped curves. The authors separated hypersensitivity characterized by a general left-shift from hyperreactivity characterized by a steeper slope of the dose–response curve. The slope of the dose–response curve provides additional valuable information that prospectively should be integrated into the diagnosis of airway hyperresponsiveness. The slope-based test performances were comparable to those of the threshold-based

analyses, which suggests that the dynamics of the dose–response curve may be regarded as an alternative or additional measure to effectively separate asthmatics from normal subjects.

In summary, this study indicates that body plethysmography adds valuable information to the question whether a subject has airway hyperresponsiveness. Its most important advantage is the reduction of false negative tests which may occur with spirometry. This is important especially in the diagnosis and compensation of occupational asthma. While we are still waiting for optimal threshold definitions based on credible normative data and reliable statistical methods, a combination of both, spirometry and body plethysmography, should offer the best information.

Conflicts of Interest: The authors declared no conflicts of interest in relation to this article.

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Chapter 2
Hospital Management of Patients with Exacerbation of Severe Chronic Obstructive Pulmonary Disease

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Abstract The article assesses the originally developed criteria of clinical stability and treatment protocol in the hospital management and discharge procedures of patients with exacerbations of severe chronic obstructive pulmonary disease (COPD). The study included 34 patients (26 males, 8 females), aged 58–80 years, hospitalized due to exacerbation of severe (23 patients) and very severe (11 patients) COPD. On admission, the mean FEV1 was 0.78 ± 0.22 L (31.7% ± 8.2% of predicted), FVC 2.52 ± 0.87 L (77.9% ± 9.8% of predicted) and FEV1/FVC 33.17% ± 10.84%. Before hospitalization, 10 out of the 34 patients were diagnosed with chronic respiratory failure. All patients were treated according the same treatment protocol which included the developed criteria of clinical stability. Meeting all these criteria in a 24-h observation period was the basis to slash the dose of systemic glucocorticosteroids by half. The maintenance of the stability criteria through the subsequent 24 h allowed discharging a patient from the hospital. Every patient was supplied with a detailed plan of out-of-hospital treatment. The results show that the mean duration of hospitalization was 6.4 ± 4.8 days. Only one patient required readmission within 4 weeks after discharge. Two patients died; one during the hospitalization time and the other after discharge. In the latter case, death was not directly related to the COPD exacerbation. In conclusion, the protocol of treatment and the criteria of stability used for patients with COPD exacerbation enabled to optimize the hospitalization time. A shortening of hospitalization was not associated with increased risk of readmission within 4 weeks after discharge.

Keywords COPD exacerbation • Clinical stability • Length of hospitalization • Chronic respiratory failure • Treatment protocol

2.1 Introduction

Exacerbations of chronic obstructive pulmonary disease (COPD) are a substantial burden for healthcare systems. The hospitalization rate due to COPD exacerbation is rising worldwide. Patients suffering from severe COPD experience, on average, 3.5 exacerbations per year, out of which about 52% require hospitalization. It has been estimated that hospitalizations constitute up to 60% of direct costs of

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COPD treatment (Hillman et al. 2000; Miravitlles et al. 2002) and up to 90% of the costs of treatment of severe exacerbations (Oostenbrink and Rutten-van Molken 2004). In addition to a considerable financial burden, hospital treatment is associated with a high risk for nosocomial infections. A key issue is to recognize the early phase of COPD exacerbation and to initiate treatment. The issue also is a proper qualification of patients either for hospitalization or outpatient treatment. COPD exacerbations result in deterioration of lung function and can be accompanied by respiratory and circulatory failure, and by impaired consciousness. Patients with respiratory failure often require non-invasive or invasive mechanical ventilation. COPD exacerbations constitute a risk of death, especially in patients with severe and very severe chronic obstructive pulmonary disease.

Clinical presentations of COPD exacerbation depend on disease severity, cause of exacerbation, its dynamics, and co-morbidities. Therefore, a definition of clinical stability should take into account a number of parameters and the natural daily variability of symptoms. It is essential to recognize that lung function, health related quality of life, and often blood gases remain abnormal after resolution of COPD exacerbation. In addition, clinical status of an individual prior to COPD exacerbation often times is unknown, making it difficult to judge whether the therapy of exacerbation brought about the optimal improvement. Thus, only some of exacerbation indicators are reliable and can be useful in clinical practice. Criteria of clinical stability should take into consideration all limitations and should reflect the variable and dynamic presentation of a patient.

Likewise, it is difficult to qualify a patient for treatment of COPD exacerbation on the outpatient or hospital basis. That mainly applies to patients suffering from severe (stage III according to GOLD) and very severe (stage IV according to GOLD) COPD. The current GOLD guidelines (2010) recognize an exacerbation of severe and very severe COPD as the indication for hospitalization. In some cases, however, alternative programs of home hospitalization (hospital at home) or support programs of early discharge home (early supported discharge) are acceptable. The GOLD guidelines do not specify the clinical and/or laboratory criteria which would help to assess the risk of failure of home-based management programs. In some countries (especially Spain and Scandinavia), the programs of early supported discharge are becoming more popular as they shorten hospital stay even twice. Such programs have been shown not to increase either the death rate or the need for additional and unexpected medical interventions when compared with exclusively hospital based management (Cotton et al. 2000; Sala et al. 2001; Hernandez et al. 2003; Ram et al. 2004; Davison et al. 2006; Salazar et al. 2009). Patients included into the programs of home hospitalization presented a significantly better quality of life, a higher degree of satisfaction, and a greater sense of safety, which was related to better education of patients (Gravil et al. 1998; Ojoo et al. 2002; Casas et al. 2006). Despite that the hospital-at-home programs are already recommended by the British Thoracic Society (BTS) guidelines of 2007, the criteria of clinical stability have not yet been clearly defined. Accordingly, the early discharge from hospital remains difficult and questionable. The average time of hospitalization due to exacerbations of COPD is long as it reaches 11–15 days worldwide.

The objectives of the present study were twofold: (1) development and assessment of the protocol of treatment and discharge from the hospital of patients with exacerbations of severe and very severe COPD and (2) development and assessment of the criteria of clinical stability, essential for the decision-making on discharge.

2.2 Methods

The study was performed in conformity with the Declaration of Helsinki for Human Experimentation and the protocol was approved by the Ethics Committee of Wroclaw Medical University (No. 157/2003). All patients gave informed written consent to participate in the clinical experiment.

Table 2.1 Pulmonary function, blood gas content, and Borg score on the first and last day of hospitalization, and 4 weeks afterward

	First day of hospitalization	Last day of hospitalization	Follow-up of 4 weeks
FEV1pre (L)	0.78 ± 0.22	0.79 ± 0.23	0.88 ± 0.26
FEV1pre (% pred)	31.7 ± 8.2	32.3 ± 8.9	34.9 ± 8.2
FVCpre (L)	2.52 ± 0.87	2.54 ± 0.77	2.89 ± 1.1
FVCpre (% pred)	77.9 ± 19.8	79.2 ± 17.9	88.4 ± 24.4
FEV1/FVCpre (%)	33.2 ± 10.8	32.7 ± 9.9	32.5 ± 11.1
FEV1post (L)	0.86 ± 0.28	0.89 ± 0.26	0.98 ± 0.29
FEV1post (% pred)	35.1 ± 10.4	36.37 ± 9.8	39.0 ± 9.4
FVCpost (L)	2.55 ± 0.87	2.74 ± 0.83	2.96 ± 0.93
FVCpost (% pred)	79 ± 20.2	85.6 ± 20.0	91.7 ± 24.0
FEV1/FVCpost (%)	36.0 ± 12.2	33.9 ± 9.5	34.9 ± 11.9
pH	7.40 ± 0.07[a]	7.43 ± 0.04[b]	7.42 ± 0.04[b]
PO_2	60.2 ± 11.7[a]	61.1 ± 11.6[b]	65.4 ± 13.0[b]
PCO_2	45.4 ± 12.0[a]	42.8 ± 8.2[b]	41.2 ± 8.1[b]
HCO_3^-	27.2 ± 5.02[a]	28.2 ± 5.2[b]	26.0 ± 4.7[b]
BE	2.1 ± 4.1[a]	3.9 ± 4.2[b]	1.8 ± 4.0[b]
SaO_2	88.9 ± 6[a]	90.3 ± 5.5[b]	91.2 ± 5.8[b]
Borg scale	5.9 ± 1.7	–	1.4 ± 0.9

Data are means ± SD; pre-post, before and after administration of a bronchodilator
[a]Arterialized blood gas analysis on optimal oxygen therapy
[b]Arterial blood gas analysis on room air

The study included 34 patients (26 males, 8 females), aged 58–80 (mean 72 ± 7SD years), admitted to the Department of Internal Medicine, Geriatrics and Allergology of Wroclaw Medical University in Wroclaw, Poland. The patients were hospitalized due to exacerbation of severe (23 patients) and very severe (11 patients) COPD. All patients were past or current cigarette smokers (10–150 pack-years, mean 60.7 ± 31.2 pack-years; 28 ex-smokers, 6 active smokers) and were diagnosed with COPD, without accompanying asthma or any other lung disease. Ten patients (29%) were previously diagnosed with chronic respiratory failure and seven patients were subjected to long-term oxygen therapy. On admission, central cyanosis was recorded in 17 patients (50%), whereas orthopneic position was recorded in 22 out of the 34 patients (65%). According to the Borg scale, the patients assessed the severity of dyspnea from moderate (3 points) up to very severe, almost the maximum (9 points). The mean Borg score was 5.9 ± 1.7 points. Pulmonary function tests performed on the first day of hospitalization showed severe airflow limitation in all individuals. Before administration of a bronchodilator, the mean group FEV1 was 0.78 ± 0.22 L (31.7% ± 8.2% predicted), FVC was 2.52 ± 0.87 L (77.9% ± 19.8% predicted), and FEV1/FVC was 33.2% ± 10.8%. After bronchodilation, the mean FEV1 was 0.86 ± 0.28 L (35.1% ± 10.4% predicted), FVC 2.55 ± 0.87 L (79.0% ± 20.2% predicted), and FEV1/FVC 36.0% ± 12.2%. On admission, all subjects were sampled for arterialized blood gas content and 17 patients (50%) were found hypoxemic (PaO_2 38.6–59.3 mmHg), 14 patients had hypercapnia ($PaCO_2$ 46–66.8 mmHg), and 5 patients had respiratory acidosis (minimum pH 7.24). Selected parameters of pulmonary function, blood gas content, and Borg score on the first day of hospitalization are summarized in Table 2.1.

All patients were subjected to the same protocol of treatment and received: (1) nebulizations with ipratropium bromide 250 μg every 6 h; (2) additional nebulizations with salbutamol 2.5 mg on demand (each administration was preceded by a physician's examination); (3) hydrocortisone hemisuccinate 100 mg i.v. every 12 h; (4) optimal oxygen therapy *via* nasal catheter, and if necessary *via* non-invasive ventilation with a BiPAP device (Bi-level positive airway pressure); (5) antibiotics and cardiovascular drugs according to indications; and (6) methylxanthines orally at previously prescribed doses, only if used on a regular basis before exacerbation. When antibiotic therapy was indicated, empirical therapy

Table 2.2 Protocols of in-hospital and out-of-hospital treatment of COPD exacerbation

In-hospital treatment	Out-of-hospital treatment
Ipratropium bromide 250 μg every 6 h (nebulization)	Ipratropium bromide 40 μg every 6 h (spacer)
Salbutamol 2.5 mg on demand (nebulization)	Salbutamol 200 μg on demand (spacer)
Hydrocortisone hemisuccinate 100 mg every 12 h (i.v.)	Prednisone 20 mg with reduction of the dose by 5 mg every 7 days (orally)
Optimal oxygen therapy (nasal catheter or BiPAP)	Methylxanthines at the previously used doses (orally)
Antibiotic and/or cardiovascular drugs according to indications	Fluticasone propionate 500 μg every 12 h (DPI-Discus or MDI-spacer)
Methylxanthines at the previously used doses (orally)	Long-acting β_2-agonist 1 dose every 12 h (inhalation)

with amoxicillin combined with clavulanic acid was given. In case of contraindications to penicillin, ciprofloxacin was administered as a second line therapy. Non-invasive mechanical ventilation using BiPAP was applied to the patients fulfilling the following criteria of arterialized blood gas content: respiratory acidosis (pH < 7.3) and/or hypercapnia (PCO_2 > 55 mmHg), and/or increase in PCO_2 by more than 20% compared with baseline. The treatment protocol was summarized in Table 2.2.

In case of reported shortness of breath, at patient's demand, it was allowed to advance a planned dose of ipratropium bromide and hydrocortisone hemisuccinate, but for no more than 1 h. In other cases of intensification of dyspnea, the patient was given extra doses of salbutamol 2.5 mg in nebulization and hydrocortisone 100 mg i.v., if required. Every extra dose of bronchodilator or glucocorticosteroid was recorded in the study documentation. All patients were continually monitored for the stability criteria which included the following elements:

1. stable vital signs for 24 h:
   (a) respiratory rate <20/min
   (b) heart rate <100/min
2. body temperature <37°C for at least 2 consecutive days
3. stable arterialized blood gases for 24 h (on optimal oxygen therapy), defined as a maximum increase in PCO_2 in the morning by less than 10% of the PCO_2 measured in the preceding evening.
4. no night-time awakenings due to dyspnea
5. necessity to use rescue β2-agonist (Salbutamol) up to 4 times/day and no extra doses of hydrocortisone hemisuccinate
6. leukocytosis <13,000
7. absence of clinical symptoms of pneumonia and resolution of COPD exacerbation cause
8. unassisted food intake and the ability to walk 10 m
9. mastery in the correct technique of drug inhalation
10. adequate nursing care at home

If a given patient fulfilled all the stability criteria above outlined, the dose of hydrocortisone hemisuccinate was reduced by 50% from 100 to 50 mg b.i.d. If these criteria were maintained through the subsequent day, the patient was administered 20 mg of prednisone orally and discharged home. All subjects continued treatment of COPD exacerbations at home in accordance with the out-of-hospital treatment protocol as shown in Table 2.2. In addition, the patients received cardiovascular and other concomitant treatment as indicated. On the day of discharge, the arterial blood gas content was checked and in the case of hypoxemia, the patient was recommended to use oxygen therapy at home. The diagnosis of chronic respiratory failure was verified at the follow-up visit.

The patients and their families were educated in regard to home management of dyspnea attacks. The choice of a dry powder inhalation system was based on the value of the peak inspiratory flow (PIF) rates related to the resistance measured with In-Check Inhaler Assessment Kit (Clement Clark

International Ltd.). The ability to use inhalers was strictly monitored and if the use was improper, the patient was instructed in the correct technique of inhalation. Once a week, a referring doctor telephoned the patient in order to assess the results of COPD treatment. When in doubt, the patients could contact the doctor 24 h a day. Four weeks after the discharge, there was a follow-up visit on site. The patients were examined, including a lung function test and sampled for arterial blood gas analysis. Based on the examination, severity of COPD and the previous diagnosis of chronic respiratory failure were verified. The need for emergency room visits due to dyspnea, hospital readmissions, or modifications of the out-of-hospital treatment protocol within 1 month after discharge were regarded as a failure and were thoroughly analyzed.

2.3 Results

The mean hospitalization time was 6.4 ± 4.8 days. Two patients died. The first patient died at the hospital on the 26th day of hospitalization. The decease was due to *enterococcal* pneumonia and was directly related to the exacerbation of COPD. The patient had right ventricular failure and deep vein thrombosis in a proximal part of the left lower extremity. The second patient died at home due to extensive myocardial infarction. The family reported that since discharge the patient felt quite well, had improved of exercise tolerance, and there were no episodes of nocturnal dyspnea. Based on this, no direct link between the death of the patient and the early discharge from the hospital after COPD exacerbation was recognized.

The 4-week follow-up visit covered 30 out of the 34 patients. Two patients refused to attend the follow-up visit on site due to a long distance between the hospital and patients' home and difficulty in moving. During a substitute phone follow-up visit, both declared satisfaction with the participation in the program and claimed satisfactory control of COPD and the stability of the disease. All remaining 30 patients also declared satisfaction with the results of the early-supported discharge program. Most patients emphasized the role of education in providing the sense of security and finally in improving the control of COPD. On the follow-up visit, all patients were examined including the lung function tests and arterial blood gas analysis. The severity of chronic obstructive pulmonary disease and previous diagnosis of chronic respiratory failure were verified. It was confirmed that all study participants manifested severe airflow limitations (stage III and IV by GOLD). In the whole group, before administration of a bronchodilator, the mean FEV1 was 0.88 ± 0.26 L (34.9% ± 8.2% predicted), the mean FVC was 2.90 ± 1.1 L (88.4% ± 24.4% predicted), and the mean FEV1/FVC was 32.5% ± 11.1%. The corresponding values after a bronchodilator were 0.98 ± 0.29 L (39.0% ± 9.4% predicted), 2.96 ± 0.93 L (91.7% ± 24.0% predicted), and 34.9% ± 11.9%, respectively. In nine individuals, the previous diagnosis of chronic respiratory failure was confirmed.

2.4 Discussion

Exacerbations of severe and very severe chronic obstructive pulmonary disease usually afflict people at old age and suffering from chronic co-morbid conditions. Due to severe airflow limitation and possible concurrent respiratory failure, prognosis at the initial phase of COPD exacerbation is difficult and uncertain. It is accepted that advanced age, FEV1 ± 35% of predicted, long-term history of the disease, male sex, chronic respiratory failure, chronic heart failure, crippling and disabling diseases (e.g., cancers), and frequent (3 or more a year) exacerbations are risk factors for unfavorable course of COPD exacerbation (Almagro et al. 2002; Plant et al. 2001; Chu et al. 2004; Patil et al. 2003). For this reason and in accordance with the GOLD guidelines, patients suffering exacerbation of severe

and very severe COPD require medical evaluation at the emergency unit of the nearest hospital regardless of the severity of exacerbation (Global Initiative for Chronic Obstructive Lung Disease 2010). There is an urgent need for further studies in this group of patients to define the safety criteria for the out-of-hospital treatment following the initial hospital-based treatment. There are new programs – 'home hospitalization' and 'early supported discharge' - to meet these needs. Based on the results of home hospitalization programs, the British Thoracic Society guidelines (BTS Guideline 2007) allow the continuation of the treatment of exacerbation of severe and very severe COPD in an out-of-hospital setting. However, treatment protocols and clinical stability criteria for early discharge are still under discussion.

In this study we present a uniform protocol of treatment of patients with severe and very severe COPD exacerbation, and new clinical stability criteria for early discharge from the hospital. The treatment regimen offered the patient-oriented flexibility of therapy by controlled increases of bronchodilator and systemic glucocorticosteroid dosing. In contrast to previously published clinical trials, our protocol did not determine in advance the number of treatment days according to a specified plan. The glucocorticosteroid dose tapering, reflecting the shortening of hospitalization duration was based on the patient's clinical status. The criteria of clinical stability presented covered respiratory and circulatory variables, resolution of COPD exacerbation cause, basic life activity assessment, and the ability for proper inhalation of a drug. We emphasize the importance of respiratory rate which reflects the severity of dyspnea and $PaCO_2$ which is an indicator of respiratory failure. The value of PaO_2 seems to be less useful due to the need for oxygen therapy. It is worth noting that current guidelines do not include gasometry parameters as the qualifying criteria for the home hospitalization procedures. Lung function parameters – FEV1 and FVC – are poor predictors of clinical status in COPD, and were not included in the stability criteria. We conclude that potential clinical predictors of clinical stability are the need for rescue medication (no more than four occasions) and no night-time awakenings caused by dyspnea. The criteria also included the resolution of COPD exacerbation cause and the absence of pneumonia. Pneumonia is an indication for hospitalization regardless of the stage and severity of COPD exacerbation. The British Thoracic Society guidelines (2007) do not recommend outpatient treatment of COPD exacerbation in patients with pneumonia confirmed by X-ray examination. The other criteria such as unassisted food intake, the ability to walk 10 m, mastery in the proper technique of drug inhalation, and adequate nursing care at home all seem to play a key role in daily practice.

The presented protocol for treatment of COPD exacerbations and the criteria for clinical stability were shown to be effective tools in the optimization of hospitalization duration. The mean hospitalization time was shortened to 6.4 ± 4.8 days. Application of both tools in clinical practice allows for safe and efficacious continuation of treatment of exacerbations of severe and very severe COPD in out-of-hospital settings. The results of this study create the rationale for further development of programs of early supported discharge from the hospital.

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

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Chapter 3
Pulmonary Rehabilitation in Patients Referred for Lung Transplantation

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Abstract Effectiveness of pulmonary rehabilitation in patients with chronic obstructive lung diseases, cystic fibrosis, and interstitial lung disease is well documented but little is known about the results of pulmonary rehabilitation in patients referred for lung transplantation. The purpose of this study is to prospectively examine the efficacy of Nordic walking, a low cost, accessible, and proven beneficial form of physical exercise, as a form of pulmonary rehabilitation in patients referred for lung transplantation. Twenty-two male patients referred for lung transplantation at the Department of Lung Diseases and Tuberculosis in Zabrze, Poland, were invited to take part in the study. The rehabilitation program, which was conducted for 12 weeks, was based on Nordic walking exercise training with ski poles. Lung function tests (FVC, FEV1), mobility (6 min walking test (6MWT)), rating of dyspnea (Oxygen Cost Index, MRC and Baseline Dyspnea Index), and quality of life assessments (SF-36) were performed before and after the completion of the exercise program. No adverse events were observed after completing the pulmonary rehabilitation program in patients referred for lung transplantation. After 12 weeks of pulmonary rehabilitation with Nordic walking we observed a significant increase in the mean distance walked in the 6MWT (310.2 m *vs.* 372.1 m, $p<0.05$). The results of lung function tests also showed improvement in FVC. There were no significant differences in the perception of dyspnea before and after completing the rehabilitation program. General health and quality of life questionnaire (SF-36) showed improvement in the domain of social functioning ($p<0.05$). In conclusion, pulmonary rehabilitation with a Nordic walking program is a safe and feasible physical activity in end-stage lung disease patients referred for lung transplantation and results in improvements in patients' mobility and quality of life.

Keywords Interstitial lung disease • Lung transplantation • Pulmonary rehabilitation • Nordic walking • Six-minute walking distance

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3.1 Introduction

Effectiveness of pulmonary rehabilitation in patients with COPD is well documented (Troosters et al. 2000). According to growing evidence, in patients with interstitial lung diseases, pulmonary rehabilitation is associated with a significant improvement in dyspnea and functional status (Holland and Hill 2008). Little is known about the impact of such medical intervention in patients with end-stage lung diseases who are referred for lung transplantation. The Silesian Center for Heart Disease in Zabrze is the only medical center in Poland which performs lung transplantations. Patients who are on the waiting list for lung transplantation often deteriorate in mobility and health status and have more pronounced dyspnea. The question arises of whether pulmonary rehabilitation could be beneficial in patients with end-stage lung diseases waiting for lung transplantation. To the best of our knowledge, there is lack of controlled studies on pulmonary rehabilitation program in patients referred for lung transplantation. In this study, therefore, we attempted to address this issue by prospectively examining the efficacy of Nordic walking, a low cost, accessible and proven beneficial form of physical exercise, as a form of pulmonary rehabilitation in patients referred for lung transplantation.

3.2 Methods

3.2.1 Patients

The study was approved by the Bioethics Committee of the Medical Academy of Silesia. Thirty patients with end-stage lung disease were referred for lung transplantation in the Department of Lung Diseases and Tuberculosis in Zabrze between November 2009 and September 2010. All of them fulfilled the ISH lung transplantation criteria for lung transplantation (Orens et al. 2006). Those without exclusion criteria for pulmonary rehabilitation were invited to take part in the study. A total of 26 male patients aged 50.4 year gave written informed consent to participate in the study. Two patients were excluded from the study because of lung transplantation, and two patients withdrew consent for participation in the study during the pulmonary rehabilitation program because of general weakness due to disease progression. The diagnoses included end-stage COPD (n = 7), idiopathic pulmonary fibrosis (IPF) (n = 3), and other than IPF forms of idiopathic interstitial pneumonia (IIP) (n = 12).

3.2.2 Physiological Measurements

Physiological testing was completed on the same day as informed consent was obtained. Spirometry was performed using Jaeger-Masterlab (Erich Jaeger GmbH, Wurtzburg, Germany). Two lung function parameters were measured: forced vital capacity (FVC) and forced expiratory volume in one second (FEV1). Results were normalized to the reference values proposed by the European Community for Coal and Steel and presented as percentage of the predicted value (% pred.). Mobility was presented as the distance covered in the 6-min walking test (6MWT). The test was performed according to the guidelines of the modified Bruce protocol (American Thoracic Society Statement 2002). The use of oxygen during the test was standardized, and all follow-up walking tests were conducted using the same flow rate supplemental oxygen that had been used at baseline. Dyspnea before and after 6MWT on Borg's scale, arterial oxygen saturation (SaO_2) before and after 6MWT, and the time and distance to desaturation <80% were also recorded.

3.2.3 Rehabilitation Program

The training program was conducted according to the same exercise prescription principles as those used for COPD (Nici et al. 2006). The training programme consisted of two 6-week cycles. Each cycle consisted of 2 weeks of hospital-based, supervised rehabilitation and a 4-week home-based rehabilitation program. The rehabilitation program was based on Nordic walking, which is walking with specially constructed ski poles. Patients received 1-h instruction by a professional Nordic walking instructor. Heart rate (HR) and (SaO_2) were monitored by pulse oximetry during the hospital-based training. Patients performed maximal exercise testing to obtain maximum HR. The preset goal for training efficiency was set at 75% of the initial maximum HR. Walking distance was established according to the distance achieved in the 6MWT and depended on the distance when oxygen saturation dropped to 80%. The patients on home oxygen therapy (HOT) used supplemental O_2 during interventions according to European Respiratory Society guidelines (Nici et al. 2006). During training, all patients were supervised and data were recorded by medical staff. Walking speed was, if necessary, adapted to bearable dyspnea and optimal oxygen saturation. All patients were equipped with a pedometer and recorded daily walking distance and events during training. During follow-up visits, medical staff checked the compliance of each patient during the rehabilitation program.

3.2.4 Quality of Life

The SF-36 questionnaire (Ware et al. 2004) was used to estimate the quality of life. The questionnaire consists of 36 questions, which includes the following basic domains describing the condition of health: physical functioning (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role emotional (RE), and mental health (MH). The higher the score the better is the general health status. Methodological rules and data analysis from the SF-36 questionnaire have been described previously (Jastrzebski et al. 2005).

3.2.5 Rating of Dyspnea

Three different clinical methods were used for the rating of dyspnea at a set point in time: a modification of the Medical Research Council questionnaire (MRC) (Fletcher 1960), baseline dyspnea index (BDI) (Baddini Martinez et al. 2002), and oxygen cost diagram (OCS) (Baddini Martinez et al. 2002). Details concerning the methodological aspects of dyspnea rating and quantification using the methods above outlined have previously been described (Jastrzebski et al. 2005).

Results were expressed as means ± SD. Statistical analysis was performed using a commercial Statistica packet. Significance was defined as $p < 0.05$.

3.3 Results

Out of the 26 patients awaiting lung transplantation and qualified for the tests, 22 (85%) completed a 12-week pulmonary rehabilitation program. Two participants withdrew after 6 weeks due to exacerbation of their disease and/or hospitalization, while the other two were excluded from the training group because of lung transplantation.

Table 3.1 Six-minute-walk distance and dyspnea (Borg score) before and after 6 and 12 weeks of Nordic walking pulmonary rehabilitation

	Baseline	After 6 weeks	After 12 weeks
6MWT (m)	310.2 ± 130.2	361.9 ± 131.5*	372.1 ± 163.7**
Borg scale before 6MWT	1.0 ± 1.7	1.0 ± 1.8	0.9 ± 0.5
Borg scale after 6MWT	6.2 ± 1.8	5.8 ± 1.8	6.3 ± 1.5
SaO_2 before 6MWT (%)	92.1 ± 3.2	92.5 ± 3.3	91.9 ± 4.6
SaO_2 after 6MWT (%)	73.1 ± 13.1	73.0 ± 11.9	73.5 ± 11.4
Time to SO_2 <80% (s)	102.0 ± 137.1	115.6 ± 51.0	124.0 ± 138.8
Distance to SaO_2 <80% (m)	128.2 ± 69.0	117.5 ± 76.4	128.1 ± 115.2

6MWT six-minute walking test, *SaO_2* arterial oxygen saturation
*p < 0.05, 6 weeks *vs.* baseline; **p < 0.05, 12 weeks *vs.* baseline

3.3.1 6MWT Distance

After 6 weeks of Nordic walking rehabilitation, we noted a significant increase in the mean distance walked in 6MWT from 310.2 ± 130.2 to 361.9 ± 131.5 m, which makes an average of 51.6 m increase (Table 3.1). The greatest individual increase was 150 m (125%) after 6 weeks and it was present in a patient whose initial distance amounted to 120 m. The patient with the lowest initial distance of 40 m increased it to 70 m (75%) after completion of the rehabilitation. In two patients (9.1%), there was a decrease in the distance walked in the 6MWT after 6-week rehabilitation. After additional 6 weeks of rehabilitation, the mean 6MWT distance further increased to 372.1 ± 163.7 m, which makes it a 61.9 m (20%) improvement compared with the initial mean result and a 10.3 m (3.3%) increase in relation to the 6 weeks' result of pulmonary rehabilitation. The increases in distance walked after both 6 and 12 weeks, compared with the baseline distance, as well as the increase between 6 and 12 weeks of rehabilitation were significant ($p < 0.05$). There were no appreciable differences in the perception of dyspnea before and after completing the rehabilitation program as assessed by the Borg scale. Neither was there an increase in the mean distance (128 m) and time (100 s) up to a drop in SaO_2 <80% after 12 weeks of rehabilitation (Table 3.1).

3.3.2 Spirometry

We noted increases in the mean values of FEV1 (42% *vs.* 34% pred.), FVC (53% *vs*. 44% pred.), and FEV1%VC (65 *vs.* 61) after 12 weeks of pulmonary rehabilitation. However, only the increase in FVC reached statistical significance.

3.3.3 Quality of Life Evaluation (SF-36)

General quality of life evaluation through the SF-36 questionnaire showed noticeable improvements in social functional of the patients (SF) and in the physical cumulative score (PCS) after just 6 weeks of rehabilitation. These improvements were sustained after 12 weeks of rehabilitation ($p < 0.05$). The other domains of the quality of life in the SF-36 questionnaire were inappreciably affected by the pulmonary rehabilitation employed in the study (Table 3.2).

Table 3.2 Quality of life evaluation – SF-36

	Baseline	After 6 weeks	After 12 weeks
PF	24.8 ± 22.9	29.6 ± 23.8	26.1 ± 22.8
RP	7.1 ± 23.1	17.1 ± 33.4	12.1 ± 24.7
BP	55.4 ± 27.8	59.7 ± 30.4	60.9 ± 25.9
GH	24.3 ± 13.9	28.9 ± 13.8	30.4 ± 15.4
VT	36.5 ± 19.6	37.1 ± 19.3	36.9 ± 15.4
SF	35.0 ± 30.5	45.3 ± 30.4*	40.0 ± 26.4**
RE	31.7 ± 42.6	36.3 ± 41.2	22.2 ± 33.9
MH	59.8 ± 17.4	53.3 ± 16.8	57.3 ± 15.0
PCS	27.2 ± 8.2	29.9 ± 9.1*	30.8 ± 7.3**
MCS	40.7 ± 11.2	39.6 ± 10.1	38.9 ± 8.5

PCS and MCS are physical and mental component summary scales, respectively, capturing 85% of the reliable variance in the eight-scale SF-36
PF physical functioning, *RP* role physical, *BP* bodily pain, *GH* general health, *VT* vitality, *SF* social functioning, *RE* role emotional, *MH* mental health
*p < 0.05, 6 weeks *vs.* baseline; **p < 0.05, 12 weeks *vs.* baseline

3.4 Discussion

Our prospective, non-randomized study investigating the effectiveness of pulmonary rehabilitation with a Nordic Walking program of 12 weeks in patients with end-stage lung diseases referred for lung transplantation shows that pulmonary rehabilitation in these patients leads to a clinically relevant improvement in mobility (6MWT), lung function (FVC % pred.), and the quality of life. Rehabilitation in patients referred for lung transplantation is difficult to perform because of various factors. Patients in the end-stage of lung diseases are susceptible to exacerbations resulting from the pathology of progressing disease. In our study, two patients (7.5%) were excluded due to exacerbations. A 15% drop-out rate in our study is similar to other studies where this rate may reach up to 31% (Troosters et al. 2000). One of the strengths of the present study is that the population was far more homogeneous and serious in terms of pulmonary restriction and functional deficits than the populations studied in all previous trials (Troosters et al. 2000; Holland and Hill 2008). To the best of our knowledge, it is the first study on pulmonary rehabilitation with Nordic Walking performed in such a group of patients. Nordic Walking is fitness walking using specially designed poles for the purpose of activating the upper body during walking (International Nordic Walking Federation). By using the poles, the muscles in the upper body are activated. Nordic Walking appears to increase gait speed, cardiovascular metabolism, and oxygen consumption (Church et al. 2002). Due to the specially constructed poles, Nordic walking can be performed independently of ground quality, and thus the rehabilitation program could be performed in the hospital and at home. A particular challenge in interventions involving patient participation, such as exercise therapy, is the issue of compliance to the prescribed exercises. It is obvious that training and exercise therapy is slightly more effective if delivered under the supervision of an instructor. In our study, after 2 weeks of supervised rehabilitation, patients were instructed to note everyday walking activity according to the indication of a personal pedometer. Because of this, the authors hope that out of hospital therapy with Nordic Walking was 'partially' supervised.

Guidelines and most papers on pulmonary rehabilitation demonstrate that the results of 6 min walking tests are a better predictor of effective pulmonary rehabilitation than improvements in dyspnea and quality of life (Troosters et al. 2000; Holland and Hill 2008; Nici et al. 2006;, Ries et al. 2007). Moreover, the baseline 6-min walking distance predicts survival in lung transplant candidates (Orens et al. 2006; Martinu et al. 2008). Martinu et al. (2008) have demonstrated that the best survival

after lung transplantation is observed in patients who were able to walk more than 400 m (1,200 ft) before surgery. In our study, three patients (14%) after Nordic Walking rehabilitation increased their walking ability to more than 400 m. The mean increase in walking ability in our study group was 61 m, which is similar to the results of other studies on pulmonary rehabilitation in patients with restrictive lung diseases. Ferreira et al. (2009) have reported increases in 6MWT by 56 m after 8 weeks of pulmonary rehabilitation in patients with different forms of interstitial lung disease. In a recent study, Salhi et al. (2010) have reported increases in 6 MW distance of 64 m after 12 weeks and 81 m after 24 weeks of pulmonary rehabilitation. In that study, a multidisciplinary rehabilitation program with occupational therapy, nutritional support, patient education, and psychosocial support has been employed. Moreover, the exercise program in that study included peripheral muscle training on fitness equipment, stair climbing, treadmill walking, and bicycle training. To our surprise, in the present study we achieved similar results of pulmonary rehabilitation using a simple, cost-effective, and easy method of Nordic-Walking. Additionally, we observed an improvement in perception of dyspnea and quality of life, although these improvements did not achieve statistical significance, due likely to a limited study population. Future studies on large cohorts of patients referred for lung transplantation could analyze the influence of pulmonary rehabilitation on dyspnea and quality of life in detail.

In conclusion, this study demonstrates that pulmonary rehabilitation with Nordic Walking results in a significant improvement in the functional status of patients referred for lung transplantation. While emphasizing the need for further research, we strongly suggest that Nordic Walking rehabilitation should be considered as a standard for care of patients referred for lung transplantation.

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

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Chapter 4
Effects of Nasal Insufflation on Arterial Gas Exchange and Breathing Pattern in Patients with Chronic Obstructive Pulmonary Disease and Hypercapnic Respiratory Failure

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Abstract High flow nasal insufflations (NI) can improve gas exchange and alleviate dyspnea in patients with acute respiratory failure. In the present study we investigated the effects of high flow nasal insufflations in COPD patients with chronic hypercapnic respiratory failure (HRF). Seventeen patients with severe COPD and HRF were recruited. We delivered a mixture of 20 L/min room air and 2 L/min O_2 through a nasal cannula either into both nostrils (NI) or into one nostril (Partial NI). Respiratory pattern and $PaCO_2$ responses under NI were compared with low flow oxygen of 2 L/min. High flow nasal insufflations led to a systematic reduction in respiratory rate from 19.8 ± 4.2 at baseline to 18.0 ± 4.7 during NI ($p < 0.008$) and 18.1 ± 5.2 breaths/min during Partial NI ($P < 0.03$). The mean group inspiratory duty cycle (T_I/T_T) and mean group $PaCO_2$ remained constant between all experimental conditions. Individual responses to NI were heterogeneous: six patients demonstrated marked reductions in respiratory rate (>20% fall from baseline), another group (n = 6) demonstrated no change in respiratory rate but marked reductions in arterial carbon dioxide of more than 8 mmHg. In conclusion, high flow (20 L/min) nasal insufflations of warm and humidified air during wakefulness for 45 min reduced respiratory rate without deterioration of hypercapnia. Our data indicate that high flow NI improved efficiency of breathing and may be used as an adjunct to low flow oxygen for preventing hypercapnic respiratory failure in severely ill COPD patients.

Keywords COPD • Dyspnea • Gas exchange • Hypercapnic respiratory failure • Nasal high flow • Respiratory rate

4.1 Introduction

Chronic obstructive pulmonary disease (COPD) has a large impact on health worldwide. It is the fourth leading cause of both chronic morbidity and mortality in Western societies (Halbert et al. 2006; Mathers and Loncar 2006; Jemal et al. 2005; Fang et al. 2011). Disturbances in oxygenation and

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ventilation are commonly observed in patients with COPD and are recognized causes of increased mortality in COPD (Anthonisen 1983). Thus, a major target for treatment is the improvement in both oxygenation and ventilation, both of which have been shown to reduce mortality, particularly in patients with severe COPD (Report of the Medical Research Council 1981; Nocturnal Oxygen Therapy Trial Group 1980).

Low flow oxygen at a rate of 2–5 L/min is the mainstream treatment option for reducing mortality in hypoxemic patients with severe COPD. Oxygen administration for at least 15–18 h/day leads to almost 50% decrease in 5 year mortality compared with untreated controls. Although long-term low flow oxygen (LTOT) clearly benefits patients' outcome, many patients do not adhere to this treatment. The primary reasons for low adherence are complaints of drying out of nasal mucosa and frequent nose bleeds, lack of alleviating dyspnea, and high cost of oxygen treatment. Non-invasive ventilation (NIV) *via* a nasal/facial mask has been proposed to offer an alternative or adjunct to LTOT, but adherence rates are even lower than those for LTOT (Clini et al. 2002; Wijkstra et al. 2003; McEvoy et al. 2009). Thus, low flow oxygen and NIV are hampered by either significant side effects or reduced adherence leaving a majority of patients with severe COPD insufficiently treated.

Recently, insufflation of high nasal airflow of warm and humidified room air has been introduced to stabilize breathing pattern in adults and children with obstructive sleep apnea (Schneider et al. 2000; McGinley et al. 2009). Moreover, several case reports indicate that this treatment can improve gas exchange and alleviate dyspnea (Roca et al. 2010). The effects of high flow nasal insufflation of room air (NI at 20 L/min) on gas exchange and breathing pattern in patients with severe COPD remain unclear. Therefore, in the present study we examined the effects of nasal insufflation on arterial blood gases, respiratory rate and inspiratory duty cycle in COPD patients who had chronic hypercapnic respiratory failure and required 1–2 L/min oxygen for maintaining normal levels of oxyhemoglobin levels. We hypothesized that nasal insufflation of room air would stabilize breathing pattern and gas exchange.

4.2 Methods

4.2.1 Subjects

This study was approved by the Ethics Committee of the University Witten-Herdecke. This study is registered under clinical trials.gov NCT01090544. Each participant was provided with the study information and enrolled in the study upon written consent. Baseline demographics and respiratory function are displayed in Table 4.1. All participants were recruited from the Pneumological Ward of

Table 4.1 Baseline demographics and respiratory function of 17 patients

Characteristics	
Age at randomization (yr)	62.5 ± 8.4
Male gender (%)	47.1
BMI (kg/m^2)	28.5 ± 8.0
PaO_2 (mmHg)	51.2 ± 7.3
$PaCO_2$ (mmHg)	59.9 ± 6.7
pH	7.41 ± 0.04
FEV_1 (L)	0.8 ± 0.4
FEV_1 (%) predicted	29.5 ± 13.5
RV (%) predicted	234.8 ± 114.2
TLC (%) predicted	115.8 ± 38.6

BMI body mass index, *PaO_2* partial oxygen pressure, *FEV_1* forced expiratory volume, *RV* residual volume, *TLC* total lung capacity

the HELIOS Klinik Hagen-Ambrock and were currently receiving treatment for an acute exacerbation of COPD. As a usual part of clinical treatment arterial blood gas analysis was performed within the 2 days prior to their planned discharge. Subjects were asked to participate if they had mild to moderate hypoxia on supplemental oxygen ($PaO_2 < 80$ mmHg) and hypercapnic respiratory failure ($pCO_2 > 50$ mmHg, pH > 7.35). Exclusion criteria included: respiratory acidosis (pH < 7.30), unstable cardiovascular conditions, decompensated renal insufficiency, acute pneumonia, disturbed metabolic status and uncontrolled diabetes mellitus.

4.2.2 Procedures

Arterial blood gas exchange was measured by obtaining ~5 μL of arterial blood at the end of each experiment from an earlobe. Blood gas analysis (Radiometer Ltd., Germany) were performed within 1–5 min after drawing each arterial sample. The PaO_2 and $PaCO_2$ values obtained at the end of each condition were recorded for statistical analysis.

Breathing responses were measured continuously by monitoring airflow with a nasal cannula and respiratory effort with inductive plethysmography. In addition, heart rate and oxyhemoglobin saturation (SaO_2) were monitored by pulse oximetry and transcutaneous CO_2 through a probe attached to the earlobe (SenTec® V-sign™ SenTec AG, Switzerland) to determine steady-state and to ensure safety of patients throughout the entire experiment. All physiologic signals were amplified and recorded continuously and digitized and stored for off-line analysis (Alice®4 Diagnostic Sleep System, Respironics-Philips, Hamburg, Germany).

A constant flow rate of up to 20 L/min was delivered at the nose. A heater and humidifier (TNI®20s oxy, TNI medical, Freiburg, Germany) were used to blend the clinically supplied compressed air and oxygen and to keep it at 30–33°C and 80%, respectively. A customized nasal cannula was used to deliver a combination of oxygen and high-flow heated humidified room air.

4.2.3 Experimental Protocol

The experiment was performed prior to midday and carried out with the patients sitting comfortably, semi-recumbent in a bed, receiving low flow oxygen at a rate of 2 L/min. Three experimental conditions were achieved by administering combination of NI and oxygen for 45 min periods in a random order as described in brief below. There was a 15-min baseline period between each condition.

- *Baseline Condition*: Standard low-flow oxygen at a rate of 2 L/min through a standard oxygen nasal cannula.
- *High-flow NI Condition*: A combination of low-flow oxygen (as in the Baseline Condition) plus room air high-flow NI at 20 L/min both delivered through a custom made nasal cannula.
- *Partial NI*: The same combination of low-flow oxygen plus room air high-flow NI at 20 L/min, delivered through only one nostril to achieve a lower PaO_2 than the High-flow NI condition.

4.2.4 Data Analysis

Variables measured were: respiratory rate (f) and inspiratory duty cycle (T_I/T_T), where T_I = inspiratory time and T_T = respiratory cycle length. The f was calculated each minute and an average value was determined from the 45-min period for an individual in every condition. In each individual, an average T_I/T_T was taken from 15 breaths of the last minute of each condition.

Parameters were expressed as the mean for each patient in each experimental condition. Group data were reported as means ± SD. To examine responses in breathing patterns to High-flow NI, two-way ANOVA were performed with the patient number treated as a random factor and the NI flow rate treated as a fixed factor. When the ANOVA revealed a significant differences ($p < 0.05$), post hoc analysis was performed with paired t-tests to determine which levels of NI differed from Baseline. A p-value of less than 0.05 was considered significant.

4.3 Results

A total of 17 subjects were included in the study. Compared with Baseline, High-flow NI and Partial NI were associated with stable physiologic and clinical conditions. No subject demonstrated dyspnea or an increase in heart rate of greater than 10 bpm. There was no severe hypoxemia as defined by a prolonged (>5 min) drop in SaO_2 below 85%. There was no group mean difference in the transcutaneous CO_2 between any conditions (Baseline: 57.3 ± 10.1; High-flow NI 55.1 ± 8.7; Partial NI: 54.3 ± 10.2 mmHg; ANOVA; $p = 0.23$).

4.3.1 Effect of Nasal Insufflation on Blood Gas Levels

During the experimental conditions, NI decreased inspired FiO_2 because of the high flow rate of room air entrained with a constant level of supplemental oxygen that was unchanged from baseline. The group mean PaO_2 fell from the Baseline 62.3 ± 8.8 mmHg to 52.5 ± 8.1 mmHg ($p < 0.01$) during High-flow NI, and to 55.3 ± 10.2 mmHg during Partial NI ($p < 0.03$) (Fig. 4.1). There was no change in $PaCO_2$ between all experimental conditions (Baseline: 63.7 ± 9.2 mmHg *vs.* High-flow: 60.6.4 ± 8.3 mmHg and Partial NI: 59.8 ± 7.9 mmHg; ANOVA; $p = 0.17$).

4.3.2 Breathing Pattern von Nasal Insufflation

For the group, the respiratory rate fell from 19.8 ± 4.2 at baseline to 18.0 ± 4.7 breaths/min during High-flow NI ($p < 0.01$) (Fig. 4.2). There was no difference in the respiratory rate between High-flow

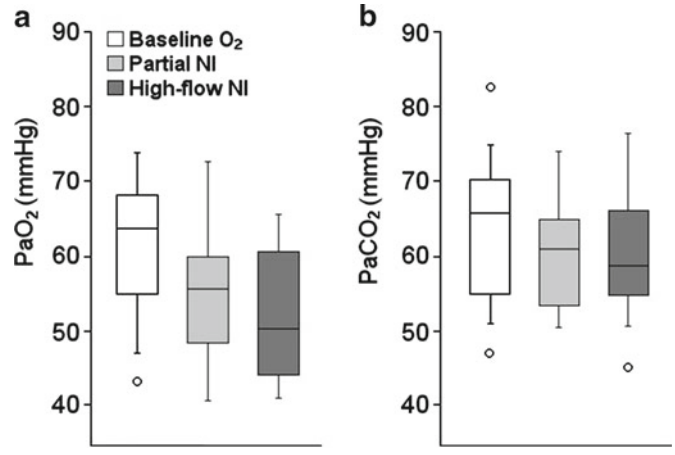

Fig. 4.1 Blood gas levels

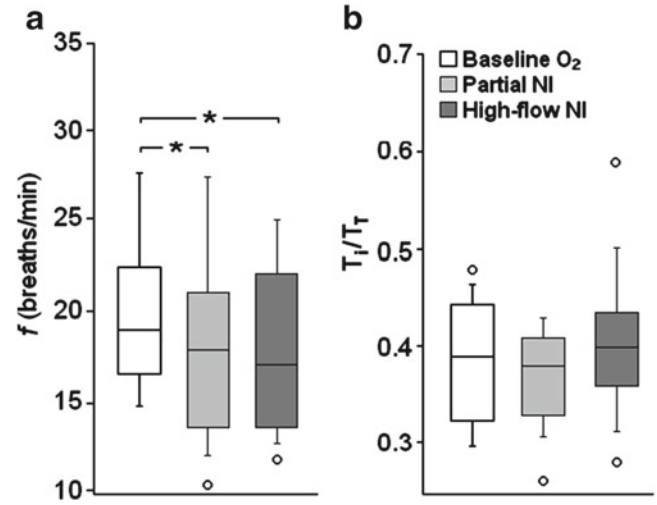

Fig. 4.2 Respiratory rate and duty cycle

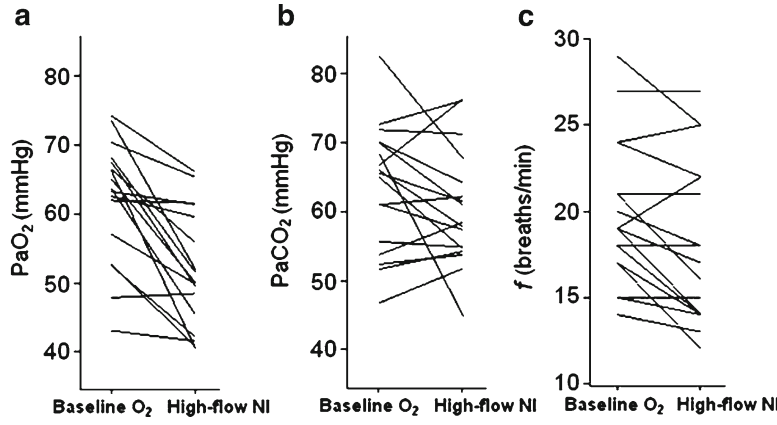

Fig. 4.3 Individual respiratory rate and arterial blood gas responses

NI and Partial NI (18.1 ± 5.2 breaths/min, p = 0.98). The inspiratory duty cycle (T_I/T_T) remained constant throughout all experimental conditions (0.39 ± 0.06 *vs.* 0.40 ± 0.07 and 0.37 ± 0.05; baseline *vs*. high-flow NI and Partial NI, respectively).

4.3.3 Individual Respiratory Rate and Arterial Blood Gas Responses

There was no association between changes in respiratory rate and either PaO_2 or $PaCO_2$. Figure 4.3 shows individual responses in PaO_2 (Fig. 4.3a), $PaCO_2$ (Fig. 4.3b) and respiratory rate (Fig. 4.3c) between baseline and high flow NI. In approximately 1/3rd of patients, PaO_2 remained above 55 mmHg during High-flow NI (n = 6). Similarly, approximately 1/3rd of the patients lowered their $PaCO_2$ more than 4 mmHg during High-flow NI (n = 6), while there were 3 individuals during High-flow NI whose $PaCO_2$ worsened more than 4 mmHg. More than 75% of patients lowered the respiratory rate by >2 breaths/min, while the remaining four individuals had no change in their respiratory rate (≤1 breath/min).

4.4 Discussion

The major finding of our study is that high flow nasal insufflation (NI) of 20 L/min over a 45-min period during wakefulness led to a systematic reduction in respiratory rate without worsening hypercapnia and dyspnea. This reduction in respiratory rate was present even after lowering PaO_2 with partial NI. Second, in approximately 1/3rd of patients, the reduction in respiratory rate was associated with a significant improvement in hypercapnia (>4 mmHg). Third, respiratory rate responses were independent of blood gas changes. Taken together, high flow (20 L/min) nasal insufflation of warm and humidified appears to improve the efficiency of breathing and may be used as an adjunct to low flow oxygen for alleviating dyspnea and improving arterial CO_2 levels in some COPD patients with severe hypoxic, hypercapnic respiratory failure.

Nasal insufflation of warm air has been used to stabilize breathing in patients with mild upper airway obstruction during sleep in adults and children. The mechanisms for alleviating upper airway obstruction appear to be through a mild (~2 cmH_2O) increase in end-expiratory pressure (PEEP) (McGinley et al. 2007; Groves and Tobin 2007; Parke et al. 2009). It is possible that the improvement in respiratory efficiency was due to an increase in end-expiratory pressure. PEEP is known to improve ventilation perfusion mismatch which helps to improve gas exchange. In the current study we show that despite lowering partial oxygen pressure, dyspnea did not develop and hypercapnia improved in 1/3rd of patients. Thus, it is possible that NI has improved ventilation perfusion mismatch, thereby improving gas exchange for carbon dioxide

A reduction in respiratory rate with both partial and high flow NI was approximately 10% compared with baseline low flow oxygen. Our data do not indicate that this reduction was associated with an increase in tidal volume, since respiratory effort and inspiratory duty cycle remained constant. Further support for this is given by a clinical observation that none of the patients developed dyspnea or an increase in heart rate that may have indicated augmented cardiovascular stress. Thus, it is likely that the reduction in respiratory rate with nasal insufflation was associated with a reduction in minute ventilation. Because we did not quantify airflow, the mechanisms of the reductions in minute ventilation remain unclear.

While the respiratory rate decreased in the majority of patients (13 of 17), there was a heterogeneous response to nasal insufflation. Some patients demonstrated marked reductions in respiratory rate (>20% from baseline) and others demonstrated no change in respiratory rate, but had marked reductions in arterial carbon dioxide of more than 8 mmHg. Thus, some patients respond to high-flow NI by lowering the respiratory rate, and presumably minute ventilation, while others appear to maintain ventilation, but decrease carbon dioxide levels. The mechanisms for this heterogeneous response are unclear. It is possible that NI has either improved alveolar ventilation through an increase in PEEP as mentioned above. Alternatively, NI may have either reduced anatomical dead space or carbon dioxide production. Regardless of the mechanisms, NI appears to improve efficiency of breathing and our data suggest may be used as an adjunct to oxygen therapy to prevent/treat hypercapnic respiratory failure in some patients.

4.5 Limitations

Our current study was designed as a pilot trial for examining the safety of NI in COPD patients with severe hypoxic, hypercapnic respiratory failure. As such our study has several limitations. First, patients did not accept a nasal or full face mask for capturing tidal volume. Similarly, we could not use a calibrated inductive plethysmography signal due to the patients' illness and the inability to prevent body movements or coughs. The lack of measuring tidal volume limits our ability to explore mechanisms of our findings. Second, our patient population consisted of patients with severe COPD and hypercapnic

respiratory failure who required supplemental oxygen. The lack of a baseline period without oxygen or NI may mask some of the physiologic effects of NI. We could not, however, remove supplemental oxygen at baseline to assess the breathing pattern and gas exchange on room air in these patients without producing significant hypoxia, dyspnea, or anxiety. Third, we did not adjust the O_2 supply to maintain a constant fraction of inspired O_2 (FiO_2) during all trials. The blend of 2 L/min oxygen with 20 L/min NI may have diluted the FiO_2 close to room-air, which resulted in lower arterial oxygen pressures during the NI trials. Nevertheless, approximately 1/3rd of the patients maintained PaO_2 above 55 mmHg during NI, indicating that some patients may maintain oxygenation with NI alone.

4.6 Implications

NI might assist in the treatment of COPD, specifically the prevention of hypoxemia and hypercapnia, both of which are independent risk factors for mortality and morbidity. Our study demonstrates that a proportion of hypoxic COPD patients may be able to maintain normoxia with high flow NI. It is conceivable that NI may be utilized as an adjunct to improve oxygenation in hypoxic COPD patients. Second, NI led to a reduction in respiratory rate of ~10%, and in some patients this reduction was associated with a reduction in hypercapnia. This finding suggests a reduction in the work of breathing, whose increase was associated with the development of muscle fatigue leading to respiratory failure. Thus, NI may serve as a treatment option to reduce work of breathing and to counteract the development of respiratory failure in some COPD patients. Third, sleep is associated with worsening of hypoxia and hypercapnia in the majority of COPD patients. High flow NI was easily tolerated in our patient population making nocturnal use of NI easily applicable. If the NI reduces the respiratory rate without worsening hypercapnia during sleep, high flow therapy may be a promising therapy option for treating sleep disordered breathing in severely ill COPD patients as well.

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Chapter 5
Exposure to Traffic-Related Air Pollutants as a Risk of Airway Obstruction

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Abstract Dynamic increases in the number of vehicles, particularly in large urban areas, cause a visible decline in the average speed of cars. Street networks are not able to efficiently handle generated traffic, which could result in increasing levels of air pollutant emissions and consequently in a greater incidence of people suffering from respiratory diseases. This study presents the effects of investigations on the influence of traffic-related air pollutants on inhabitants of two Polish cities living in the proximity of busy roads. As a control group rural area residents were taken. In 2005–2006 and 2008–2009 respiratory function tests were conducted on a group of 3,506 people (including residents of non-urban areas). The investigation has shown that people living near busy urban roads had a significant increase in the risk of bronchi obstruction.

Keywords Airway obstruction • Air pollution • Health • Municipal environment • Pulmonary function

5.1 Introduction

Direct proximity of busy main roads within urbanized areas is characterized by increased levels of air pollutants compared with urbanized areas remote from busy roads, and particularly with rural areas. As a result, the inhabitants living close to the busiest traffic arteries might be more exposed to the harmful influence of traffic than those living in other areas. Generally air pollutants have been recognized

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as increasing factors of chronic obstructive pulmonary disease (COPD) for over 50 years. That led to implementing air quality standards, which resulted in significant decreases in the levels of air pollutants from fossil fuels combustion, in particular dust and sulphur dioxide. However, a dynamic rise in road traffic density has led to increased levels of other pollutants, such as ozone, particulate matter with diameter below 10 μm (PM_{10}), or nitrogen oxides (MacNee and Donaldson 2000). These pollutants are currently the most serious problem of air quality in Europe (Martin et al. 2010).

Numerous epidemiological research results show that there is a relation between reported air pollution levels and harmful health effects, including a higher intensity of respiratory system ailments, and even a higher number of deaths caused by respiratory and cardio-vascular system diseases. Several publications report higher intensity of symptoms of pulmonary diseases among children and secondary school students living in the proximity of main roads with heavy traffic. An investigation made in Nottingham, UK (Venn et al. 2001), shows that, although there is no clear evidence to show that air pollutants lead to increased asthma incidence, a higher risk of respiratory problems can be noted among children. The risk is inversely proportional to the distance from busy traffic arteries and is the highest among the inhabitants who live within the distance of 90 m from busy main roads. Having reported the results of research done with a group of almost 1,000 children, based on odds ratio calculations, the authors show that for children living within 150 m of main roads, each 30 m closer to the road increases the risk of asthma symptoms (wheezing) by 1.08 and 1.16 for the age-groups $4 \div 11$ and $11 \div 16$ years, respectively.

Research results for the group of 1,129 children coming from different areas (with low or high level of SO_2 and PM_{10}) of Cracow, Poland (Jedrychowski and Flak 1998) show a strong relation between air pollution levels and some respiratory system symptoms (amount of secretion). Much more frequent cough and wheeze were reported among children who did not have allergy symptoms, who lived in areas with higher levels of air pollutants. In case of children diagnosed as having an allergy, coming to such conclusions seems more difficult, because asthma symptoms can result from numerous factors, including air pollution. A school-based, cross-sectional study in the San Francisco Bay Area (Kim et al. 2004), based on results of a group of 1,109 children, shows that there is a slight, although statistically significant, increase in bronchitis symptoms and asthma among children living in the areas with higher levels of traffic-related air pollutants. The research was carried out in urban areas with relatively clean air compared with the rest of the region, where local air pollutants originate mainly from road traffic. For particular pollutants (NO, NO_2, NO_x, $PM_{2.5}$, PM_{10}), the odds ratios were calculated with reference to the concentration increase by a value equal to the interquartile range of distribution of a particular pollutant concentration. Depending on the kind of pollutant, OR amounted to 1.02–1.06 for bronchitis and 1.01–1.08 for asthma.

One of the earliest results of research on the long-term influence of road traffic air pollutants on the progress of chronic obstructive pulmonary disease (Schikowski et al. 2005), carried out for 10 years in 4,757 women (living in the Ruhr Area in Germany), shows that an increase of average concentration of PM_{10} (interquartile range) by 7 $\mu g/m^3$ within 5 years causes a noticeable decrease of spirometric indicators. Forced expiratory volume during the first second of expiration (FEV_1) decreased by 5.1% (95% confidence level: 2.5–7.7%), while forced vital capacity (FVC) decreased by 3.7% (95% confidence level: 1.8–5.5%). At the same time, the authors point out that women who lived closer than 100 m to busy roads showed significantly lower spirometric parameters, and the risk of COPD incidence was 1.79 times higher (odds ratio with 95% confidence level: 1.06–3.02) compared with inhabitants of areas located further from main roads.

The results of research made close to a busy street in Gliwice, Poland (Grynkiewicz-Bylina et al. 2005) show that average daily PM_{10} concentrations in the street canyon are over 70% higher, and for polycyclic aromatic hydrocarbons over 60% higher, compared with the values of these pollutants within 100 m distance from the road. The author expects a 10% higher rate of respiratory system disease in the population exposed to higher levels of the PM_{10} of over 90 $\mu g/m^3$ in the road canyon.

Similar conclusions are drawn from the epidemiological studies conducted in the region of Pisa Cascina, Central Italy (Nuvolone et al. 2011). This study analyzed the epidemiological data and based on subjective assessments of residents (the questionnaire) and objective tests (spirometry and skin tests) shows that living at a distance of 100 m from the road is associated with an increased risk of wheeze, COPD and airways obstruction among men, and a higher risk of asthma attacks, shortness of breath, dyspnea, wheezing breath and positive skin tests among women.

According to data presented by Lubinski and Chcialowski (2003), concentrations of PM_{10} higher than 10 μg/m^3 lead to a 3% higher rate of death caused by respiratory system disease, but also to a 3% growth in the frequency of bronchial asthma attacks and to over 12% higher use of bronchodilators in case of patients suffering from asthma and chronic obstructive pulmonary disease (COPD). Likewise, an investigation conducted in east London (Peacock et al. 2011) clearly shows an impact on the respiratory system of PM_{10} pollution, black smoke, and NO_2 in patients with COPD. Dyspnea was particularly associated with the occurrence of PM_{10} among patients participating in the study.

Investigations conducted in selected US metropolitan areas (Schwartz et al. 1996) indicate that the daily percentage of deaths is related to changes in $PM_{2.5}$ concentrations, but not to those in PM_{10} concentration. The results show that each growth of 2-day average concentration of $PM_{2.5}$ by 10 μg/m^3 is related to 1.5% (95% confidence level: 1.1 ÷ 1.9%) growth of daily death rate. A further study by the authors carried out in six cities in the USA (Schwartz et al. 2002) shows that there is a linear relation between $PM_{2.5}$ concentration and death rate. Moreover, the authors show that there is no minimum value of a concentration of this pollutant that could be considered safe. The relation above given between the change in $PM_{2.5}$ concentration and mortality rate also holds for concentrations below the minimum permissible levels, according to the US Environmental Protection Agency. This indicator grows by 3% for each 10 μg/m^3 increase of solid particles coming from emissions from road transport.

A study of 8,111 adults in six cities of the US (Dockery et al. 1993) shows that the mortality level is highly dependent on tobacco smoking. After taking into account this and other risk factors, a statistically significant relation was observed between air pollution caused by respiratory dust and death rate. Interpretation of survival analysis showed that the mortality risk coefficient for deaths caused by lung cancer and respiratory and circulatory disease among inhabitants of the most polluted cities amounts to 1.26% (95% confidence level: 1.08 ÷ 1.47) compared with the cities characterized by the lowest level of air pollutants.

The results of long-term tests (lasting 8 years), carried out in Holland in a group of 5,000 persons aged 55 ÷ 69 (Hoek et al. 2002), based on the assessment of the correlation between road pollution level and mortality resulting from different causes, shows that the mortality risk coefficient among persons living along main roads amounts to 1.41 (95% confidence level: 0.94 ÷ 2.12) for all causes of death and 1.95 (95% confidence level: 1.09 ÷ 3.52) for the deaths caused by respiratory and circulatory system disease. The authors come to a conclusion that long-term exposure to traffic-related pollutants may shorten life expectancy, showing that the mortality caused by diseases not related to respiratory and circulatory system and tumors other than lung tumors are not related to air pollution levels – the risk coefficient amounted to 1.03 (95% confidence level: 0.54 ÷ 1.96).

In the present study, we report on the influence of traffic-related air pollutants on ventilation efficiency of inhabitants of large urban areas. The research was conducted among inhabitants of two Polish cities living along the main roads. The reason to conduct the study was that other studies on this subject, especially those from the US, cannot be directly applied to the corresponding situation in Polish urban areas, where the characteristics of exposure to traffic-related pollutants are different from those in other countries because of a different traffic structure, a higher average age of vehicles, different climatic and meteorological conditions, etc. Preliminary results of the Polish research concerning just one city have been presented elsewhere (Badyda and Lubinski 2009).

5.2 Methods

Pulmonary function tests were carried under two scientific projects, the first of which was conducted in the capital city of Warsaw, Poland, in 2005–2006 and the second one in the city of Gliwice, Poland, in 2008–2009. The investigations, performed by the Military Institute of Medicine and the Faculty of Environmental Engineering of Warsaw University of Technology, were carried out in the vicinity of selected busy roads as well as in the rural areas isolated from the direct impact of traffic-related air pollutants emissions. The results of the tests of the patients presently treated for chronic obstructive pulmonary disease (COPD) or bronchial asthma as well as those who did not cooperate with the doctor during the examination have been excluded from further analysis.

In Warsaw, 750 examinations were performed, including 333 women and 417 men. The tests involved 512 non-smokers and 238 smokers aged 14–90 (mean 50.9 ± 19.7 year). The control group consisted of the tests performed in 756 persons (423 women and 333 men), inhabitants of non-urban areas (29 towns located in various regions of Poland). 445 non-smokers and 311 smokers aged 18–85 (mean 47.8 ± 14.3) participated in the examination.

The Gliwice study encompassed 1,581 persons, including 854 women and 727 men. Among the examined individuals there were 875 non-smokers persons and 706 smokers aged 10–96 (mean 47.4 ± 18.3). In this investigation the control group covered 419 people (226 women and 193 men) from 6 selected spots situated near the city of Gliwice, characterized by a relatively low traffic.

5.2.1 Tests

All tests were conducted using an EasyOne spirometer in the period from May to September. The period of research resulted from the necessity to reduce the influence of pollutants from sources other than road traffic.

An outline of the research was as follows:

- presenting the aims of the test to the examined person and informing him that the test will not have any harmful impact on their health condition;
- subjective research – a questionnaire was carried out, taking into consideration anthropometric features, load of respiratory system disease, smoking habits, exposure to harmful factors in workplace and place of living, presence of symptoms that might show respiratory system disease, allergies, etc.;
- objective research – spirometric test carried out in the sitting position, at a specially prepared research place, after a few-minute time given to adapt to the new breathing conditions. Then several flow-volume curves were recorded, to gain repeatability of results in accordance with the American Thoracic Society. The test result included the following variables:
  - FVC (*Forced Vital Capacity*) – capacity of air, which is exhaled by a tested person during a forced exhalation after maximum slow inhalation;
  - FEV_1(*Forced Expiratory Volume during the First Second of Expiration*) – capacity of air, which is exhaled by a tested person within the first second of expiration;
  - PEF (*Peak Expiratory Flow*) – maximum velocity of flow measured during forced exhalation;
  - FEF_{50} (*Forced Expiratory Flow at 50% of FVC*) – velocity of air flow in middle phase of exhalation;
  - FEV_1%FVC – percentage indicator of FEV_1 capacity, in its relation to the present forced vital capacity (so called pseudo-Tiffeneau indicator).

According to the guidelines of the American Thoracic Society (1991, 1995) and the Polish Lung Disease Association, the trials were performed until at least three repeatable results were gained,

i.e., the results for which the values of indicators for a particular measurement did not vary by more than 5%. The results were standardized according to the European Coal and Steel Community (Quanjer et al. 1993) guidelines. The subjects were divided into two groups, according to the burden of the smoking habit. The results were analyzed in accordance with this division, comparing them with those of the control group, after taking into account analogous division.

5.3 Risk Assessment of Airways Obstruction

Pulmonary function indicators enable to confirm or eliminate airway obstruction. As mentioned above, the first indicator demonstrating pulmonary disorders is a pseudo-Tiffeneau indicator (FEV_1%FVC) lower than 70%. Persons with the result of FEV_1%FVC ≥ 70% are considered not to show symptoms of obstruction. Therefore each investigated person can be described by a dichotomous variable. Further in the study a person for which the value of this variable is '0' will be considered healthy, while '1' will refer to an ill person. The aim will be to determine a relation, similar to regression function, of a probability of obstruction appearance, with a group of independent variables such as age, gender, smoking habit burden and place of living. In this type of analysis it is not possible to apply multiple regression, therefore logistic regression is used.

Logistic regression describes the influence of independent variables on a dichotomous dependent variable. Let Y refer to the dependent variable with values: 0 – does not show symptoms of COPD (FEV_1%FVC ≥ 70%), 1 – shows symptoms of COPD (FEV_1%FVC < 70%). The model of logistic regression for such a dichotomous variable has a form shown by Eq. 5.1:

$$P\left(Y=1\middle|x_1, x_2, \ldots, x_k\right)=\frac{e^{\left(a_0+\sum_{i=1}^{k} a_i x_i\right)}}{1+e^{\left(a_0+\sum_{i=1}^{k} a_i x_i\right)}} \tag{5.1}$$

where

$P(Y=1|x_1,x_2,\ldots,x_k)$ – conditional probability that the Y variable will equal 1 for independent values $x_1, x_2,\ldots, x_k$; $a_{i,}$ $i=0,\ldots, k$ – regression coefficients; $x_1, x_2,\ldots, x_k$ – independent values.

Apart from assessing regression coefficients and their statistical significance, the odds ratios were calculated. The term 'odds' was defined as a ratio of probability of a phenomenon appearance (A), e.g. a disease, to the probability that it will not appear. The definition can be shown as in the Eq. 5.2:

$$S(A)=\frac{p(A)}{p\left(notA\right)}=\frac{p(A)}{1-p(A)} \tag{5.2}$$

where

$S(A)$ – odds of a phenomenon appearance; $p(A)$ – probability of A phenomenon appearance; $p(notA)$ – probability of A phenomenon non-appearance.

Logistic models presented and discussed below were worked out on the basis of pulmonary function results and values of selected anthropometric indicators, smoking burden and place of living. The estimation of the models' parameters was carried out separately for the investigated group as a whole, as well as taking into account the division into smokers and non-smokers. The presented logistic models include only the independent variables that showed significance (for $p<0.05$). For each case, the mean square error estimator and the quasi-Newton method was used, and it must be mentioned

that an application of any other available estimator or estimation method generally did not cause noticeable changes in the forms of models or values of regression coefficients. The ratio of product of properly classified cases to product of not properly classified ones significantly exceeded 1, which shows that the classification was much better than the one expected to occur by coincidence. Moreover, for each model the odds ratios were calculated for a single variation of analyzed parameters. They were presented in the tables with the estimation results.

5.3.1 Estimation for All Considered Cases

In the Warsaw study, a model calculated for all of the considered cases (all examined persons) is shown by Eq. 5.3:

$$P(X) = \frac{e^{-6.608+0.075\cdot AGE-0.528\cdot GEN+0.780\cdot SMK+1.014\cdot LIV}}{1+e^{-6.608+0.075\cdot AGE-0.528\cdot GEN+0.780\cdot SMK+1.014\cdot LIV}} \tag{5.3}$$

where

AGE – age of investigated person (years); *GEN* – gender – dichotomous variable: man (*GEN* = 0), woman (*GEN* = 1); *SMK* – smoking habit – dichotomous variable: non-smokers (*SMK* = 0), smokers (*SMK* = 1); *LIV* – place of living – dichotomous variable: control group (rural area inhabitants, *LIV* = 0), investigated group (urban area inhabitants, *LIV* = 1).

The model shows that the probability of a bronchial stricture appearance increases when the values of the variables 'AGE', 'SMK' and 'LIV' increase. For the latter two variables, the increase will be understood as the change of value from '0' to '1'. In this case the probability of developing the disease rises among smokers and urban area inhabitants. Analogically, the probability decreases when 'GEN' variable increases, which shows a lower probability of disease appearance among women.

The results show that smoking increases the risk of the appearance of bronchial airflow disorders twofold, which is equivalent to developing COPD, while living along a busy main road (compared with rural areas) causes an increase of the risk nearly three times. Men are 1.7 times (0.59^{-1}) more at risk than women.

Logistic regression model was also made for the results of the study conducted in Gliwice. The subjective study of this investigation included some additional information that was not considered in the previously realized study in Warsaw. Some of these data, represented by the relevant independent values, were reflected in the logistic model. The model for all test cases is as follows:

$$P(X) = \frac{e^{-4.777+0.033\cdot TLV+0.481\cdot SMK+0.718\,LIV}}{1+e^{-4.777+0.033\cdot TLV+0.481\cdot SMK+0.718\,LIV}} \tag{5.4}$$

where *TLV* – length of residence in the specific location (years).

The results obtained in Gliwice indicate no significant differences in the occurrence of obstruction among men and women. The 'AGE' variable also showed to be irrelevant. However, significance ($p < 0.0001$) was shown in the differences of the obstruction prevalence depending on the period of residence (in many cases, this variable may also reflect the age of examined individuals). As in the Warsaw study, the probability of obstruction increases among people living in the proximity of busy roads in comparison with the rural areas residents and is higher among smokers compared with non-smoking persons.

In both above listed logistic models, the quality factor test for chi-square fitting (χ^2) representing a variation between the presented model and the one with only one absolute term shows significance ($p < 0.0001$) proving that independent variables in the model influence the possibility of disease

Table 5.1 Estimation of parameters of the logistic regression model of the entire investigated group of the Warsaw study

	Variable			
	AGE	GEN	SMK	LIV
Estimated parameter values	0.075	−0.528	0.780	1.014
Significance level	<0.05			
95% confidence interval for parameters	0.063 ÷ 0.087	−0.862 ÷ −0.193	0.412 ÷ 1.142	0.659 ÷ 1.369
Odds ratio for unit change of parameter	1.07	0.59	2.18	2.76
95% confidence interval for odds ratios	1.06 ÷ 1.09	0.42 ÷ 0.82	1.52 ÷ 3.13	1.93 ÷ 3.93

Table 5.2 Estimation of parameters of the logistic regression model of the entire investigated group of the Gliwice study

	Variable		
	TLV	SMK	LIV
Estimated parameter values	0.033	0.481	0.718
Significance level	<0.05		
95% confidence interval for parameters	0.020 ÷ 0.045	0.042 ÷ 0.920	0.086 ÷ 1.350
Odds ratio for unit change of parameter	1.03	1.62	2.05
95% confidence interval for odds ratios	1.02 ÷ 1.05	1.04 ÷ 2.51	1.09 ÷ 3.86

development. Values of the model parameter estimators are also statistically significant ($p < 0.05$). Tables 5.1 and 5.2 present selected values of the parameter estimators for both models calculated for the entire investigated groups, as well as odds ratios for single variations of particular parameter.

The above presented results allow to conclude that the risk of disturbance of air flow through the bronchi is significantly associated with smoking (more than 2 times higher in the Warsaw study and more than 1.6-fold higher in the Gliwice study), as well as with residence in the vicinity of busy roads. In comparison with the control groups (rural area residents), the risk of bronchial obstruction is almost 2.8-fold higher among inhabitants of Warsaw and more than 2 times higher amid residents of Gliwice.

5.3.2 Estimation for Non-smoking Group

In both studies, analogical models were created with the division for smokers and non-smokers, in order to analyze the influence of their place of living on probability of obstruction appearance. The models for non-smokers are shown in Eqs. 5.5 and 5.6, for the Warsaw and Gliwice studies, respectively:

$$P(X) = \frac{e^{-7.249+0.081 \cdot AGE - 0.764 \cdot GEN + 1.470 \cdot LIV}}{1 + e^{-7.249+0.081 \cdot AGE - 0.764 \cdot GEN + 1.470 \cdot LIV}} \tag{5.5}$$

$$P(X) = \frac{e^{-6.863+0.025 \cdot AGE + 0.797 \cdot GEN + 1.150 \cdot LIV + 0.024 \cdot TLV}}{1 + e^{-6.863+0.025 \cdot AGE + 0.797 \cdot GEN + 1.150 \cdot LIV + 0.024 \cdot TLV}} \tag{5.6}$$

According to these models, in both cases the probability of developing the disease among non-smokers increases with age (in the Gliwice study also with the duration of residence in a particular location) and it is higher in the urban area groups than in the control groups. Different observations in

Table 5.3 Estimation of parameters of the logistic regression model for the non-smoking group investigated in the Warsaw study

	Variable		
	AGE	GEN	LIV
Estimated parameter values	0.081	−0.764	1.470
Significance level	<0.05		
95% confidence interval for parameters	0.065 ÷ 0.098	−1.204 ÷ −0.324	0.945 ÷ 1.994
Odds ratio for unit change of parameter	1.08	0.47	4.35
95% confidence interval for odds ratios	1.07 ÷ 1.10	0.30 ÷ 0.72	2.57 ÷ 7.35

Table 5.4 Estimation of parameters of the logistic regression model for the non-smoking group investigated in the Gliwice study

	Variable			
	AGE	GEN	LIV	TLV
Estimated parameter values	0.025	0.797	1.150	0.024
Significance level	<0.05			
95% confidence interval for parameters	0.002 ÷ 0.049	0.039 ÷ 1.554	0.086 ÷ 2.215	0.004 ÷ 0.044
Odds ratio for unit change of parameter	1.03	2.22	3,16	1.03
95% confidence interval for odds ratios	1.00 ÷ 1.05	1.04 ÷ 4.73	1.09 ÷ 9.16	1.00 ÷ 1.05

both studies are related with gender: while in the Warsaw study a higher probability of obstruction among men was noted, in the Gliwice study women were more likely to be affected. Based on the collected data, this phenomenon is at the moment difficult to be explained. Similarly to the previous models, χ^2 value and values of the estimators of the model parameters were significant. The detailed values of models calculated for non-smoking persons are presented in Tables 5.3 and 5.4.

Among non-smokers, the risk of obstruction increases with age and in the Gliwice study, as it was mentioned above, an increased risk with each passing year of living near a busy road was indicated (a more detailed analysis shows that the risk of bronchi obstruction concerns only urban area inhabitants, while in the control group this parameter remains statistically insignificant). Non-smoking persons living in the proximity of busy roads are more exposed to obstruction appearance than those from rural areas (above 4 times higher risk in the Warsaw study and more than 3 times in the Gliwice study). It both cases it should be noted that the range of 95% confidence level is relatively high for both the estimated parameters and for a single variation of a parameter.

5.3.3 Estimation for Smoking Group

Logistic regression models calculated for the smoking group are presented in Eqs. 5.7 and 5.8, for the Warsaw and Gliwice studies respectively:

$$P(X) = \frac{e^{-6.858+0.075 \cdot AGE+0.018 \cdot BM}}{1+e^{-6.858+0.075 \cdot AGE+0.018 \cdot BM}} \tag{5.7}$$

$$P(X) = \frac{e^{-5.113+0.045 \cdot AGE}}{1+e^{-5.113+0.045 \cdot AGE}} \tag{5.8}$$

where *BM* – body mass of investigated person (kg).

Table 5.5 Estimation of parameters of the logistic regression model for the smoking group investigated in the Warsaw study

	Variable	
	AGE	BM
Estimated parameter values	0.071	0.017
Significance level	<0.05	
95% confidence interval for parameters	0.052 ÷ 0.091	0.001 ÷ 0.032
Odds ratio for unit change of parameter	1.07	1.02
95% confidence interval for odds ratios	1.05 ÷ 1.10	1.00 ÷ 1.03

Table 5.6 Estimation of parameters of the logistic regression model for the smoking group investigated in the Gliwice study

	Variable
	AGE
Estimated parameter values	0.045
Significance level	<0.05
95% confidence interval for parameters	0.024 ÷ 0.066
Odds ratio for unit change of parameter	1.05
95% confidence interval for odds ratios	1.02 ÷ 1.07

In the group of smokers, the influence of gender on the probability of disease appearance turned out to be irrelevant. However, in the Warsaw study, body mass had a slight but statistically significant ($p = 0.04$) positive effect. Other independent variables, including the variable describing place of living, were statistically insignificant. The values of the quality factor test for χ^2 fitting model was highly statistically significant. The detailed list of estimation results was presented in Tables 5.5 and 5.6.

The results calculated for smokers show that the influence of their place of living on the risk of the appearance of obstruction was irrelevant. This observation was confirmed by more detailed calculations (not shown), according to which the difference of average values of one of the most important pulmonary function indicators (FEV_1) between the urban and rural area inhabitants turned out to be statistically insignificant. In the Gliwice study, the differences in the FEF_{50} and FEV_1 %FVC average values were statistically irrelevant either. The gathered results show that the increased risk of the appearance of obstruction for smokers results mainly from the fact of smoking itself. Among independent variables, which showed to be significant in logistic regression models for the group of smokers, the only important factor was the age of the examined individuals. It seems that the factor associated with body weight, which was statistically significant in the Warsaw study, from the meritorious standpoint was not of particular importance concerning the risk of developing bronchi obstruction.

5.4 Conclusions

To summarize the above analysis, there exists a significant increase in the appearance of obstruction among non-smokers living in the vicinity of busy roads comparing with the control groups from rural areas. The results quoted in this study show a significant role of air pollutants in the development of diseases causing bronchial stricture (mainly COPD). Logistic regression models, which imply an increased probability of bronchoconstriction among smokers and among older people, also demonstrate an increased risk of obstruction with the degree of exposure to traffic-related air pollution impact – the likelihood of bronchi obstruction is higher in urban population groups living in the vicinity of roads with a high traffic volume compared with those of non-urban areas (nearly 3 times higher among Warsaw residents and more than 2 times higher among inhabitants of Gliwice in comparison with corresponding control groups).

Logistic models do not classify cases of disease in the expected way (the cases of lack of COPD symptoms are classified very well), which may suggest that there are other factors, which influence the appearance of obstruction and were not taken into consideration in the tests. A low level in classification of disease cases shows too small a patient sample. In the currently available database, the models could not precisely diagnose the influence of pathogenic factors or work out the expected high level of correct classification, similarly to those for healthy persons.

Despite these limitations, among the factors taken into account, the fact of living in proximity of busy urban roads increases the risk of the appearance of obstruction, particularly among non-smoking persons – in comparison with rural area residents the risk of bronchoconstriction is more that 4-times higher among inhabitants of Warsaw and above 3-times higher amid residents of Gliwice. In conclusion, the results based on the above presented models do not reflect the reality in satisfactory way, although they show a relevant and statistically significant influence of living in the proximity of busy roads on the increased risk of COPD appearance.

Further long-term studies should be performed on larger cohorts of subjects living near busy roads in cities, in areas isolated from the direct impact of traffic-related air pollutants, as well as in rural areas. Such studies may enable to determine the variations in the appearance of obstruction, pointing to the influence of various air pollutants on the incidence of respiratory system diseases.

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

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Chapter 6
Occupational Immediate-Type Allergic Asthma due to Potassium Tetrachloroplatinate in Production of Cytotoxic Drugs

E. Thanasias, I. Polychronakis, V. van Kampen, T. Brüning, and R. Merget

Abstract Allergic immediate-type reactions by halogenated compounds of platinum (Pt) (platinum salts) have been described in workers in precious metal refineries and catalyst productions. In both industries there are exposures to many different Pt compounds. It is believed that the most important allergens are those compounds with the highest number of halide ligands. It is unknown whether sensitizations to compounds with a lower number of halide ligands represent co-sensitizations or are due to cross-reactivity. We report a worker engaged in the production of cytotoxic drugs with occupational asthma and exposure to only one Pt salt with four halide ligands. The 22-year-old worker developed work-related sneezing, runny nose, and variable dyspnea about a year after he had started to work in the cytotoxic drugs production with exposure to potassium tetrachloroplatinate(II) (K_2PtCl_4). He was immediately removed from his workplace and admitted for a medical opinion about 6 months afterwards. Spirometry was normal, but asthma was corroborated by a positive response to methacholine. The results of skin prick testing could not be interpreted due to urticaria factitia. Challenge with K_2PtCl_4 by a dosimeter method yielded a clear immediate-type reaction with an increase of exhaled nitric oxide from 32 to 156 ppb after 24 h indicating an increased airway inflammation. Pt salts with four halide ligands like K_2PtCl_4 may cause an allergic immediate-type reaction and occupational asthma. Workers in the production of Pt-containing cytotoxic drugs with exposure to these substances should be included in medical surveillance programs for the prevention of occupational asthma caused by Pt salts.

Keywords Bronchial challenge • Immediate reaction • Occupational asthma • Platinum salts • Potassium tetrachloroplatinate(II)

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6.1 Introduction

Due to its outstanding catalytic properties platinum (Pt) and its halogenated compounds have an extensive use in a variety of industries. The first case reports on asthma due to Pt salts in humans were published at 1911 in a small number of photographers (Karasek and Karasek 1911). However, allergic occupational asthma by halogenated compounds of Pt (Pt salts) have been described in recent years only in workers of precious metal refineries and catalyst productions. In both industries there are exposures to many different Pt compounds. Longitudinal cohort studies in a large number of exposed subjects reported high incidences in both industries (Calverley et al. 1995; Merget et al. 2000; Venables et al. 1989) and it has been suggested that the cumulative incidence of sensitization after 5 years may be higher than 50% (Linnett and Hughes 1999). In addition, Pt salts were the third most frequent cause of occupational asthma and represented 12% of all occupational asthma cases in the South Africa (Hnizdo et al. 2001). Cisplatin (cis-stereoisomer of diammonium chloroplatinate or cis-DDP) and carboplatin (cis-diammine (1,1-cyclobutanedicarboxylate) platinum(II)) (Fig. 6.1) are Pt complexes which react *in vivo*, binding to and causing crosslinking of DNA, which ultimately triggers programmed cell death (apoptosis) (Wheate et al. 2010). Halogenated Pt compounds are used in the production of these anti-cancer drugs (Keller and Moeller 1963).

Whereas hypersensitivity reactions to carboplatin and cisplatin are well known in patients after several courses of anticancer treatment (Kawaoka et al. 2010; Syrigou et al. 2010) occupational allergic diseases after exposure due to these cytotoxic drugs are limited to a case of a nurse with contact urticaria (Schena et al. 1996).

It is believed that the most important allergens are those compounds with the highest number of halide ligands (Cleare et al. 1976). As exposure to halogenated Pt compounds in refineries and catalyst productions is complex and comprises Pt compounds with varying numbers of halide ligands, it is unknown whether positive skin prick test reactions with, e.g., tetrachloroplatinates in workers with allergic symptoms are due to cross or co-sensitizations (Cristaudo et al. 2005).

6.2 Case Report

A 22-year-old subject suffered from asthma and rhinoconjunctivitis due to animal danders (hair of cats, dogs and rabbits) since his childhood and he was a non-smoker. In the family of the patient neither allergic nor respiratory diseases were known. About a year after he had started to work in the

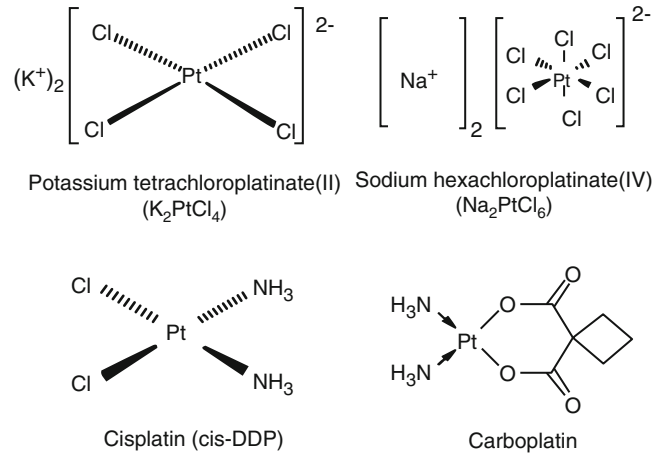

Fig. 6.1 Molecular structures of K_2PtCl_4 (MW = 415.09 g/mol), Na_2PtCl_6 (MW = 453.77 g/mol), cisplatin (cis-stereoisomer of diammonium chloroplatinate or cis-DDP), carboplatin (cis-diammine (1,1-cyclobutanedicarboxylate) platinum(II))

cytotoxic drugs production in 11/2007 he developed work-related sneezing, runny nose and variable dyspnea and was immediately removed from his workplace. His symptoms occurred only at the workplace and were relieved during weekends and holidays, while they did not change substantially over the different seasons of the year. He was exposed to K_2PtCl_4 which is used in the production of cisplatin, but not to further halogenated Pt salts. The patient was admitted to our institute for a medical opinion about 6 months afterwards. He gave written consent for the investigations and publication of his case.

6.3 Methods

The study was performed in conformity with the Declaration of Helsinki of the World Medical Association and was approved by a local Ethics Committee.

6.3.1 General Diagnostic Tests

After a detailed medical and occupational history was taken, the patient underwent a comprehensive diagnostic examination including basic blood chemistry tests, complete and differential blood count, serum protein electrophoresis, semi-quantitative urine examination, total IgE and antigen-specific antibodies to environmental allergens in serum (ImmunoCAP, Phadia, Freiburg, Germany), electrocardiogram (ECG), chest X-rays, spirometry (reference values according to Quanjer et al. 1993) and body plethysmography. Exercise testing was carried out on a cycle ergometer in a semi-sitting position using a Masterlab system (Jäger, Würzburg, Germany). Capillary blood gases were determined from the hyperemic earlobe. Skin prick testing (SPT) was performed with 13 common environmental allergens. Bronchial hyperresponsiveness was evaluated with a 4-step reservoir method. Briefly, the patient inhaled doubling doses with a starting dose of about 30 µg methacholine, using a 3.3 mg/100 mL freshly prepared solution aerosolized by Provotest II (Pari, Starnberg) (Baur et al. 1998).

6.3.2 Specific Diagnostic Tests

Specific testing was performed with K_2PtCl_4 (SPT and inhalation challenge) and sodium hexachloroplatinate (IV) (Na_2PtCl_6, SPT) (Fig. 6.1). Both substances were provided by Heraeus (Hanau, Germany). SPT with both substances were done with concentrations up to 100 mg/mL. Tests were performed on the volar side of the patient's forearm and the skin reaction was evaluated after 15 min. Histamine 10 mg/mL and saline were used as positive and negative controls, respectively.

The inhalation challenge was performed with a 646-DeVilbiss nebulizer and an APSpro dosimeter (Jäger, Würzburg, Germany) with a freshly prepared K_2PtCl_4 solution (diluted in phosphate buffer (PBS) from a 10 g/L stock solution) in quadrupling doses from 2.7 pg to 2.8 µg (11 steps). A 10 min pause was made between steps. PBS was used as placebo. The response was evaluated by spirometry, body plethysmography, blood gas analysis, serial methacholine testing and exhaled nitric oxide (eNO, NIOXFlex, Aerocrine, Bad Homburg, Germany). As end-of-test criterion we used a 20% fall of the forced expiratory volume in 1 s (FEV_1) and a doubling of specific airway resistance (sRt) to >2 kPa/s. Follow-up measurements were performed on the same day up to 2 h afterwards and again on the next morning.

6.4 Results

The general medical examination showed no pathological findings, but total IgE was 757 kU/L. Increased specific IgE antibodies to dogs and rabbits (CAP class 3) and cats (CAP class 5) were measured. FEV_1 was 107% predicted, but asthma was corroborated by a positive response to methacholine after inhalation of a cumulative dose of 92 μg ($PD_{20}FEV_1$: 78 μg). The results of SPT to environmental allergens and both Pt salts could not be interpreted due to urticaria factitia.

After inhalation of a cumulative dose of 3.75 μg K_2PtCl_4, the patient reported shortness of breath; there was a significant maximal fall of FEV_1 of 38% from baseline (Fig. 6.2) and a maximal increase of sR_t from 0.58 to 5.1 kPa/s (Fig. 6.3). There was a fall of oxygen partial pressure from 73 to 56 mmHg (after 20 min) and an increase of eNO from 32 to 156 ppb (after 24 h Fig. 6.4). Serial methacholine testing on the day after the specific challenge with K_2PtCl_4 did not show higher bronchial hyperresponsiveness ($PD_{20}FEV_1$: 49 μg) than before the challenge with K_2PtCl_4.

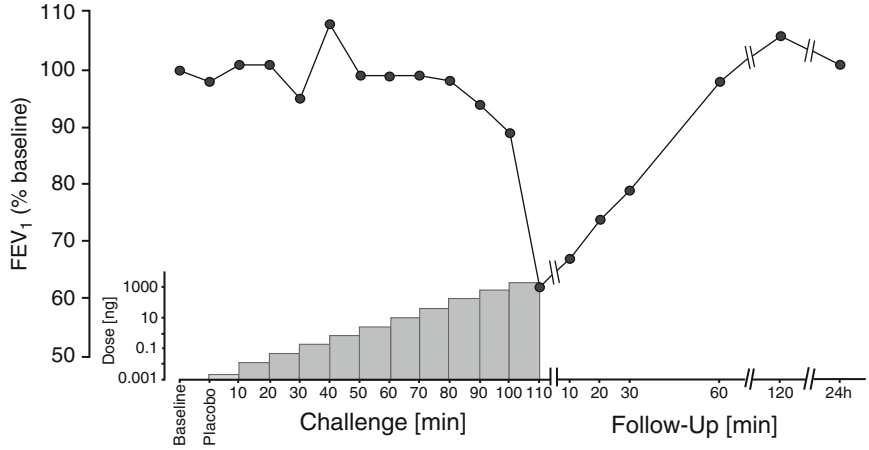

Fig. 6.2 Time-response curve of forced expired volume in 1 s (FEV_1) for specific inhalant challenge with K_2PtCl_4

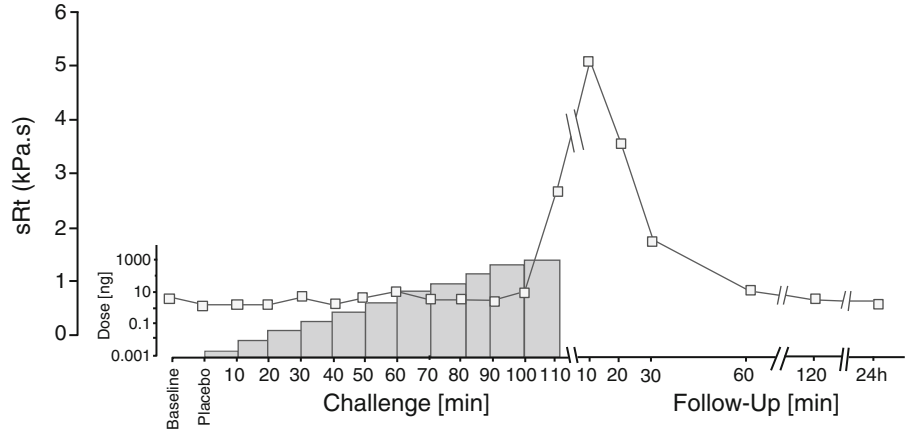

Fig. 6.3 Time-response curve of specific airway resistance (sR_t) for specific inhalation challenge with K_2PtCl_4

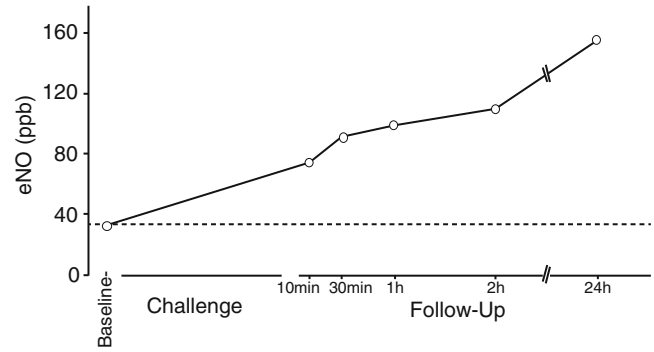

Fig. 6.4 Time-response curve of exhaled nitric oxide (eNO) for specific inhalation challenge with K_2PtCl_4

6.5 Discussion

In the present case, a diagnosis of allergic occupational asthma was made by typical work-related symptoms and an immediate-type reaction after inhalation challenge with K_2PtCl_4. Although no specific challenge testing was performed for rhinitis, the subject's symptoms suggest also occupational allergic rhinitis which is generally associated with asthma in subjects with Pt salt sensitization (Merget et al. 2000). Sensitizations to various animals were documented by in vitro-testing, compatible with a history of allergy to animal dander since childhood. SPT to environmental as well as to Pt salts could not be interpreted due to urticaria factitia.

The increase in eNO after challenge testing with K_2PtCl_4 indicates an increased airway inflammation (Lim and Mottram 2008; Quirce et al. 2010), suggesting an immunologic mechanism that could not be substantiated by the demonstration of sensitization in this case. *In vitro* demonstration of sensitization to halogenated Pt compounds is of limited value for an individual diagnosis (WHO 1991) and has not been attempted in the present case. Pt salt allergy seems to be IgE-mediated because there is a clear SPT reactivity and total IgE increased during the sensitization period, as shown in longitudinal studies (Merget et al. 2001). However, atopy seems not to be associated with Pt salt allergy (Calverley et al. 1995; Merget et al. 2000).

This is the first case report of a pharmaceutical plant worker with an exclusive exposure to K_2PtCl_4. This proves that Pt salts with four halide ligands like K_2PtCl_4 may cause an allergic immediate-type reaction and occupational asthma. In precious metals refineries and catalyst productions workers are exposed to Pt compounds with six halide ligands and it remains unknown whether sensitizations to compounds with a lower number of halide ligands represent co-sensitizations or are due to cross-reactivity. The present case clearly demonstrates that Pt salts with four halide ligands may be hazardous.

There is evidence of hypersensitivity reactions to Pt-containing cytotoxic agents like cisplatin and carboplatin in patients treated with these agents, but occupational allergy to these substances seems extremely rare and has not been described in the production of these substances. In the present case we did not perform skin testing with these substances due to their cytotoxic effects and urticaria factitia in the patient which did not allow interpretation of skin testing results.

The prevalence and incidence of sensitization and allergic reactions resulting from Pt salt exposure remain high in spite of rather low exposure degrees both in precious metals refineries and catalyst productions (Bolm-Audorff et al. 1992; Merget et al. 1988, 2000). In the present case, no exposure data were made available by the company, and no further assessment was possible.

It has been shown that medical surveillance is effective in workers of a catalyst production with exposure to Pt compounds if subjects with symptoms are immediately transferred to areas without contact to Pt salts (Merget et al. 2001). The present case was transferred a few days after

he developed work-related symptoms by his plant physician and became free of symptoms afterwards. Persisting bronchial hyperresponsiveness was attributed to his preexisting allergy to animal dander. Workers in the production of Pt-containing cytotoxic drugs with exposure to these substances should be included in medical surveillance programs for the prevention of occupational asthma caused by Pt salts.

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

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Chapter 7
Comparison of Different Non-invasive Methods for Detection of Allergic Asthma

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Abstract Non-invasive methods to assess inflammation of lower airways are induced sputum (IS), exhaled nitric oxide (eNO), and exhaled breath condensate (EBC). Here we focused on the assessment of airway inflammation with a panel of non-invasive methods in health care workers (HCWs) with suspected latex allergy with and without current allergic respiratory symptoms about 10 years after the latex ban in German health care facilities. Seventy-seven non-smoking subjects were examined by skin prick test and specific IgE measurements, eNO, IS, and EBC. Sensitivity, specificity, and positive and negative predicted values for relevant biomarkers were calculated using current asthma symptoms as the gold standard. Twenty-nine subjects (38%) reported ongoing asthmatic symptoms (AS). In these subjects the EBC concentrations of nitrogen oxides (NO_x; $p=0.027$) and leukotriene B_4 ($p=0.025$) were significantly higher than in subjects without AS. In addition, in the subjects with AS the numbers of eosinophils ($p=0.015$) and the concentrations of IL-5 ($p=0.021$) in IS samples were significantly higher than in the subjects without AS. A good correlation between several inflammatory markers in IS was detected. The maximum Youden Index was reached for IS total eosinophils $\geq 3.5 \cdot 10^4$ with a test efficiency of 0.72. In conclusion, non-invasive inflammatory monitoring with EBC and IS may assist the diagnosis of allergic asthma. Self-reported current asthmatic symptoms were reflected by eosinophilic inflammation and the best parameter to support the asthma diagnosis is a total number of eosinophils $\geq 3.5 \cdot 10^4$ in IS.

Keywords Allergic asthma • Diagnosis • Exhaled breath condensate • Exhaled nitric oxide • Induced sputum • Non-invasive methods

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7.1 Introduction

The lung represents the route of entry for many environmental and occupational pollutants which may induce inflammatory processes, hallmarks in the pathophysiology cascade leading to respiratory diseases. To assess these inflammatory processes especially in the lower airways the most widely used non-invasive methods are induced sputum (IS), fractional exhaled nitric oxide (eNO) and exhaled breath condensate (EBC).

In asthma and chronic obstructive pulmonary diseases (COPD), the analysis of cells and mediators in sputum induced by inhalation of a hypertonic saline solution has been widely applied and it has been proved to be reproducible, safe and valid for studying airway inflammation (Quirce et al. 2010). In addition to the determination of the cellular composition of the induced sputum sample an array of mediators can be measured in the cell-free supernatant of IS samples by using immunoassays. The mediators and the cell compositions reflect different aspects of airway inflammation and remodelling including, e.g., eosinophilic activation and or microvascular leakage. In the case of occupational asthma induced by high molecular weight substances, the majority of subjects developed eosinophilic airway inflammation after exposure, e.g., during a specific inhalation challenge with the relevant culprit. In the EAACI Task Force Consensus Paper concerning the relevance of non-invasive methods for the assessment of airway inflammation in occupational settings the authors (Quirce et al. 2010) concluded that an increase in sputum eosinophilic counts greater than 3% after specific inhalation challenge often precedes the occurrence of functional changes on subsequent exposure.

EBC is the liquid phase of the exhaled air sampled by cooling. It contains no cellular components, but metabolic products released by cells from the lungs or substances originating from inflammatory reactions in the airway mucosa reflecting biochemical changes of airway lining fluid (Hoffmeyer et al. 2009). Therefore, inflammatory markers like the concentration of hydrogen ions (pH measurements), metabolites of the arachidonic acid (like leukotriene B_4 or prostaglandins) and cytokines are often measured. In addition, the assessment of oxidative and nitrosative stress (like nitrogen oxide derivatives NO_x) is also possible. As summarized by the authors of the EAACI Task Force Consensus Paper (Quirce et al. 2010), EBC analysis may be useful in occupational studies on the group level and in individuals when serving as their own controls, but the current status of EBC collection and analysis makes the method a good research tool, not yet suitable for the clinical diagnosis setting.

The aim of the study was the implementation of the sputum induction, the collection of EBC, and the marker analysis of the biological material for supporting the diagnosis of allergic asthma. Our study subjects were recruited from health care workers with previously suspected occupational latex allergy who were examined about 10 years after the latex ban in German health care facilities. These subjects (77 non-smoking health care workers) were chosen in order to obtain a non-smoking young adult population with a high prevalence of atopy and asthma and thus to minimize misclassification and confounding factors.

7.2 Methods

7.2.1 Study Design and Subjects

The study was approved by the Ethics Committee of the Ruhr-University (Bochum, Germany) and was conducted in accordance with the Helsinki Declaration of the World Medical Association. All study participants gave written informed consent to the study protocol.

Ninety-one health care workers (HCWs) of the mean age 43.6 years, 15% current smokers, 92% females, 67% with current sensitization to latex (positive SPT or sIgE to latex), and 66% who were atopic (positive sIgE to sx1) were examined in a our institute in the scope of a cross-sectional study to test the hypothesis that nationwide preventive measures enable HCWs with latex allergy to work without health risks about 10 years afterwards (Merget et al. 2010). This included physical examination, a detailed questionnaire, lung function test, skin prick test (SPT) to environmental allergens (various manufacturers) and latex (Allergopharma, Reinbek & Stallergenes, Kamp-Lintfort, Germany), and measurements of specific IgE to latex and environmental allergens (sx1) (sIgE; Phadia, Uppsala, Sweden). In skin prick testing, a wheal diameter of at least 3 mm in at least one of duplicate tests was defined as positive. Atopy was defined as a positive skin prick test result to at least one of the common aeroallergens or sx1 of at least class 1. Latex sensitization was defined as either a positive skin prick test with at least one of the two latex extracts or a positive CAP result with latex (≥0.35 kU/L). Exhaled nitric oxide (eNO; NIOX Flex, Aerocrine, Bad Homburg, Germany), the collection and analysis of induced sputum (IS), and exhaled breath condensate (EBC) were also performed. Here we focused on the analysis of IS and EBC.

7.2.2 Sputum Induction and Processing

The sputum induction was performed with hypertonic saline solution according to the method of Holz et al. (1998) and Vagaggini et al. (2002). Briefly, lung function was measured before sputum induction. After 10 min the sputum induction started with the inhalation of 3% nebulized saline solution for 5-min periods for up to 30 min. At 10 min intervals, saline concentration was increased from 3% to 4% to 5%. Every 5 min after the start of nebulisation, patients were asked to rinse their mouths and throats carefully to discard saliva and to try to cough sputum into a clean container. Forced expiratory volume in 1 s (FEV_1) was measured and the inhalation of saline was stopped after 30 min or when the FEV_1 decreased by >20% from baseline values.

Sputum samples were stored for transportation at 4°C. The sputum processing was described in detail by Raulf-Heimsoth et al. (2011). Briefly, the procedure started with selecting all viscid portions (or portions of higher density) from the expectorated samples for minimizing contamination with saliva. The volume of the IS was determined and an equal volume of 0.1% sputulysin (Dithiothreitol) was added. The samples were mixed gently by vortex mixing and incubated for 30 min at 37°C to ensure a complete homogenization. After centrifugation the cell-free supernatants were aliquoted and stored at −80°C under argon protection until further analysis of soluble markers. The cell pellets were re-suspended and the total cell number was determined. For differential cell counts slides were prepared by cytospin (Cytospin 2, Shandon Corp., Pittsburgh, PA) and stained with May-Grünwald-Giemsa and three independent observers counted 200 cells on each slide by light microscopy. Their results were expressed as percentages of the total cell numbers and as the absolute numbers of the cell population (without correction of squamous cells).

7.2.3 Collection of EBC

EBC was collected with the commercially available ECoScreen device (Cardinal Health, Hoechberg, Germany) and described in detail by Hoffmeyer et al. (2007). EBC was collected for 10 min in a Teflon-coated condenser cooled to a temperature of −15°C. The pH value of the EBC was determined using a pH-meter with a glass-electrode (Mettler Toledo, Giessen, Germany) immediately and after deaeration with argon at 2 bar for 10 min, resulting in a stable pH. The samples were aliquoted and stored at −80°C under argon protection until further analysis of soluble markers.

7.2.4 Analysis of Soluble Mediators and Other Markers in IS and EBC

The inflammatory mediators were determined in the thawed cell-free supernatants of IS and EBC samples. All samples underwent only a single freeze-thaw cycle.

In EBC samples, the concentrations of leukotriene B_4 and 8-isoPGF$_{2\alpha}$ were measured with specific enzyme competitive immunoassays (Assay Designs, Ann Arbor, USA; detection limit 11.7 pg/mL for LTB_4 and 6.1 pg/mL for 8-isoPGF$_{2\alpha}$) and the amount of NO derivatives with a colorimetric assay kit (Alexis™ Cayman Chemicals, Grünberg, Germany) determining the total nitrate/nitrite concentration with a sensitivity of 5 μM and a standard range: 0–35 μM.

In IS samples, the following soluble markers were measured: interleukins (IL-1β, IL-5, IL-6, and IL-8), LTB_4, NO derivatives, and total protein and eosinophilic cationic protein (ECP; using the ImmunoCAP system from Phadia, Uppsala, Sweden). IL-1β was measured with the respective PeliKine™-Tool set (CLB, Amsterdam, Netherlands) in a standard range of 0.4–300 pg/mL for IL-1β. IL-5 and IL-8 were measured with the OptEIA™ ELISAs (BD Biosciences Pharmingen, Heidelberg, Germany) in a standard range of 2–500 pg/mL for IL-5 and in a standard range of 3–200 pg/mL for IL-8. Determination of IL-6 was performed with the DuoSet™ ELISA Development system (R&D Systems, Wiesbaden, Germany) in a standard range of 3–600 pg/mL for IL-6.

Total protein content in the IS samples was determined according to the method of Bradford with bovine serum albumin as standard solution (range 10–100 μg/mL) (Bradford 1976).

7.2.5 Statistical Analysis

Values distribution was assessed using the D'Agostino & Pearson omnibus normality test. Values below the limit of quantification (LOQ) were set 2/3 of the LOQ. Comparisons of unpaired data were performed with a Mann–Whitney test. A two-sided significance level of 0.05 was chosen for all tests. To estimate specific parameters in EBC and IS as suitable diagnostic parameter for the detection of asthmatic symptoms (AS), the self-reported current asthmatic symptoms were taken as the gold standard to calculate sensitivities, specificities, positive predictive values (PPV), negative predictive values (NPV), and test efficiencies. For the evaluation of a parameter, the mediator or cell concentration leading to the maximum Youden Index (sensitivity + specificity − 1) was chosen as the optimal cut-off level (as described by van Kampen et al. 2009). The data were analyzed by using GraphPad Prism version 5.01 for Windows (GraphPad Software, San Diego, CA).

7.3 Results

7.3.1 Characterization of the Study Group

In the group of 91 HCWs examined in the scope of the whole study (Merget et al. 2010), exhaled nitric oxide (eNO) was significantly correlated with the atopy status (quantified *via* sIgE to ubiquitous environmental allergens; sx1) ($r = 0.438$; $p < 0.0001$; Pearson). Seventy-seven of the HCWs (85%) were non-smokers and included in our evaluation. Forty-six (60%) of them were atopic and 40 (52%) had latex sIgE (≥0.35 kU/L). Twenty-nine of the non-smoking subjects (38%) reported ongoing asthmatic symptoms and 21 of them reported also rhinitis. For the further evaluation, we divided the 77 non-smokers in two groups: 29 with ongoing asthmatic symptoms (AS) and 48 without current asthmatic symptoms (non-AS). No significant difference between eNO was measured between the AS (median: 16.7 ppm; range: 2.4–114.8 ppm) and the non-AS groups (median: 15 ppm; range: 3.5–102.3 ppm).

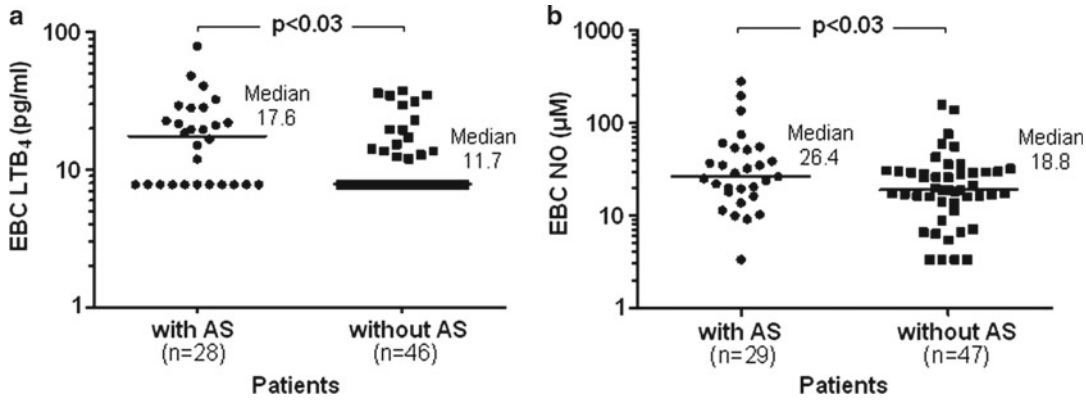

Fig. 7.1 (**a**) **Leukotriene (LT) B_4 and** (**b**) **NOx concentrations** in exhaled breath condensate (*EBC*) in patients with asthmatic symptoms (*AS*) and without asthmatic symptoms (without AS)

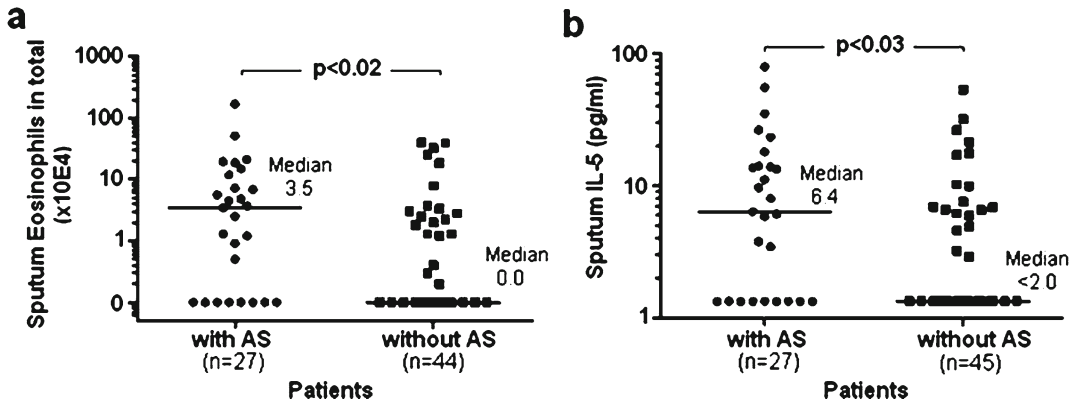

Fig. 7.2 (**a**) **Total numbers of eosinophils and** (**b**) **interleukin (IL-5) concentration** in induced sputum samples in patients with asthmatic symptoms (*AS*) and without asthmatic symptoms (without AS)

7.3.2 Analysis of EBC

In subjects with AS, the concentrations of LTB_4 ($p=0.025$; Fig. 7.1a) and nitrogen oxides (NO_x; $p=0.027$; Fig. 7.1b) were significantly higher than in the non-AS subjects. In contrast, the EBC pH values (median pH in AS: 7.04 and in non-AS: 6.91) and the concentrations of 8-isoPGF$_{2\alpha}$ (median 8-isoPGF$_{2\alpha}$ in AS: 198.9 pg/mL and in non-AS: 143.7 pg/mL) were not different. No significant correlation was measured between the pH, 8-isoPGF$_{2\alpha}$, LTB_4, and NOx in EBC samples (data not shown).

7.3.3 Analysis of IS

In IS samples of subjects with AS, the numbers of eosinophils ($p=0.015$; Fig. 7.2a), the percentage of eosinophils ($p=0.015$), and the concentrations of IL-5 ($p=0.021$; Fig. 7.2b) were significantly higher than in subjects without AS. In contrast, ECP, IL-8, IL-6 concentrations, and the numbers (and percentages) of neutrophils were not different (data not shown). In addition, in IS samples significant correlations between several cell and soluble parameters were calculated (Table 7.1).

Table 7.1 Spearman (rs; *upper line*) and Pearson (*rp; lower line*) correlation coefficients of cellular and soluble parameters in induced sputum samples of all 77 non-smoking subjects

	Eosinophils (%)	IL-5	ECP	Total protein	IL-8	IL-6	NO_x	IL-1β	LTB_4
Eosinophils %	1.0	–0.065	**0.515*** **	**0.445*** **	**0.526*** **	**0.449*** **	0.137	–0.016	0.088
		–0.014	***0.402*** **	***0.383*** **	*0.115*	*0.188*	*0.074*	*0.005*	*0.015*
IL-5		1.0	0.020	0.041	–0.019	–0.127	–0.164	**0.335** **	–0.069
			0.090	*0.064*	*0.093*	*0.037*	*–0.155*	***0.351*** **	*0.130*
ECP			1.0	**0.721*** **	**0.783*** **	**0.596*** **	0.173	**0.372*** **	**0.492*** **
				0.742 **	***0.373*** **	***0.416*** **	*0.210*	***0.279*** **	*0.123*
Total protein				1.0	**0.714*** **	**0.606*** **	***0.407*** **	**0.252***	**0.290***
					0.641 **	***0.616*** **	***0.398*** **	***0.513*** **	***0.287***
IL-8					1.0	**0.737*** **	0.229	**0.351** **	**0.399*** **
						0.411 **	*0.213*	***0.642*** **	*0.202*
IL-6						1.0	0.160	**0.245***	**0.244***
							0.271*	***0.244****	*0.128*
NO_x							1.0	–0.019	–0.019
								0.078	*–0.050*
IL-1β								1.0	**0.351** **
									0.431 **
LTB_4									1.0

Significant values are indicated in bold
*p < 0.05; **p < 0.01 ***p < 0.001

Table 7.2 Estimation of soluble EBC and cellular and soluble IS parameters as optimal test parameter for the detection of asthma

Parameter	Sensitivity (tp/(tp + fn))	Specificity (tn/(tn + fp))	PPV (tp/(tp + fp))	NPV (tn/(tn + fn))	Test efficiency ((tp + tn)/N)	Youden Index at the cut-off level
EBC LTB_4 ≥17.64 pg/mL	**0.50**	**0.80**	**0.61**	**0.73**	**0.69**	**0.30**
EBC LTB_4 ≥20 pg/mL	0.39	0.85	0.61	0.70	0.68	0.24
EBC LTB_4 ≥25 pg/mL	0.25	0.87	0.54	0.66	0.64	0.12
EBC NO ≥25 μM/mL	0.52	0.64	0.47	0.68	0.59	0.16
EBC NO ≥32.1 μM/mL	**0.44**	**0.83**	**0.60**	**0.70**	**0.67**	**0.27**
EBC NO ≥50 μM/mL	0.28	0.89	0.62	0.67	0.66	0.17
Sputum Eos ≥2 %	**0.33**	**0.89**	**0.64**	**0.68**	**0.68**	**0.22**
Sputum Eos ≥3%	0.30	0.90	0.67	0.68	0.68	0.20
Sputum Eos ≥5%	0.04	0.93	0.25	0.61	0.59	–0.03
Sputum Eos total $\geq 3.5 \cdot 10^4$	**0.51**	**0.84**	**0.67**	**0.74**	**0.72**	**0.35**
Sputum Eos total $\geq 5 \cdot 10^4$	0.37	0.86	0.63	0.69	0.68	0.25
Sputum Eos total $\geq 7.5 \cdot 10^4$	0.26	0.86	0.54	0.66	0.63	0.12
Sputum IL-5 ≥5 pg/mL	0.59	0.67	0.52	0.73	0.63	0.26
Sputum IL-5 ≥7.5 pg/mL	**0.48**	**0.80**	**0.60**	**0.72**	**0.68**	**0.28**
Sputum IL-5 ≥10 pg/mL	0.41	0.84	0.61	0.70	0.68	0.25
Sputum Eos $\geq 3.5 \cdot 10^4$ and Sputum IL-5 ≥7.5 pg/mL	0.22	1.00	1.00	0.68	0.71	0.22
Sputum Eos $\geq 3.5 \cdot 10^4$ and EBC LTB_4 ≥17.64 pg/mL	**0.30**	**0.98**	**0.89**	**0.70**	**0.72**	**0.28**
Sputum Eos $\geq 3.5 \cdot 10^4$ and EBC NO ≥32.1 μM	0.26	1.00	1.00	0.69	0.72	0.26
EBC NO ≥32.1 μM and EBC LTB_4 ≥7.64 pg/mL	0.30	0.96	0.80	0.69	0.71	0.26

For each parameter results with highest Youden Index are indicated in bold

7.3.4 *Estimation of the Optimal Parameter for the Detection of Asthma*

To estimate the best cut-off value of LTB_4 and NO_x concentrations in EBC, and eosinophils (total and percentage) and IL-5 concentrations in IS, for the detection of asthma sensitivity, specificity, positive predictive value (PPV), negative predictive values (NPV), test efficiencies, and the Youden Index were calculated with different mediator concentrations (Table 7.2). The maximum Youden Index was reached for LTB_4 with a concentration of ≥17.64 pg/mL, with test efficiency of 0.69, and for NO_x with a concentration of ≥32.1 μM, with a test efficiency of 0.67. The maximum Youden Index was reached for total eosinophils with number of $\geq 3.5 \cdot 10^4$, with test efficiency of 0.72. For IL-5 it was reached with a concentration of ≥7.5 pg/mL, with test efficiency of 0.68.

Additionally, IS and EBC parameters with the best outcome (in IS eosinophils $\geq 3.5 \cdot 10^4$ and IL-5 ≥7.5 pg/mL, and in EBC LTB_4 ≥17.64 pg/mL and NO_x ≥32.1 μM) were combined. The maximum Youden Index was reached for IS total eosinophils $\geq 3.5 \cdot 10^4$ combined with LTB_4 ≥17.64 pg/mL, with a test efficiency of 0.72, PPV of 0.89, and NPV of 0.70.

7.4 Discussion

Induction of sputum with hypertonic saline was shown to be safe in our subjects and was not associated with any adverse event. Using the ECoScreen device it was possible to collect EBC in a sufficient amount from 76 of the 77 non-smoking subjects of the study group.

The amount of eosinophils and the concentration of IL-5 in IS samples, and the concentrations of LTB_4 and NO_x in EBC were significantly higher in subjects with current asthmatic symptoms. Therefore, these parameters were tested for their suitability to discriminate between 'with current asthmatic symptoms and without current asthmatic symptoms' and to support the diagnosis of allergic asthma as predictive values. Our results indicate that although IL-5 in IS and LTB_4 and NO_x concentrations in EBC were adequate parameters, the optimal parameter to support the asthma diagnosis in our study group is the total number of eosinophils $\geq 3.5 \cdot 10^4$ in IS. The present study was performed in non-smoking HCWs with and without current allergic asthmatic symptoms 10 years after the latex ban in German health care facilities. For all these parameters the specificity was >0.8 and therefore sufficient, but the sensitivity ranged between 0.22 and 0.59 which was not adequate to detect all subjects with asthmatic symptoms with these methods. Nevertheless, it has to be considered that all these evaluations are influenced by the selected 'gold standard' which is in our case the self-reported asthmatic symptoms. Whereas predictive values depend largely on the prevalence rates of cases under study, sensitivity and specificity are presumably inherent characteristics of the test (Feinstein 1975; van Kampen et al. 2009). Thus, we used the Youden Index, considering sensitivity and specificity equally to define the optimal positivity criterion (cut-off level) for each parameter, because this index should be independent of selection bias.

Our results confirmed the previously reported importance of eosinophilic inflammation in allergic asthma induced by high molecular weight occupational sensitizers (Quirce et al. 2010; Motojima et al. 1993). Interleukin-5, a protein produced by several different cells including $CD4^+$ T cells, mast cells, and eosinophils, is involved in the development, survival, and activation of eosinophils. Therefore, it is not surprising that we found also a significantly higher IL-5 concentration in sputum samples of subjects with current asthmatic symptoms, but without correlation to the numbers and percentage of IS eosinophils. In contrast to IL-5, the concentrations of the eosinophil granule-derived cationic protein (ECP) in the sputum samples were nearly similar in both groups. Similar to other

studies (Fahy et al. 1993; Motojima et al. 1993; Gibson et al. 1998; Barck et al. 2005) we measured a significant but not very strong correlation between the eosinophils and ECP in the sputum samples ($r_s = 0.515$; $r_p = 0.402$). In addition, Gibson et al. (1998) and Barck et al. (2005) described that measuring ECP in the sputum cell pellet lysate which reflects the number of eosinophils (in contrast to ECP in the supernatant, which better estimates the eosinophilic activation) is often better correlated to the count of eosinophils in patients with a different airway inflammatory disease to asthma. They recommended the measurement of ECP in the cell pellet lysate as an estimate of eosinophilic inflammation in clinical trials and epidemiological surveys.

Additionally, our data also indicate a significant correlation between the total protein content and eosinophil count as well as all other soluble parameters, with the exception of IL-5 concentrations. Especially for IL-5 concentrations, it has to be kept in mind that more than 50% of the values measured in sputum samples of the subjects without asthmatic symptoms were below the limit of quantification and therefore the parameter was not very robust. Overall, the good correlation of the different markers supported that the inflammatory process is characterized by multiple mediators released by different activated cells. Kulkarni et al. (2010) mentioned that sputum eosinophilia is only present in about 50% of asthmatic subjects across all severities which introduced the possibility that other inflammatory pathways (e.g., with different granulocytic composition) are also important in different asthma subphenotypes. Therefore, one should not focus solely on the assessment of mediators of eosinophilic inflammation, but consider further pathways for the characterization of the asthmatic reaction.

In parallel to the collection and analysis of induced sputum, we also collected and analysed EBC. This method offers the possibility with a save, non-invasive, and easy to handle diagnostic procedure to indirectly point to biochemical changes that occur in the fluid lining airway surfaces (Cepela and Dodig 2007; Hoffmeyer et al. 2009). Of the available EBC biomarkers, the majority of published data refer to hydrogen peroxide, pH (airway acidity), nitric oxide metabolites, various arachidonic acid metabolites (leukotrienes and prostanoids), and products of the lipid peroxidation. The literature data (summarized in Cepela and Dodig 2007) suggest that the determination of 8-isoprostane and other arachidonic acid products appears to have the highest differential diagnostic potential for the detection of inflammatory processes in asthma and COPD. Our data show that the EBC NO_x and LTB_4 concentrations were significantly different between the patients with and without asthmatic symptoms and that according to the Youden Index LTB_4 concentrations ≥17.64 pg/mL seem to be a suitable predictive marker for asthmatic symptoms. Caballero Balanzá et al. (2010) also reported that LTB_4 concentrations in EBC were higher in children with asthma than in healthy controls and in contrast to our data they also found that the 8-isoPGF$_{2\alpha}$ concentrations were significantly higher in asthmatic than in healthy children.

We found a good correlation between eNO concentrations and the atopy status of our subjects, but no significant eNO difference between the subjects with and without current asthmatic symptoms. Henriksen et al. (2000) reported that eNO is significantly elevated in atopic *vs.* non-atopic suspected asthmatics and that suspected asthmatics with both airway hyperresponsiveness and atopy have the highest eNO levels. They concluded that measurements of eNO alone are not a useful tool in diagnosing asthma in population surveys.

7.5 Conclusions

The present study demonstrates that the collection of EBC and induced sputum is safe and the analysis of these fluid concerning mediators and cells can be useful in supporting the asthma diagnosis. Although LTB_4 and NO_x concentrations above a defined level are suitable parameters, the optimal parameter to support the asthma diagnosis in our study group was a total number of eosinophils ($\geq 3.5 \cdot 10^4$) in induced sputum.

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Chapter 8
Deep Nasal Inspirations Increase the Cough Threshold in Children with Mild Asthma

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Abstract Asthma is a chronic inflammatory disease characterized by bronchospasms accompanied with frequent coughing, the pathogenesis of which is not clear. In healthy adults deep inspirations (DIs) provide a protective effect against bronchoconstriction triggered by methacholine inhalation, which correlates with the number of accompanying cough efforts. The aim was to study the effect of deep nasal inspirations representing the voluntary equivalent of the sniff-like aspiration reflex on the capsaicin-induced cough in children with mild asthma. The cough reflex sensitivity to capsaicin was determined using a compressed air-driven nebulizer in 21 children (8 girls and 13 boys of median age 13.3 year) suffering from mild asthma ($FEV_1 \sim 80\%$). The effect of five previous DIs through the nose was examined on the elicitability of two and five or more cough efforts (C2, C5). Under control conditions, the concentration of 20.86 (14.58–29.8) μmol/l of capsaicin provoked two cough efforts (C2). After five DIs similar reaction required significantly higher concentrations of capsaicin: 29.02 (18.88–44.6) μmol/l; $P = 0.016$. Five or more cough efforts (C5) were not significantly changed after previous DIs 161.49 (77.31–337.33) μmol/l and without DIs 141.52 (68.77–291); $P = 0.54$. A series of five deep inspirations decreases the cough reflex sensitivity to evoke two efforts (C2) in children with mild asthma. The inhibitory effect of similar DIs disappeared after repeated applications of increasing doses of capsaicin, aiming to evoke five or more cough efforts, suggesting a reflex character of protective effect of DIs.

Keywords Asthma • Capsaicin • Cough • Cough sensitivity • Deep inspirations • Sniff-like aspiration

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8.1 Introduction

A series of five nasal deep inspirations (DIs) provides a bronchoprotective effect significantly decreasing the intensity of a bronchospasm provoked by inhalation of methacholine in the absence of other DIs for 20 min at least in healthy persons (Kapsali et al. 2000; Scichilone and Togias 2000; Crime et al. 2002). In mild asthmatics, a bronchodilating effect also was observed, which decreased with aging (Scichilone et al. 2004) and with the severity of asthma (Scichilone et al. 2007). The inconsistent presence of the bronchodilating effect in asthmatics might be caused by measurement of FVC, starting with maximal inspiration, which could modify the results in earlier studies. Measuring of the forced expiratory flow, starting with normal tidal inspiration immediately after the five DIs, in the absence of other deep breaths 10 min before and 40 min after the test, proved the bronchoprotective effect of previous DIs in healthy subjects (Crime et al. 2002). The effect, however, lasted less than 10 min, suggesting a reflex origin. In asthmatics the results obtained in functional residual capacity (FRC) and specific airway conductance (SGaw), suggested a transient modification of the airway lumen with an unclear mechanism, rather than a persistent structural bronchodilation (Crime et al. 2002). Asymptomatic airway hyperreactivity has been associated with the later development of asthmatic symptoms (Laprise and Boulet 1997) or with an accelerated decline in lung function (Lange et al. 1998). In the present study we examined the role of DIs (equivalent of sniff-like aspiration reflex – AR) (Tomori et al. 2010) on cough reflex sensitivity in asthmatic children.

8.2 Methods

The study was approved by the Ethics Committee of Jessenius Faculty of Medicine, Comenius University in Martin and Srobar's Institute of Pediatric Tuberculosis and Respiratory Diseases, Dolny Smokovec, Slovak Republic. Formal consent was obtained from the parents of all children participating in the study.

Twenty one children (median age 13.3 year, 8 girls and 13 boys) suffering from bronchial asthma completed the study. They had no upper respiratory tract infection in the preceding 2 weeks before examination, no history of diabetes mellitus. Lung function testing performed prior to capsaicin challenge demonstrated practically normal lung function in all subjects. Cough reflex sensitivity was performed with and without DIs on successive days. The cough reflex sensitivity to capsaicin (SIGMA) was determined using a compressed air-driven nebulizer (KoKo DigiDoser; nSpire Health Inc., Louisville, CO) which is modified by the addition of an inspiratory flow regulator valve and a dosimeter with an inspiratory flow regulator valve (RIFR; nSpire Health Inc., Louisville, CO). The valve limits inspiratory flow rate to 0.5 l/s regardless of excessive inspiratory force, thereby guaranteeing a consistent and reproducible inspiratory effort with each breath. Thus, with an appropriate instruction to inhale with sufficient force, all subjects achieve an identical inspiratory flow rate during each successive single-dose inhalation of aerosol. Each subject inhaled up to 12 capsaicin aerosol concentrations (0.6–1,250 μmol/l) during 400 ms at 1 min intervals. In order to increase cough challenge blindness, inhalations of physiological saline (placebo) were randomly interspersed between incremental concentrations of capsaicin. This strategy reduced the effect of voluntary suppression or conditioned responses in subjects, who would otherwise be anticipating progressively higher concentrations of a tussive agent. Only coughs occurring within 15 s of capsaicin delivery were counted. For each test, the concentrations of capsaicin causing two (C2) and five cough efforts (C5) were reported. The C2 and C5 values were obtained by determining the first administered concentration that resulted in two or more and five or more coughs (Chang et al. 1996; Morice et al. 2007).

8.3 Results and Discussion

We found that compared to the control concentrations of capsaicin of 20.86 (14.58–29.86) μmol/l, evoking two or more coughs, a series of five nasal DIs, representing an equivalent of AR, significantly decreased the C2 cough reflex sensitivity as the higher concentrations of capsaicin were required to evoke cough after DIs −29.02 (18.88–44.62) μmol/l, $p = 0.016$ (Fig. 8.1a). The concentrations of capsaicin evoking 5 cough efforts (C5) compared with the control values of 141.52 (68.77–291.2) were not increased significantly by a series of nasal DIs amounting to 161.49 (77.31–337.33) μmol/l, $p = 0.54$ (Fig. 8.1b). These results suggest that repeated applications of higher doses of the irritant cause inhibition of the reflex reaction.

In asthma, chronic obstructive pulmonary disease, airway hyperreactivity, cough variant of asthma, chronic rhinitis, and in many other disorders with airway hyperreactivity, the presence and intensity of bronchoconstriction induced by the methacholine broncho-provocation test could be easily quantified, which has a great practical importance. The presupposed bronchodilation might manifest with a significant reduction of FEV_1, IVC, and FVC, using the forced expiratory maneuver starting with a normal and not forced inspiration. Also, the contribution of allergy and atopy could be assessed in these and many other conditions. Application of the methacholine broncho-provocation and capsaicin tussive-tests could be useful for differential diagnostics of airway hyperreactivity in asthma and other respiratory disorders. The inhalation of capsaicin evokes more frequent cough reactions in patients with seasonal allergic rhinitis (Pecova et al. 2008) and chronic rhinosinusitis (Tatar et al. 2009), compared with healthy controls.

Complex analysis of the cough mechanisms allows differentiating the sensory part of the reaction from the motor expression of coughing. The so-called ‘urge to cough model’ consisting of six stages allows different management of the sensory and motor parts (Davenport 2008). In cases of airway hyperreactivity, causing non-specific cough, in paradoxical vocal fold movements, and during reflux to the distal esophagus, there is urge to cough without entering of irritants into the larynx. The urge to cough can be managed by simple behavioral and pharmaceutical methods (Vertigan and Gibson 2011). After entering of irritants into the larynx and lower airways, the expiration reflex seems to be a useful reaction expelling the irritants rather than the cough reflex, which may allow aspiration to the lungs (Tomori et al. 2010; Korpas 1979). However, there may be a difference in reaction to airway

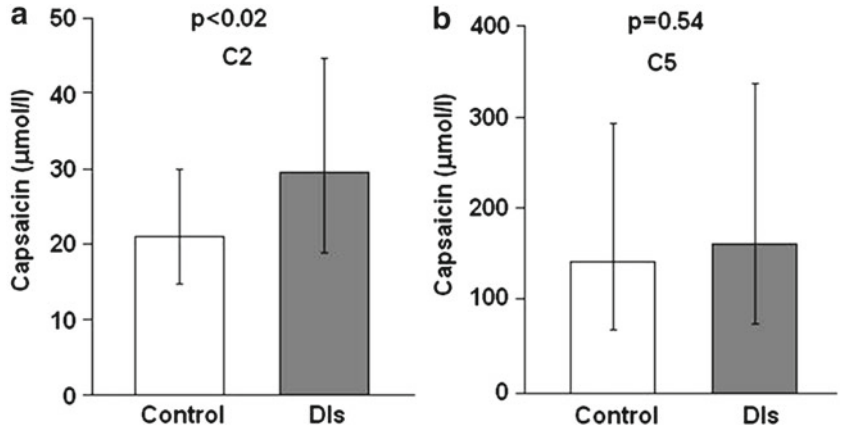

Fig. 8.1 Cough reflex sensitivity to capsaicin in children with bronchial asthma after a series of deep inspirations (*DIs*) compared with control; (**a**) C2 – concentration of capsaicin which induces two coughs and (**b**) C5 – concentration of capsaicin which induces five coughs

sensory stimuli evoking the expiration reflex, with an immediate inhibitory effect on inspiration (Korpas 1979) and a switch to the cough reflex starting with a deep inspiration, which might allow aspiration (Tomori et al. 2010). Experiments in cats indicate that mechanical stimulation of the trachea evoking cough starts in two thirds of cases with the expiration reflex. This reflex is less frequent and weaker than the typical expiration reflex from the larynx (Poliacek et al. 2008). In gastroesophageal reflux to the larynx and lower airways, with or without aspiration, the onset of necessary cough effort may be postponed by a previous slow voluntary inspiration and breath holding followed by swallowing of the bolus to the esophagus (Vertigan and Gibson 2011; Hegland et al. 2011).

8.4 Conclusions

Asthma is characterized by bronchospasms accompanied by frequent coughing, but the pathogenesis is still unclear. In healthy adults, deep inspirations provide a protective effect against bronchoconstriction triggered by methacholine, which correlates with the number of accompanying cough efforts. In adult asthmatics, deep inspirations have some spasmolytic effect which decreases with age and severity of the disease. Our aim in the present study was to test the elicitability of the cough reflex by capsaicin in children with mild asthma and their presupposed decrease by preceding deep inspirations. We conclude that a series of five deep inspirations decreases the cough reflex sensitivity (C2) in children with mild asthma. The inhibitory effects of deep inspirations disappear after repeated applications of increasing doses of capsaicin, aiming to evoke five or more cough efforts (C5), suggesting a reflex character of the protective effect of deep inspirations.

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Chapter 9
Reproducibility of Sensitivity to Capsaicin Assessed by Single Breath Inhalation Methodology

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Abstract The hallmark of sensory hyperreactivity is an enhanced capsaicin induced cough reflex. The cough reflex can be modified by activation of nociceptive (capsaicin-sensitive) nerve terminals. The aim of our study was to assess the influence of exposure to CO_2 concentrations up to 2.0 vol% on capsaicin induced cough reflex on four different occasions. Sixteen healthy volunteers were exposed to CO_2 concentrations of 0.5, 1.0, and 2.0 vol% for 4 h and to clean air in a repeated measures cross-over design. After exposure the capsaicin induced cough reflex was assessed by the single breath dose–response method according to ERS 2007 guidelines. After blank solutions, capsaicin doses (n = 12, range 0.49 to 1000 μM) were administrated from a nebulizer combined with a provocation system (Masterscope, software APS version 5.02). Doses were doubled every minute and the concentration causing five or more coughs (C5) was fixed as the end point. The inter-individual C5 capsaicin responsiveness reflected a representative range (0.95–1000 μM). On an intra-individual basis, a good reproducibility could be demonstrated for four tests within 3 weeks. There was no influence of CO_2 challenge on the cough reflex. The first capsaicin test demonstrated a lower C5 threshold independent of the CO_2 concentration applied. In conclusion, assessing the capsaicin cough reflex by single breath inhalation is reliable. However, the at cough sensitivity might be overestimated at the first test occasion. Exposure to CO_2 in concentrations of up to 2.0 vol% has no effect on sensory reactivity.

Keywords Capsaicin • Irritants • Exposure • Cough reflex • Cough sensitivity

9.1 Introduction

In daily life, people encounter numerous substances capable of causing unpleasant effects, irritation, and in some cases clear disorders of the upper and lower respiratory tracts, as asthma or COPD (Sigsgaard et al. 2010). Irritants are often found in the air at workplaces and around half of the German binding limit values for hazardous substances at workplaces are directed at the avoidance of irritation.

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Human studies performed under controlled exposure conditions can help to define the irritative impact of substances (Raulf-Heimsoth et al. 2010).

Cough is a major symptom in allergic asthma, a disease characterized by airway hyperreactivity due to a specific interaction of an allergen with the immune system (Smith and McFadden 1995). In contrast, an irritant causes a reversible inflammatory response mediated by chemical actions and a repeated or severe irritant-induced epithelial injury of the airways can also result in cough (Brooks 2008). Finally, there is a group of people complaining about irritation of the airways and cough on exposure to chemicals or odors usually not followed by intense symptoms. Many of these complaints occur in the context of occupational exposures (Millqvist 2008). This phenomenon is referred to as sensory hyperreactivity which can be characterized by an extensive coughing after inhalation of capsaicin (Millqvist et al. 1998).

An enhanced cough reflex seems to be mediated by a C-fiber hyperreactivity of the airway sensory neurons. The C-fibers' terminals contain neuropeptides such as tachykinins and CGRP (calcitonin gene-related peptide) which are released upon activation. Neuronal mechanisms play a role in the initiation and modulation of airway inflammation and hyperresponsiveness also called 'neurogenic inflammation' (Pisi et al. 2009).

The transient receptor potential vanilloid-1 (TRPV1) cation channel was identified as a receptor involved in activation of bronchopulmonary C-fiber afferents and transducing the response to inhaled irritants (Brooks 2008). Capsaicin is a potent activator of the TRPV1 receptor and its inhalation triggers a cough response in humans in a dose-dependent matter (Johansson et al. 2002). Provocation is safe and capsaicin is the most commonly used method for determination of cough sensitivity (Dicpinigaitis and Alva 2005). In 2007, a task force of the European Respiratory Society (ERS) recommended guidelines for standardization (Morice et al. 2007). For the single breath dose–response method, the end point is the threshold concentration of capsaicin delivered resulting in at least two (C2) or five (C5) coughs. A good short- and long-term reproducibility could be demonstrated in healthy adult volunteers; the C5 threshold was recommended for short-term reproducibility (Dicpinigaitis 2003). A long-lasting unchangeably increased cough sensitivity was observed in patients with airway symptoms induced by chemicals and scents (Ternesten-Hasséus et al. 2007).

There is evidence that the cough reflex could be modified by afferent inputs and there is plasticity at the central nervous system in terms of sensitization or desensitization of the reflex (Widdicombe et al. 2011). Studies revealed that the sensitivity of bronchopulmonary C-fibers can be modified, e.g., enhanced during airway inflammation (Lee et al. 2002). As an irritant causes a reversible inflammatory response, the assessment of cough receptor sensitivity to capsaicin might be a valuable tool in irritant research. CO_2 is not a typical irritant but hydration of CO_2 forms carbonic acid which rapidly dissociates to bicarbonate and hydrogen ions (H^+) and an increase of the broncho-alveolar H^+-concentration is characteristic for airway inflammation (Antus et al. 2010).

As CO_2 is easy and safe to handle, it was used for this study. The study was designed to investigate whether: (1) the C5 parameter of the single breath technique applied is reliable concerning reproducibility within 3 weeks and (2) whether capsaicin induced cough reflex is altered after exposure to different CO_2 concentrations.

9.2 Methods

9.2.1 Experimental Design and Subjects

The study was performed in accordance with the ethical principles of the Declaration of Helsinki. The local Ethics Committee approved the study and all participants gave written informed consent. The study was conducted in our exposure laboratory (ExpoLab), a gas-tight room built of glass and stainless

Table 9.1 Demographic and clinical characteristics of subjects (eight female, eight male)

	Mean	Range
Age (year)	36.7	(20–56)
Height (cm)	176	(163–193)
Weight (kg)	76.3	(58–100)
VC (% predicted)	119.4	(90.8–144.4)
FEV_1 (% predicted)	107.4	(86.8–125.7)
FEV_1/VC (%)	77.3	(62.9–96.7)

FEV_1 forced expiratory volume in 1 s,, *FVC* forced vital capacity

steel with spatial dimensions of 3.92 m length, 2.91 m width and 2.50 m height. The resulting volume of the unit is 28.6 m³. In a repeated measures cross-over design, 16 healthy volunteers were exposed to CO_2 concentrations of 0.5, 1.0 and 2.0 vol% and to clean air for 4 h. The sequence of exposures was blinded and assigned by chance. Four volunteers were simultaneously exposed and the interval between the sessions was 1 week. All exposures were done at the same daytime (from 9 a.m. to 1 p.m.).

Eight subjects were female and eight were male. A self administered questionnaire concerning the previous und current medical history was answered by each subject. All participants had no history of chronic respiratory disorders and reported no symptoms of an upper respiratory infection within the previous 6 weeks. All volunteers underwent evaluation of lung function using a MasterLab pro (Software version 4.67a, Cardinal Health, Hoechberg, Germany). According to the American Thoracic Society (ATS) criteria, forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV_1) were obtained from three acceptable lung function tests (ATS 1995). The mean age was 36.7 years (20–56 years); the demographic and clinical characteristics of the study population are shown in Table 9.1.

9.2.2 Capsaicin Cough Challenge

We closely followed general methodological recommendations on the assessment of cough (Morice et al. 2007). The single breath dose–response method was applied for capsaicin challenge. Capsaicin powder (35 mg, Sigma Aldrich, Steinheim, Germany) was dissolved in 1 ml ethanol and 1 ml Tween-80 and further diluted in 8 ml 0.9% saline resulting in a stock solution of 0.01 M capsaicin (Kopec et al. 2008). Dilutions were prepared at the day of use in log 2 concentrations from 0.49 to 1000 µM. After blank solution, capsaicin doses (n = 12) were administrated by a compressed air-driven DeVilbiss 646 nebulizer (DeVilbiss, Malsch, Germany) combined with a provocation system (Masterscope, software APS version 5.02; Jaeger, Würzburg, Germany). Each concentration was given after three slow inspirations in the fourth one from functional residual to near total lung capacity while the nebulizer was actuated over 0.6 s. The mean mass median diameter (MMD) of droplets was 2.5 µm and the output 900 mg/min; calculated doses delivered are presented in Table 9.2. The time interval between each dosage was 1 min and the tussive response was recorded within 10 s after each dose of capsaicin. The test concentration inducing two (C2, data not shown) and five or more (C5) coughs were documented. Subjects were not informed that C5 was the end point of the study. Recording of respiratory resistance (R_{occ}) was performed after each inhalation (data not shown).

9.2.3 Statistical Analysis

Value distribution was assessed using the D'Agostino & Pearson omnibus normality test. Comparisons of paired data were performed with Wilcoxon matched-pairs signed rank test. Data are expressed as mean with range or median with interquartile range (IQR) when appropriate. Spearman rank

Table 9.2 Dosimeter protocol for capsaicin testing

Test	Capsaicin (μM)	Dose delivered (μg)	Cumulative dose (μg)
0	–	0.9% saline	–
1	0.49	0.0013	0.0013
2	0.98	0.0027	0.0040
3	1.95	0.0054	0.0095
4	3.9	0.0107	0.0202
5	7.8	0.0214	0.0416
6	15.6	0.0429	0.0845
7	31.2	0.0858	0.1703
8	62.5	0.1716	0.3419
9	125.0	0.3432	0.6851
10	250.0	0.6864	1.3715
11	500.0	1.3728	2.7443
12	1000.0	2.7456	5.4899

Interval between consecutive test steps was 1 min. The output of the De-Vilbiss 646 nebulizer used in the calculation was 900 mg/min, the duration 0.6 s; Aerosol provocation system: Masterscope, APS version 5.2. software

correlation test was used to determine correlations between the concentrations or time-points studied. Bland & Altman analysis was performed to elucidate the repeatability between the values by the concentrations or time-points. The data were analyzed using GraphPad Prism version 5.01 for Windows (GraphPad Software, San Diego, California, USA).

9.3 Results

Cough sensitivity in terms of the capsaicin concentration inducing five or more (C5) coughs was measured in all subjects post CO_2 exposure. The median C5 value for all exposure conditions of the subjects was 62.5 μM with an IQR of 31.2–750.0 μM. There was no significant gender difference. Respiratory resistance was not altered by the capsaicin challenge in the subjects and the CO_2 exposure, respectively (data not shown). No significant differences could be observed in the median values of C5 according to the different CO_2 exposure concentrations (Fig. 9.1a). More precisely, when comparing clean air and 2.0 vol% CO_2, both measurements significantly correlated ($r=0.667$, $p=0.009$; Fig. 9.1b). In all but two subjects, the C5 thresholds determined were within two log 2 concentrations. There was no correlation between the difference and the height of the C5 threshold ($r=0.157$, $p=0.577$; Fig. 9.1c).

An influence on the C5 threshold was identified according to the order of the measurements. The median capsaicin concentration of the first measurement was lower compared to the following ones irrespectively of the administered CO_2 concentration (Fig. 9.2a). Compared to the first exposure, the median concentrations in the following three samplings in weeks 2–4 were not significantly different (Friedman test, $p=0.836$). When comparing the first and second measurement independently from the CO_2 exposure intensity, there was a significant correlation ($r=0.788$, $p<0.001$; Fig. 9.2b). Only one subject demonstrated a higher sensitivity to capsaicin at the second occasion. A clear bias could be revealed with lower C5 average values of one doubling concentration for the very first measurement compared to the second one. The difference did not correlate with the average C5 concentration ($r=0.162$, $p=0.548$; Fig. 9.2c).

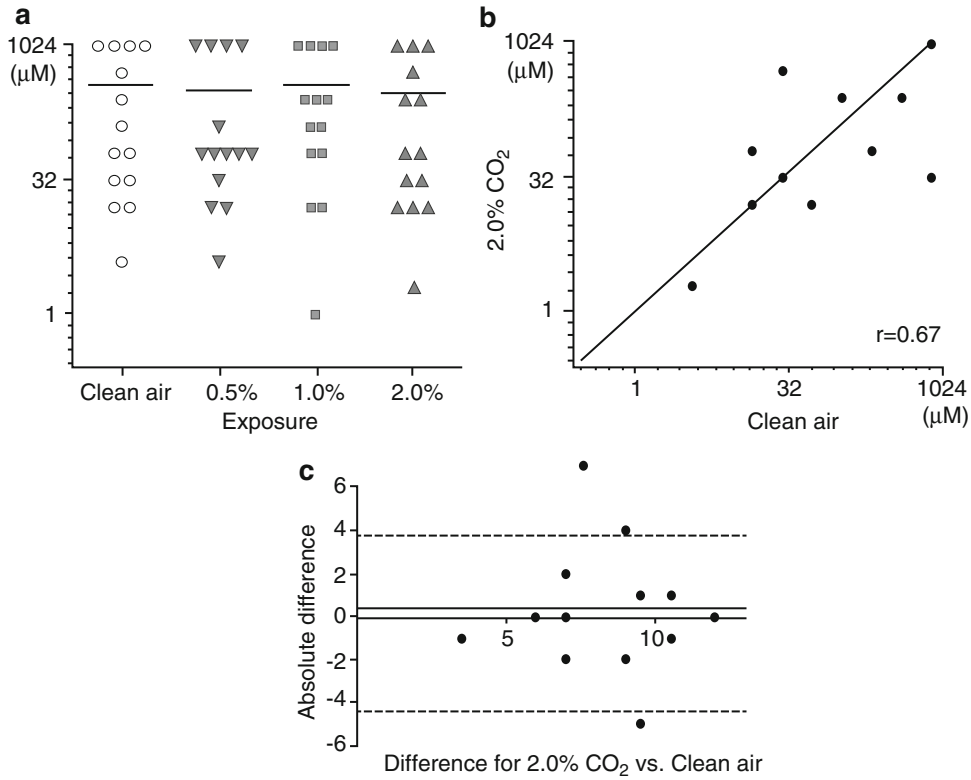

Fig. 9.1 Capsaicin cough threshold (C5) by CO_2 concentration in 16 subjects repeatedly exposed (**a**); correlation between capsaicin threshold (C5) measurements for clean air and CO_2 2.0% (**b**); and difference in capsaicin cough threshold between 2.0 vol% CO_2 and clean air (measurements are shown as log 2) (**c**)

9.4 Discussion

Inhalative exposure to hazardous substances poses a common health risk at the workplace. Studies performed under controlled exposure conditions could help characterizing the irritant potential of a substance. A receptor involved in transducing the response to inhaled irritants is TRPV1, which activates C-fiber afferents. Capsaicin is a potent activator of this receptor and triggers a cough response in humans in a dose-dependent matter.

Studies revealed that the sensitivity of bronchopulmonary C-fibers can be modified, e.g., enhanced during airway inflammation which is characterized by broncho-alveolar acidification. In this study the capsaicin induced cough reflex was not altered after exposure to different CO_2 concentrations. We applied a cross-over design with four subjects tested simultaneously in our ExpoLab in a total of 16 volunteers. The results of the applied C5 parameter of the single breath technique showed sufficient reliability within the three weeks comprising four exposures.

Protocols for capsaicin testing vary. Preferred methods are: (1) counting the total number of coughs induced by a standardized amount of capsaicin resulting from a fixed concentration and time or (2) increasing concentrations to reach a threshold of two (C2) or five coughs (C5). In our study the single breath technique using increasing capsaicin concentrations was performed in adults with respect to current recommendations (Morice et al. 2007). As previously reported, we found no indication that the capsaicin inhalation test induced bronchial obstruction (Dicpinigaitis and Alva 2005).

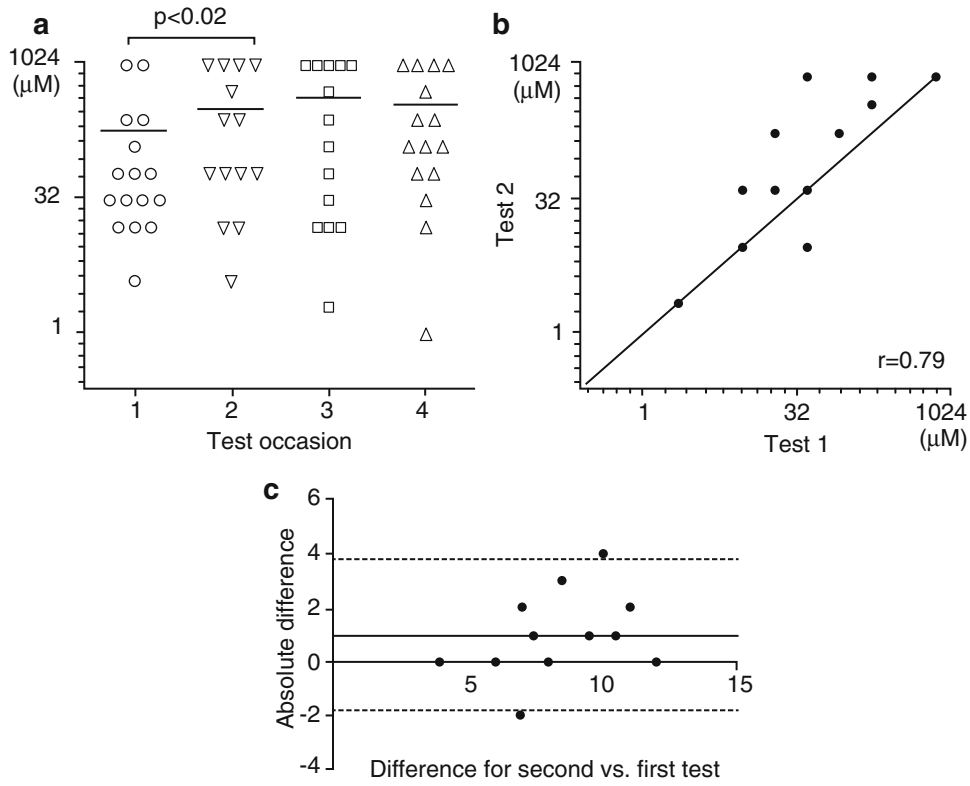

Fig. 9.2 Capsaicin cough threshold (C5) by test occasion in 16 subjects repeatedly exposed (**a**); correlation between capsaicin threshold (C5) measurements for first and second test (**b**); and difference in capsaicin cough threshold between second and first test occasion (measurements were shown as log 2) (**c**)

We preferred this method as it could be performed within 15 min, including instructions for the volunteers. Moreover, in the fixed time and concentration technique based on saline solution and two capsaicin concentrations delivered in a total of 30 min, the cough responses reported could be up to a 100 single coughs and a cut-off point of 10 and 35 coughs was recommended for the positive test in case of the capsaicin concentrations of 0.4 and 2.0 µmol/l, respectively (Johansson et al. 2002). We assume that this intensity of coughs could be quite unpleasant, distressing and exhausting.

The median C5 for all exposure conditions (clean air, 0.5, 1.0 and 2.0 vol% CO_2) of the subjects was 62.5 µM with an IQR of 31.2–750.0 µM. The capsaicin concentrations causing five or more coughs in our study group were comparable to previously reported results obtained with the single breath technique (Holst et al. 2010).

The cough response of volunteers to inhalation of capsaicin depends on their inspiratory flow and is modified by the diameter of inhaled aerosol particles (Hansson et al. 1992; Barros et al. 1991). Therefore we applied a validated delivery system protocol including control of the inspiratory flow rate (Merget et al. 2009). A more peripheral deposition of aerosolized capsaicin was reported to trigger an enhanced coughing response. Therefore, characteristics determining the deposition should be reported. In our study, a small droplet aerosol (MMD 2.5 µm) was generated for inhalation.

Our study included subjects with lower and higher sensitivity concerning capsaicin induced cough. The study group was balanced concerning the number of male and female subjects and their age, respectively. It was reported that age is not a confounder for cough sensitivity evaluated by capsaicin (Brooks 2008). In our study a trend could be observed for subjects younger than 29 years

demonstrating a lower sensitivity (data not shown). However, the age distribution in our study was not representative of the common workforce (20–29 years (n = 8); 41–54 years (n = 8)) and all of our subjects would have been classified as "young" beings in the above referred study.

For all the CO_2 concentrations, no changes in C5 could be observed compared to the results after exposure of clean air. Hydration of CO_2 forms carbonic acid which rapidly dissociates to bicarbonate and hydrogen ions (H^+). Moreover, an increase of the alveolar pCO_2 is usually followed by hyperventilation for compensation reasons. Potential stimuli that can increase the sensitivity of pulmonary C-fibers comprise inflammatory mediators, such as prostaglandin E2 or H^+ ion. It was shown that lowering pH can enhance the response to capsaicin in nociceptive neurons in rats (McLatchie and Bevan 2001). Moreover, in vagal bronchopulmonary C-fibers CO_2 sensitivity could be demonstrated which could be pronounced by transient alveolar hypercapnia probably mediated by an increase of hydrogen ion (Gu and Lee 2002). In addition, upon lung inflation and when increasing the inspired volume during hyperventilation, C-fibers can be activated (Ho et al. 2001). Our results suggest that in healthy humans without airway inflammation, the sensitivity of C-fibers is not enhanced toward acute CO_2 challenges in concentrations up to 2 vol%.

We observed an influence on the results of the order of provocation, with the first test showing a higher sensitivity. This could not be attributed to different CO_2 concentrations as volunteers were exposed in a randomized order. Using a similar approach with capsaicin aerosol in log 2 concentrations, Varechova et al. (2006) reported a lower mean capsaicin concentration for the C2 threshold of the first test (61.5 µmol/l) compared to the second one (120.3 µmol/l) in children, aged 7–17. Referring to our own experience, we agree with their conclusion of this being caused by an unusual sensation. Consequently, we are going to implement a test day for the volunteers to get used to the method and also for the doctors to get a clue in terms of volunteers being rather sensitive or insensitive to capsaicin. In summary, the single breath dose–response approach in conjunction with the C5 threshold seems reliable and may add further information when elucidating substances for their irritant potential.

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

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Chapter 10
Occupational Non-immediate Type Allergic Asthma due to Ammonium Persulfate

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Abstract While numerous cases of immediate-type occupational asthma due to persulfates with positive skin prick test reactions to ammonium persulfate are well documented, few non-immediate type reactions have been described in the literature. We report the case of an atopic worker who developed work-related asthmatic symptoms shortly after he began his job in persulfate production. The diagnosis of asthma was corroborated by methacholine testing. The patient showed a positive patch test reaction to ammonium persulfate, while skin prick test was negative. He presented an isolated late symptomatic airway obstruction after a cumulative dose of 0.6 mg ammonium persulfate administered by a dosimeter method. An immunologic mechanism was demonstrated by a significant increase in exhaled nitric oxide and the number of eosinophils in induced sputum. These findings suggest that isolated late bronchial reactions to persulfates are mediated by eosinophilic inflammatory responses.

Keywords Ammonium persulfate • Bronchial challenge • Occupational asthma • Exhaled nitric oxide • Eosinophilic inflammation

10.1 Introduction

An increasing number of published studies over the last decade have associated exposure to persulfates with the development of asthma. Ammonium persulfate (APS) is the predominant substance in this group, and occupational asthma to this low molecular weight substance has been reported among hairdressers as it is widely used in hair bleaches (Pang and Fiume 2001; Moscato et al. 2005). Also, cases among production workers have been described (Munoz et al. 2004).

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The most frequent manifestations are immunologic immediate-type asthmatic reactions and positive skin prick tests (SPT) which have been described repeatedly in the literature. Convincing demonstration of specific IgE antibodies to APS is lacking, although there is a report about an *in vitro* identification of such antibodies (Aalto-Korte and Makinen-Kiljunen 2003). To our knowledge only two case histories of isolated late bronchial reactions to persulfates have been published (Yawalkar et al. 1999; Harth et al. 2006). The underlying mechanism has so far been assumed to be immunologic, but there is still limited information about this.

10.2 Case History

A 32-year old technician in APS production was referred to our institute for an expert medical opinion regarding his respiratory symptoms. The patient complained of asthma attacks, rhinitis, and generalized skin rash starting 2 years before the examination, shortly after his employment in a persulfate production plant, where his tasks involved the bagging of bleaching powders. At the time of diagnosis he had remained away from exposure for 6 months. According to his medical history he had been previously healthy and his symptoms were initially attributed to house dust mite allergy. Although endoscopic ethmoid surgery and hyposensitization against house dust mite was performed, his symptoms did not improve and deterioration of his lung function was described by a pulmonary physician.

While there was no relation of the patient's symptoms with exposure to house dust (mite), the temporal pattern of his symptoms suggested a potential relationship with working tasks involving exposure to APS. Both the respiratory problems and the skin rash occurred more frequently at the workplace and were relieved during weekends and holidays, while they did not change substantially over the different seasons of the year. Initially, the patient was temporarily removed from his workplace because of his symptoms, but the attempt to return to his tasks induced a relapse of the symptoms. The serial peak expiratory flow (PEF) measurements performed by the patient during this trial indicated a significant decrease in PEF parallel to increased symptom scores, during and after working activity, with an increasing difference between morning and evening (post-shift) values (Fig. 10.1).

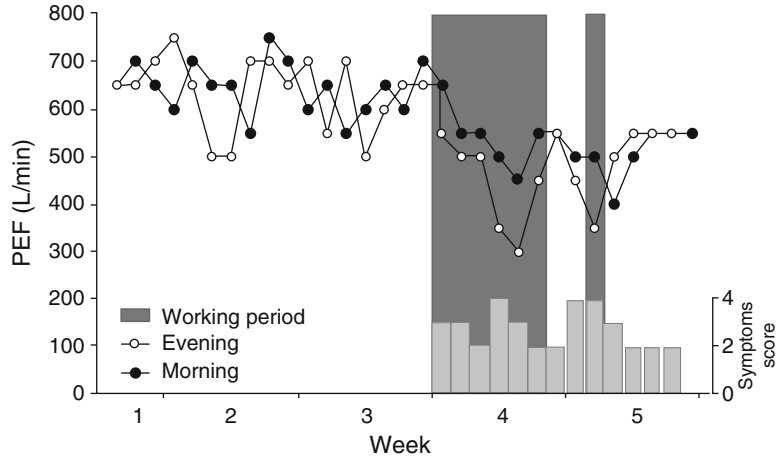

Fig. 10.1 PEF measurements and symptom scores (dyspnea and cough, each graded from 0 (no symptoms) to 4 (strong symptoms) before and during the working period (*shaded areas*). PEF was measured twice daily (morning (*filled dots*) and evening (*open dots*))

10.3 Methods

The study was performed in conformity with the Declaration of Helsinki of the World Medical Association and was approved by a local Ethics Committee.

The patient underwent a full general medical examination which included basic blood chemistry, blood count, serum protein electrophoresis, semi-quantitative urine examination, total serum IgE, determination of specific IgE antibodies to environmental allergens (ImmunoCAP, Phadia, Freiburg), electrocardiogram and chest X-rays. Body plethysmography, spirometry, diffusion capacity testing, and ergospirometry were performed with equipment from Jäger (Würzburg, Germany). Repeated lung function measurements took place during the first day in order to document a stable respiratory status. Finally, the diagnostic procedure included skin prick testing (SPT) to a battery of environmental allergens (various manufacturers).

APS was bought from Sigma-Aldrich (Deisenhofen, Germany). SPT with APS was performed with a freshly prepared 10% (w/v) solution, and patch testing with an APS preparation from Hermal (Reinbek, Germany). SPT was read at 20 min and the patch test after 24, 48, and 72 h (the patch was removed after 24 h). The inhalation challenge with APS was carried out with the use of a 646-DeVilbiss nebulizer and an APSpro dosimeter (Jäger) with freshly prepared APS in quadrupling doses from 0.4 μg to 0.45 mg (cumulative dose of 0.6 mg; concentrations of 0.01–10 mg/mL). Briefly, each dose was administered in five consecutive slow inspirations from functional residual to near total lung capacity, while the nebulizer was actuated over 0.6 s. Inspiratory airflow was maintained close to 1 L/s by observation of a visual scale. The time interval between consecutive steps was 10 min. The nebulizer was actuated 0.5 s after the start of inspiration to ensure a significant airflow upon nebulization. The response was evaluated by spirometry, body plethysmography (Masterlab, Jäger), exhaled nitric oxide (Lim and Mottram 2008) (eNO; NIOX Flex, Aerocrine, Bad Homburg, Germany), serial methacholine testing, and induced sputum analysis (Quirce et al. 2010).

Methacholine testing was performed with a reservoir method (Baur et al. 1998) (Provotest II; Pari, Starnberg, Germany). The patient was exposed to doubling (cumulative) doses of 31–215 μg methacholine, using a standard solution of 3.3 mg/100 mL. Methacholine testing was done on the day before and 24 h after the specific challenge testing with APS. For each challenge, a provoking dose causing a 20% decline in forced expiratory volume in 1 s ($PD_{20}FEV_1$) was derived by linear interpolation, whereby doses were plotted logarithmically and responses linearly (Crapo et al. 2000). Sputum induction with saline 0.9% and analysis were performed, as described recently (Bacci et al. 1996; Raulf-Heimsoth et al. 2007), immediately before the challenge with APS and about 1 and 24 h afterward. Follow-up measurements of lung function and eNO were carried out after 10 and 30 min, 2 h, hourly from 4 to 6, 24, and 48 h.

10.4 Results

There were no significant abnormal findings in the laboratory values apart from an eosinophilia of 6% in the differential blood count. Total IgE was 702 kU/L. While there were positive SPT reactions to *Dermatophagoides pteronyssinus* and a mixture of grasses (3 mm wheal diameter both), only were specific IgE antibodies to *Dermatophagoides pteronyssinus* and *D. farinae* (CAP-class 2) detected. No significant findings were identified in the patient's resting electrocardiogram and chest X-ray, while ergospirometry revealed no pulmonary limitation. Spirometry showed borderline airway obstruction FEV_1 was 89.4% of predicted and the FEV_1/FVC ratio was 71% with no significant intra-day variability (data not shown).

SPT with APS produced a negative result. In the patch test, after 24 h a slight local erythema was observed which progressed to homogenous erythema and vesicles after 48 h, +++ reaction according to Brasch and Fartasch (2009), and then regressed to a slight erythema at 72 h. While no significant

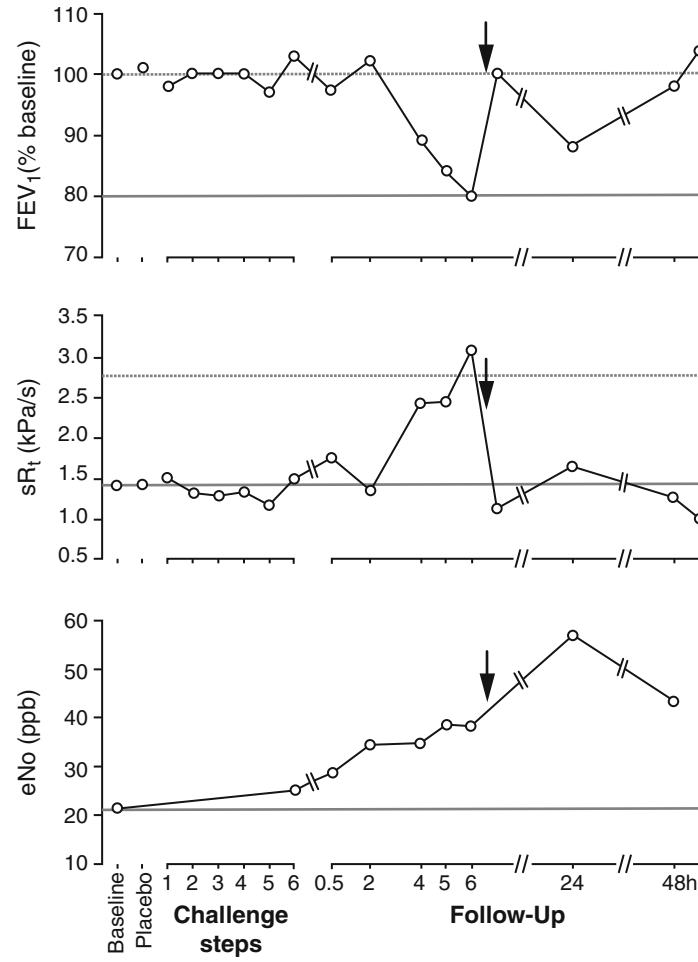

Fig. 10.2 Time-response relationships of FEV_1 (*upper part*), sR_t and eNO (*lower part*) of specific inhalation challenge with ammonium persulfate (APS). Measurements during the challenge represent the values that were obtained 10 min after the application of each APS concentration, for further details see Methods

reaction was observed regarding the patient's lung function parameters during the challenge, 4 h after the test the patient presented symptoms (dizziness and persistent cough), followed by wheezing on auscultation, a 20% fall of FEV_1 from baseline, and an increase of specific airway resistance (sR_t) from 1.43 to 3.08 kPa/s 6 h after the challenge (Fig. 10.2). At that point the patient was administered 300 μg salbutamol to relieve his symptoms and was admitted to the hospital for further monitoring. The respiratory reaction persisted 24 h after the exposure (FEV_1 88% of baseline), while eNO increased from 21 ppb at baseline to 57 ppb (24 h) and 43 ppb (48 h). Baseline $PD_{20}FEV_1$ methacholine (154 μg) was unchanged 24 h after the specific challenge with APS (118 μg).

The total cell numbers in induced sputum were 37×10^5 (baseline), 42×10^5 (30 min), and 50×10^5 (24 h) after the challenge with APS. This corresponded to 5%, 9%, and 12.5% eosinophils, respectively.

10.5 Discussion

Occupational asthma was suspected in this patients based on his work-related symptoms and PEF measurements. The present examination corroborated this diagnosis and identified APS as the causative substance, while house dust mite sensitization was considered of minor importance.

Interestingly, no immediate type reaction could be demonstrated (symptoms, SPT, and inhalation challenge with APS), but a clear isolated late reaction (symptoms, patch test, and inhalation challenge with APS) was observed 4–6 h afterward.

Similar cases of isolated late reactions to APS are extremely rare in the literature. A case of a late asthmatic reaction to APS with a negative SPT has been recently described in a hairdresser by Harth et al. (2006). An immunologic reaction was suggested in that case by positive patch testing and an increase of bronchial hyperresponsiveness after specific inhalation testing with APS. The highest APS concentration in SPT in that study was 1 mg/mL, thus 100-fold lower than in the present study. In the present study, the APS solution was freshly prepared a few minutes before the application to obtain the highest possible sensitivity for the detection of SPT reactions.

Yawalkar et al. (1999) have also reported a case of an isolated late asthmatic reaction which occurred after a nasal challenge with APS. In that case, SPT showed a late reaction 24 h after the application of APS, while the histologic examination demonstrated an infiltration by T lymphocytes at the site of the skin reaction. While a hypothesis of a potential involvement of T lymphocytes has been suggested, a specific methodology to elucidate the immunological background of similar phenomena has not yet been established in the literature. In the present case study, control tests with APS, especially challenge tests, in non-exposed subjects were not performed, because an irritant reaction was not considered likely due to the typical symptoms and the reaction pattern of an isolated late reaction, with an indication of an immunologic mechanism. SPT with the APS solution in ten healthy volunteers were normal (data not shown).

In the present study, the immunologic mechanism was convincingly demonstrated by an increase of eNO and eosinophils in induced sputum after the challenge. Thus, although an isolated late reaction pattern is less common in occupational asthma, an eosinophilic inflammation was shown as the underlying mechanism, as in the case of immediate-type occupational asthma (Sastre et al. 2003). The exact mechanism underlying the simultaneous manifestation of the late respiratory and skin reaction due to APS in our patient is not completely clear. In general, substances that induce contact sensitizations are not considered causative for airways disease. The present, however, demonstrates that this may be not true for persulfates. This is important in clinical practice because patch testing has to be included in the standard diagnostic procedure for patients with suspected occupational asthma due to persulfates and special attention should be paid to the monitoring of bronchial late reactions.

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

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Chapter 11
Bronchial Allergen Challenges: Doubling or Quadrupling Dose Steps?

S. Mousalli, V. van Kampen, and R. Merget

Abstract Inhalation challenges with allergens are considered the gold standard for the diagnosis of occupational asthma. However, no standardized methods are available. One open question is the degree of dose augmentation in the stepwise challenge protocols. Recently, it was recommended to increase the allergen concentrations by no more than doubling between dosing steps for safety reasons. We analyzed retrospectively our dosimeter allergen challenges performed with quadrupling dose steps during the last 10 years. Allergens were inhaled by an APSpro dosimeter and a DeVilbiss 646 nebulizer. The test was terminated after a fall of FEV_1 of at least 20%. Seventeen tests in 13 subjects were considered positive. The mean FEV_1 decreases 10 and 20–30 min after the last allergen dose were 26.7 ± 6.4 and 26.2 ± 6.5%baseline, respectively. Terminal dose response slopes did not differ between doubling (Cockcroft and Davis, J Allergy Clin Immunol, 122:1034–1035, 2008) and quadrupling doses, nor were there any differences concerning the maximal responses. The results suggest that quadrupling dose steps may be an acceptable alternative, without serious increase in risk of severe asthmatic reactions. We assume that by shortening the test duration, physicians might choose lower starting doses and thus make allergen inhalation challenges safer.

Keywords Allergen challenge • Asthma • Inhalation • Dose-response slope • Dosimeter • Tidal volume breathing

11.1 Introduction

Inhalation challenges with allergens are considered the gold standard for the diagnosis of occupational asthma. However, no standardized methods are available. One open question is the degree of dose augmentation in the stepwise challenge protocols. Recently, Cockcroft and Davis (2008) have recommended increasing the allergen concentrations by no more than doubling between dosing steps for safety reasons. These authors compared retrospectively the dose-response slopes of the last two doses of methacholine and allergen in the same individuals. The mean forced expired volume in 1 s (FEV_1) decrease at the second-to-last concentration of allergen was significantly lower than that seen for the second-to-last concentration of methacholine. However, the ratio of the last to

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second-to-last response (slope) was higher for allergen than for methacholine. A direct comparison of doubling and quadrupling allergen doses has not been performed.

We reviewed allergen challenges with quadrupling doses performed in our laboratory over the past 10 years that we considered positive. Inspired by Cockcroft and Davis (2008), we analyzed retrospectively our dosimeter allergen challenges.

11.2 Methods

In contrast to Cockcroft and Davis (2008) who used a tidal volume breathing method, the allergen was inhaled with 5 or 10 breaths (depending on the allergen) by an APSpro dosimeter (Jaeger, Würzburg, Germany) and a DeVilbiss 646 nebulizer (DeVilbiss Healthcare, Mannheim, Germany). Inhalations were performed as described by the ATS for methacholine challenges, with minor modifications (American Thoracic Society 2000; Merget et al. 2009). Ten-minute intervals were chosen between dose steps. The test was terminated if a fall of FEV_1 of at least 20% occurred within 30 min after allergen inhalation. After termination, another measurement was performed about 20–30 min after stopping the allergen inhalation. If a fall of FEV_1 between 15% and 19% was measured (near positive), spirometry was performed after another 10 min. Isolated late reactions were not included.

All spirometric maneuvers were performed according to the ATS and met reproducibility criteria (American Thoracic Society 1995). All subjects were without medication that might influence the test results. Inhalations were performed for the diagnosis of occupational asthma and approved by the Ethics Committee of the Ruhr University. Allergens were platinum salts (n = 7 tests; final dose range 175–700 ng), rhodium salt (n = 1; 36 ng), barn mites (n = 3; 1,125–18,000 ng protein), house dust mites (n = 3; 4,500–18,000 ng protein), α-amylase (n = 1; 616 ng protein), cow dander, and soapnut (n = 1 each; 348 and 2,814 ng protein).

11.3 Results

Seventeen tests in 13 subjects were considered positive. The mean age was 41 ± 14 years. The mean baseline FEV_1 was 95.5 (83.1–132.2)%predicted (Quanjer et al. 1993). The mean FEV_1 decreases 10 and 20–30 min after the last allergen dose were 26.7 ± 6.4 and 26.2 ± 6.5%baseline, respectively. The maximal decreases of FEV_1 after 10 and 20–30 min were not different either, amounting to 39% baseline after 10 min and 37%baseline, respectively. All positive reactions occurred after the second dose step or later. One subject preferred to inhale a short acting bronchodilator after the reaction had been documented. Terminal dose-response slopes did not differ between doubling (values from Cockcroft and Davis 2008) and quadrupling doses, nor were there any differences concerning the maximal response (Fig. 11.1). There was no difference between high and low molecular weight substances (data not shown). All but two positive reactions occurred after 10 min (two near positive reactions).

11.4 Discussion

The results of this retrospective analysis of routine challenge tests need to be interpreted with caution due to a low number of subjects. However, such data are difficult to obtain because they can be performed only with few occupational allergens that are water-soluble and there are often subjects' characteristics such as severe asthma, need for medication or unrelated diseases that represent

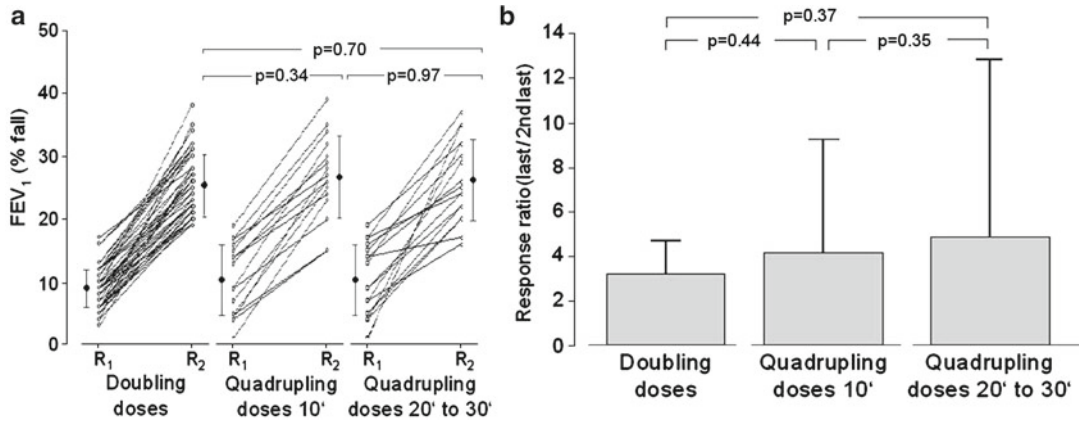

Fig. 11.1 (**a**) **Individual terminal dose-response-slopes** (means ± SD). A decline of FEV_1 from baseline after the second-to-last dose is designated R_1, after the last dose – R_2. FEV_1 values after doubling doses were provided by Cockcroft and Davis (2008) (n = 54). FEV_1 values after quadrupling doses (n = 17) are shown as 10 and 20–30 min after allergen inhalation; (**b**) **Mean ratios of FEV_1 decline defined as R_2 divided by R_1**. Comparisons were performed by paired and unpaired two-sided *t*-test

contraindications for the challenges. Prospective controlled studies are unlikely to be performed and a comparison between different methods may be questioned due to ethical reasons.

We are aware of the fact that a comparison of the present data with the literature data cannot be performed, because the methods differed in many respects. However, as no direct comparisons are available in the literature, we wanted to provide a rough estimate about the effects of increasing the dosing steps by more than doubling. Also, the different inhalation methods (tidal volume breathing method with doubling concentrations *vs.* dosimeter method with quadrupling doses) should not bias the comparison to a relevant degree, as dosing intervals, but not absolute doses, were compared.

A further weakness of this study is the lack of standardization with respect to the number of breaths during each inhalation step. This is due to the retrospective design of the study. By increasing breath numbers we applied a higher allergen dose, which was considered important for allergens that were less potent. However, we believe that this should not bias our results to a high degree.

Considering safety aspects, the maximal fall of FEV_1 after quadrupling doses was acceptable and was not different from Cockcroft and Davis' (2008) maximal decreases. Also complications such as severe asthma exacerbations needing medication did not occur. However, somewhat steeper dose-response slopes and higher standard deviations of the final dose-response slopes indicate that further increases of dosing intervals should not be considered.

Although the selection bias cannot be excluded, the study suggests that quadrupling doses may be performed without notable increase in risk of severe asthmatic reactions. This is accompanied by a noticable shortening of the test duration. It should be noted that in the present study near-positive reactions did not immediately entail the next inhalation step, but a further spirometry was performed after another 10 min for safety reasons. We assume that by shortening the test duration, physicians might choose lower starting doses and thus make allergen inhalation challenges even safer. However, further observations about the potential risk of dose augmentation in allergen challenges are needed, preferably in prospective studies in larger numbers of subjects.

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Chapter 12
Evaluation of Laryngopharyngeal Reflux in Pediatric Patients with Asthma Using a New Technique of Pharyngeal pH-Monitoring

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Abstract There is a debate about the association between asthma and gastroesophageal and/or laryngopharyngeal reflux (LPR). Pharyngeal pH-monitoring is a new technique that allows a physician to assess whether reflux passes the upper esophageal sphincter barrier. The aim of the study was to assess the prevalence of LPR in children with difficult-to-treat asthma. The present study was an open, prospective one. A total of 21 subjects of the mean age 12.7 years were enrolled in the study. All children were asked to fill out a Reflux Symptoms Index questionnaire and a 24-h pharyngeal pH monitoring was performed, using the Dx-pH Measurement System. The LPR was diagnosed in 13 (61.9%) children. There was a positive correlation between LPR diagnosis and the degree of asthma control. The LPR was more frequent in children treated with a higher than lower doses of fluticasone ($p = 0.019$, OR = 17.3) and in those using montelukast compared with non-users ($p = 0.008$, OR = 19.0). The mean Reflux Symptoms Index score was almost twice greater in children with LPR than in those without it (13.2 *vs*. 6.8, respectively, $p = 0.003$). We conclude that the prevalence of laryngopharyngeal reflux in children with difficult-to-treat asthma is substantial.

Keywords Asthma • Children • Laryngopharyngeal reflux • pH monitoring • Reflux symptoms index

12.1 Introduction

In children, gastroesophageal reflux disease (GERD) is defined as the passage of gastric contents into the esophagus, which causes troublesome symptoms and complications (Vandenplas et al. 2009). When the refluxate arises into the pharynx, the condition is often called pharyngeal or laryngopharyngeal reflux (LPR). Many studies, mainly observational, have demonstrated an association between asthma and GERD by esophageal pH-monitoring or pH-impedance. In a recent review assessing the extraesophageal symptoms of gastroesophageal disease in children, the prevalence of diagnosed asthma in children

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with GERD was 13.2%, compared with 6.8% in controls (Tolia and Vanndenplas 2009). In children with asthma, GERD is diagnosed in 19–65% of them (Debley et al. 2006; Barakat et al. 2006). The discrepancy in the results is probably related to the methodology used to identify GERD and different definitions of GERD and asthma used by the authors.

Patients with asthma are probably more predisposed to GERD than healthy people. The known predisposing factors include autonomic dysregulation, an increased pressure gradient between the thorax and the abdomen, altered crural diaphragmatic function, airway obstruction, medication used in asthma therapy and lifestyle (Harding and Sontag 2000). The mechanisms by which refluxate aggravates asthma are the following: (i) airway inflammation due to aspirated gastric contents, with damage to the upper airway epithelium resulting in the release of cytokines and adhesion molecules, (ii) airway hyper-responsiveness triggered by lower airway aspiration of minute amounts of acid refluxate that may aggravate asthma by increasing bronchomotor responsiveness to other stimuli, (iii) vagally mediated bronchial or laryngeal spasms, in which the decrease of pH in the esophagus is associated with an increase in airway resistance, and (iv) neurally mediated inflammation (Vandenplas et al. 2009; Harding and Sontag 2000).

To-date, a 24-h pH-monitoring is considered the gold standard for the diagnosis of GERD, but it is unable to detect non-acid refluxate. Despite the use of a dual-channel probe, it is still impossible to assess precisely the proximal extent of reflux. A more modern technique, pH-monitoring combined with multichannel, intraluminal impedance (pH-MII), allows to detect both acid and non-acid reflux episodes and also makes it possible to identify the nature (liquid, gas. or mixed liquid–gas) of the refluxate and the proximal extent of the reflux. The lack of normal ranges for children limits the value of this test in pediatrics. However, none of these techniques examine whether reflux really crosses the upper esophageal sphincter barrier, which is crucial in the pathogenesis of gastroesophageal reflux in asthma.

Pharyngeal pH-monitoring is a new technique that allows assessing whether the mechanisms mentioned above are really present in the reflux-asthma association. This technique has some advantages compared with classic pH-monitoring or pH-monitoring combined with MII. Firstly, pH-monitoring takes place in the pharynx, the most proper place for the diagnosis. Secondly, thanks to the flashing LED diode located at the tip of a probe, it can be easily placed in the oropharynx with no need of X-ray imaging or esophageal manometry. Thirdly, a novel pH sensor has been designed specifically to monitor pH in the pharynx. This sensor detects aerosolized or liquid acid, resists drying, and does not require contact with fluid or tissue for electrical conduction. The probe has a teardrop shape with the sensor oriented downward to avoid becoming covered with food or mucus. Finally, because of wireless signal transmission, the recorder may be up to 4 m from the patient and can be placed safely on a bedside table during the night. Although this technique is new, normal values have been well established in several studies (Sun et al. 2009; Chheda et al. 2009). The aim of the present study was to estimate the prevalence of laryngopharyngeal reflux in pediatric patients with difficult-to-treat asthma.

12.2 Methods

The protocol for this study was approved by the Bioethics Committee of the Warsaw Medical University in Warsaw, Poland. This was an open, prospective study to evaluate the frequency of laryngopharyngeal reflux in children with asthma. From April to September 2010, patients over 6 years of age with difficult-to-treat asthma (defined according to GINA 2009) (GINA 2009) diagnosed at the Department of Pediatric Pneumology and Allergy, were referred to the Department of Pediatric Gastroenterology and Nutrition, Warsaw Medical University in Warsaw, Poland for the evaluation of laryngopharyngeal reflux. A total of 21 subjects (13 males) of the mean age of 12.7 years (range 7–17 years) were enrolled in the study. All patients (or their parents) were asked to fill out a Reflux Symptoms Index (RSI)

questionnaire. The questionnaire assessed the severity (0 = no problem, 5 = severe problem) of the following nine symptoms: hoarseness or problems with one's voice, clearing one's throat, excess throat mucus, difficulty swallowing food, liquids or pills, coughing after eating or after lying down, breathing difficulties or choking episodes, troublesome cough, sensation of something sticking in one's throat or a lump in the throat, heartburn, chest pain, indigestion or stomach acid coming up (Belafsky et al. 2002).

12.2.1 Pharyngeal pH-Monitoring

The 24-h pharyngeal pH-monitoring test was performed using a Dx-pH Measurement System (Restech, San Diego, California), consisting of a disposable catheter-based probe (containing an antimony sensor and reference electrodes) that connects to a wireless transmitter and a separate data recorder, which periodically saves data to a removable memory card (SD). The special design of the probe allows it to function properly in the pharynx without drying; it is moisturized with water vapour from the exhaled air. The catheter was placed transnasally and positioned in the oropharynx (approximately 10 mm below the uvula) with visual confirmation using a light-emitting diode (LED) located on the tip of the probe. Patients were asked to maintain their normal daily activities or eating habits and to record meal periods, changes in body position (supine and upright) and chief complaints digitally by pressing buttons on the recorder and manually in a daily activity log.

The data from the card were transferred to a computer with the Restech Dx-pH DataView Lite analysis software installed. Each record was manually reviewed and compared with a paper log to remove errors and artefacts. Meal times with the 5-min pre- and postprandial periods were excluded from the analysis. An acid reflux event was defined as a drop in the pH level in the oropharynx below 5.0 in the upright and 5.5 in the supine position. Recordings were automatically analyzed with DataView software, which calculated the composite score (RYAN score) based on the percentage of time below baseline pH, the number of reflux episodes and the duration of the longest episode in each body position. According to the criteria proposed by DeMeester, an abnormal value in the RYAN score indicated a diagnosis of laryngopharyngeal acid reflux.

12.2.2 Sample Size

On the basis of the literature (Khoshoo et al. 2003; Teixeira et al. 2007) we estimated the mean prevalence of GERD in pediatric patients with asthma at 62% (confidence interval 56–68%). We used a sequential test to verify the null hypothesis that the prevalence of GERD in asthma is within this interval (power of the test 80%). The sequential test is a type of statistical method that allows assessing the prevalence of a disease without examining a large number of patients; however, the assessment is less precise. During the study, the result of each consecutive examination (LPR diagnosis or not) was put into the statistically generated program, which determined (after each patient) whether to continue the study.

12.2.3 Statistical Analysis

We performed a statistical analysis, considering the anthropometric parameters, spirometry, degree of asthma control, medications, reported symptoms (RSI), level of total IgE and variables of pH-metric measurements in two groups of patients: with and without laryngopharyngeal reflux. Anthropometric

differences between both groups of patients were tested with logistic regression and using the Mann–Whitney method. Akaike's information criterion was used as a measure of the fit of the model. The significance of the Dx-pH characteristics (22 variables) was investigated with a multiple hypothesis testing procedure based on a permutation method (Troendle 1995). Fisher's exact test was used in case of contingency tables with small expected frequencies. Results were regarded as statistically significant at $p<0.05$. Cohen's kappa coefficient was used as a measure of agreement between LPR diagnosis and RSI. The bias-corrected bootstrap (BCa) method was used to construct a 95% confidence interval for the regression coefficients. All data were analysed using R 2.2.1 version (www.r-project.org).

12.3 Results

Demographic data are shown in Table 12.1. Laryngopharyngeal reflux was diagnosed in 13 (61.9%) children, so the prevalence of LPR was between 56% and 68%. No association among LPR diagnosis and anthropometric data (sex, age, height and BMI) was found.

We found a positive correlation between LPR diagnosis and the degree of asthma control. Ten of the 13 (77%) LPR-diagnosed patients and only 1 of the 8 (12.5%) LPR-negative had their asthma at the fourth level of asthma treatment ($p=0.012$). There were no significant intergroup differences regarding the age of asthma diagnosis and the total IgE level. The analysis of correlation between LPR diagnosis and medications used showed that the LPR was more frequent in the users of higher than lower fluticasone doses ($p=0.020$, OR = 17.3) and in those using montelukast treatment ($p=0.008$, OR = 19.0).

The evaluation of Reflux Symptom Index revealed that the score >11 had no correlation with LPR diagnosis; the mean RSI score was almost two times higher in the LPR group (13.2 *vs*. 6.75, $p=0.003$). No specific symptom listed in the RSI was related to LPR diagnosis. Table 12.2 shows the details of RYAN scores and RSI scores. Additional analysis revealed that a combination of symptoms of difficulty swallowing, sensation of a lump or mass in the throat and heartburn or chest pain was almost 14 times higher in the LPR group (3.5 *vs*. 0.25, $p=0.001$). A cut-off value of RSI ≥2 for these three symptoms resulted in LPR diagnosis based on the RSI being compatible with the diagnosis based on pH-monitoring ($p=0.001$ using the Fisher test; Cohen's kappa coefficient 0.78, $p=0.001$).

Table 12.1 Characteristics of patients

	LPR (+)	LPR (−)	p
	(n = 13)	(n = 8)	CI95 (56%, 68%)
Age (year)	13.2 ± 3.06	12.1 ± 3.08	0.19
Sex (female/male)	9/4	4/4	0.62
Weight (kg)	47.8 ± 20.7	45.4 ± 18.7	0.94
Height (cm)	152.2 ± 15.7	152.5 ± 16.1	0.24
BMI (kg/cm^2)	19.8 ± 5.9	18.9 ± 4.4	0.97
Total IgE (U/mL)	352 ± 206	262 ± 82	0.89
Asthma			
Third level of control	3	7	0.012
Fourth level of control	10	1	
Medications			
Fluticasone 200 μg/day	3	7	0.019
Fluticasone 500 μg/day	9	1	
Montelukast	10	1	0.008

LPR (+) laryngopharyngeal reflux positive group, *LPR* (−) laryngopharyngeal reflux negative group

Table 12.2 RYAN score and Reflux Symptom Index score

	LPR (+)	LPR (−)	p
RYAN score			
Upright	22.2 ± 16.4	2.1 ± 0	<0.001
Supine	20.7 ± 19.2	3 ± 1.6	NS
RSI score			
n	10	8	–
Mean	13.2 ± 6.4	6.8 ± 3.6	0.003
Score >11	4	2	NS
Hoarseness or a problem with your voice	2.0	1.3	NS
Clearing your throat	2.5	1.4	NS
Excess throat mucous	1.3	1.1	NS
Difficulty swallowing food, liquids or pills	0.5	0	NS
Coughing after eating or after lying down	0.9	1.1	NS
Breathing difficulties or choking episodes	1.8	0.6	NS
Troublesome or annoying cough	1.2	1.1	NS
Sensations of something sticking in your throat or a lump in your throat	1.5	0	NS
Heartburn, chest pain, indigestion, or stomach acid coming up	1.5	0.2	NS

RSI reflux symptoms index

12.4 Discussion

The study demonstrates that the incidence of laryngopharyngeal reflux diagnosed by 24-h pharyngeal pH-measurement in children and adolescents with difficult-to-treat asthma lies between 56% and 68%; the incidence is higher than previously assessed.

The data regarding the role of gastroesophageal reflux or pharyngeal reflux in asthma are differential, but most studies have reported a higher prevalence of GERD in children with asthma compared with healthy controls (Debley et al. 2006; Chopra et al. 1995). According to a systematic review published in 2010, the estimates of the prevalence of GERD in children with asthma varies between 19% and 80%, giving a pooled, sample-size-weighted average prevalence of 22.8% (Thakkar et al. 2010). The authors found serious methodological limitations in previously published studies, of which only five had control groups. The variations in the results were probably related to the methodology used to identify GERD and to different definitions of asthma employed. Twelve of the studies measured esophageal pH (but only one included a control group), three studies included endoscopic evaluation, two studies used two different questionnaires, one study used scintigraphy, and one study used barium swallowing. The definition of asthma used was not reported in most of the studies; only five studies provided criteria for asthma diagnosis. Moreover, these studies varied according to age groups and timing in relation to the patients' symptoms. None of these studies directly assessed pharyngeal reflux. From the medical standpoint, evaluating the results of these studies could lead to confusion.

Thus far, there are only limited data to confirm the relationship between the presence of refluxate in the pharynx or larynx and asthma, mainly because of lack of proper diagnostic tools (Stapleton and Brodsky 2008). According to NASPGHAN/ESPGHAN (Vandenplas et al. 2009) recommendations, pH-monitoring is the gold standard in diagnosing GERD. The 24-h pH-monitoring procedure allows monitoring the pH level at 5 cm above the lower esophageal sphincter, but it can only register acid reflux episodes, whereas the non-acid episodes can cause some extraesophageal symptoms of GERD. Even the use of dual-probe pH-monitoring (the second channel is located above the upper

oesophageal sphincter) does not allow assessing the non-acid reflux episodes and the actual upward extension of a bolus. In the pediatric population, the proper location of the upper channel is often undone because of the varying, age-dependent length of the esophagus.

Regarding the unproven clinical utility of pH-monitoring in the detection of extraesophageal symptoms (including asthma) in GERD, there is a need for more sensitive and accurate techniques for defining proximal reflux in the esophagus. Pharyngeal pH-monitoring is a new technology that detects episodes of reflux in the pharynx and provides information about the correlation between episodes of reflux and symptoms. To-date, only a few studies evaluating extraesophageal symptoms of GERD using this technique have been performed, but the usefulness of pharyngeal pH-monitoring in adult patients with laryngopharyngeal symptoms has been established (Golub et al. 2009; Wiener et al. 2009; Friedman et al. 2011). Moreover, all studies have emphasized that the new catheter is easy to use and more comfortable because of the tip's location in the upper oropharynx (Stordal et al. 2006), which we confirmed in our pediatric population.

Our study revealed that the level of asthma control (intensity of treatment) is correlated with the prevalence of a pathological reflux. It conforms to the previously reported association between those two conditions (Stordal et al. 2006). The study shows that the Reflux Score Index was about twofold higher in patients with reflux than without it. However, a total score ≥11 was not consistent with a reflux diagnosis based on the RYAN score ($p = 0.51$). The lack of correlation between RYAN and RSI scores observed could be a result of the differences between adults and children, or even adolescents, and suggests the need to develop new symptom scores for younger age groups.

Our study evaluated the diagnostic value of a new, promising technique, pharyngeal pH-metry, in the work-up of two common childhood diseases. We chose a group of difficult-to-treat asthma patients because of the potential role of GERD in the pathogenesis of this common disease in the pediatric population. A limitation of the study is the lack of a control group. However, due to ethical issues it is very difficult to perform pharyngeal pH-metry in a group of healthy children. That is the reason why there is no normal value for different age groups, either for pH-monitoring alone or for pH-monitoring combined with impedance. The sample size was small, but it was similar to that in some other published studies (Sun et al. 2009) and the statistical methods were appropriately adjusted.

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

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Chapter 13
Latent Airway Hyperresponsiveness: A Phenomenon Bordering Bronchial Asthma Definition

Lubomir Legath, Slavomir Perecinsky, Marek Varga, Martin Orolin, Zoltan Tomori, and Jaroslav Legath

Abstract The basic features of bronchial asthma are dyspnea with wheezing and objectively confirmed obstructive respiratory disorder reversible after inhalation of bronchodilators. In stable intermittent bronchial asthma, these features are not present; therefore confirmation of asthma consists of the presence of bronchial hyperresponsiveness (BHR). In the present study, there were 902 bronchoprovocation tests performed for the verification of BHR. A significant criterium for BHR is a decrease of FEV_1 of 20% from the baseline level. Every test either positive or negative was finished with inhalation of four doses of salbutamol through a spacer. We obtained 675 bronchoprovocation tests negative and 227 positive. Among the 675 subjects with a negative test there were 49 subjects who after inhalation of salbutamol had an increase in FEV_1 of ≥20% above baseline. The bronchodilatatory response of these 49 subjects, makes one think about the so-called latent bronchospasm present already at baseline, limiting further constriction during bronchoprovocation tests. The detection of such latent bronchospasm in BHR increases the number of patients with an objectively confirmed bronchial asthma from 25.0% to 30.5%. Our results suggest that bronchodilation test be performed in all patients with suspected bronchial asthma to allow detecting latent bronchospasm as an initial stage of the disease.

Keywords Airway hyperresponsiveness • Bronchial asthma • Bronchoprovocation test • Bronchodilation • Latent bronchospasm

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13.1 Introduction

The basic features of bronchial astma are dyspnea with wheezing and objectively confirmed obstructive respiratory disorder reversible after inhalation of bronchodilators. In stable intermittent asthma these symptoms are not present. Therefore, confirmation of asthma consists of the presence of bronchial hyperreactivity (BHR), which is connected with eosinophilic and mastocytes inflammation of airways. BHR is defined as excessive narrowing of airways resulting from a significantly increased bronchoconstrictive response to various inhalation stimuli (Trigg et al. 1994). Besides inflammation, BHR represents a key element of bronchial asthma which is associated with the severity of the disease and is the target of therapeutic interventions (Grootendorst and Rabe 2004). BHR can be recognized as a bronchospasm caused by physical triggers or by chemical substances affecting the respiratory system and the whole organism and can be verified by bronchoprovocation test. Execution and interpretation of the bronchoprovocation test are well defined by a consensus of the European and American Medical Societies (AARC 2001; ATS 2000; Sterk et al. 1993). The test most often consist of histamine and methacholine challenges to cause bronchoconstriction by a direct effect on the effector cells of smooth muscles. In contrast, indirect stimuli acting through release of mediators from inflammatory cells, mostly mastocytes, and through neurons in response to stimulation due to osmolality changes cause contraction of bronchial smooth muscles (Joos et al. 2003). Direct tests of bronchial hyperreactivity, based on inhalation of bronchoconstrictive agents, are used most commonly and have greater sensitivity for the diagnosis of bronchial asthma. Indirect tests, on the other hand, in which broad spectrum of mediators is released including histamine, leucotriens, prostaglandins, acetylcholine and neuropeptides, have greater specificity (NHLBI/WHO 2010).

13.2 Methods

The study was performed in conformity with the Declaration of Helsinki for Human Experimentation and the protocol was approved by a local Ethics Committee.

There were 902 bronchoprovocation tests performed for verification of bronchial hyperreactivity in the pulmonary function lab of the Department of Occupational Medicine and Clinical Toxicology at the University Hospital of L. Pasteur in Kosice, Slovakia. The group studied consisted of 360 men and 542 women, mean age 40 (range 16–77 years). Subjects with absolute or relative contraindications for performing a test were not included in the group.

For verification of bronchial hyperreactivity, aerosol was generated by a jet mechanism in a standardized bronchoprovocation unit, which allows powerful, fast and reproducible application of aerosol to the respiratory system without contamination of external environment. Airflow stream generated by a compressor creates a satisfactory amount of respirable fraction of aerosol (output 1 ml in 1–3 min). In 235 cases, aerosol of methacholine was generated (acetyl-β-methylcholine chloride) in sequentially doubled concentrations (0.125, 0.25, 0.5, 1.0, 2.0, 4.0, 8.0, and 16.0 mg/cm^3), with a total cumulative dose of 230.9 μg. In 671 cases, aerosol of histamine (dichloride or biphosphate) was used in doubled concentrations (0.1, 0.2, 0.4, 0.8, 1.5, 3.0, 6.0, and 12.0 mg/cm^{-3}), with a total cumulative dose of 172.8 μg. According to the international guidelines presented by ERS and ATS, a significant criterium for the verification of bronchial hyperreactivity is a decrease of FEV_1 (forced expiratory volume in 1 s) of 20% from the baseline level. An example of a positive bronchoprovocation test is shown in Fig. 13.1a. The test was terminated in case of both positive and negative reactions, i.e., after reaching the highest concentration of a provocation substance. Every test either positive or negative was finished with a so-called ‘lysis inhalation’ – of 2 or 4 doses of

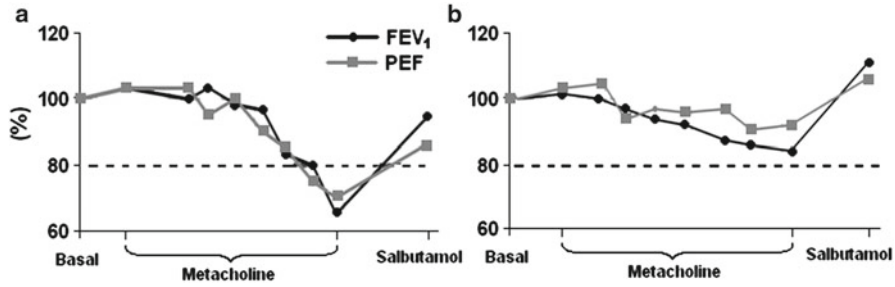

Fig. 13.1 A schematic display of a typical bronchoprovocative test. **(a)** Positive result – a decease in FEV_1 and PEF of >20% off baseline in response to inhalation of a bronchoconstrictive mediator; the parameters remaining below baseline after a bronchodialator given at end-test; suggestive of the existence of asthma; **(b)** 'spuriously' negative result – less than 20% decrease in FEV_1 and PEF off baseline, but >20% bronchodilatory rebound overpassing baseline after a bronchodialator given at end-test; suggestive of a degree of pretest existing bronchospam and thus of latent asthma

salbutamol through a spacer. We considered the tests as 'truely' positive and being suggestive of the existence of asthma, when there was a decease in FEV_1 of >20% off baseline in response to a bronchoconstrictive mediator; which did not revert to the over-baseline-level after successive application of salbutamol at end-test.

13.3 Results

We recorded 675 negative and 227 positive test results. In a group with negative results of the bronchoprovocation test, the curve of FEV_1 values did not decrease by >20% even after the highest cumulative doses of methacholine. However, FEV_1 tended to decrease continuously up the last points corresponding to the highest concentrations of the mediator. Administration of a β-adrenergic agent, in turn, led to an increase of FEV_1 which exceeded the baseline level (Fig. 13.1b). Such a curve represents a gradually decreasing downward trend in FEV_1 after administration of increasing doses of inhalant methacholine. In effect, dynamic pulmonary function parameters did not fall below the required 20% off baseline for a bronchoprovocation test to become positive. However, there was an apparent bronchodilating effect of a β-adrenergic mimetic.

For further analysis, from among the 675 subjects with negative tests results, we sorted out those who did not have a decrease of FEV_1 by ≥20% of baseline after the highest concentrations of a mediator, but whose FEV_1 increased by ≥20% after the subsequent inhalation of a β_2-adrenergic mimetic. We found a group of 49 subjects, 17 men and 32 women, mean age 39 (range 18–68 years) who manifested this feature. Such a positive bronchodilatory effect, in otherwise negative bronchoprovocation test, allows assuming the presence of so-called latent hyperreactivity or latent readiness for bronchospasm. The acceptance of this seemingly reasonable assumption would increase the number of subjects with bronchial hyperreactivity from 25.0% to 30.5%, i.e., with objectively confirmed bronchial asthma in the cohort studied (Fig. 13.2).

As a typical example we can present a 50-year old non-smoker with a history of paroxysmal dyspnea at night, chest wheezing, and intermittent coughing with expectoration of mucoid sputum. At admission he complained of difficulty in breathing, but physical examination was unremarkable, with no spastic symptoms over the lungs. After inhalation of methacholine in gradually increasing concentrations from 0.125 to 16.0 mg/ml (highest concentration used) we did not observe a 20% decrease of FEV_1 off baseline. However, after inhalation of four doses of a β-adrenergic agent we

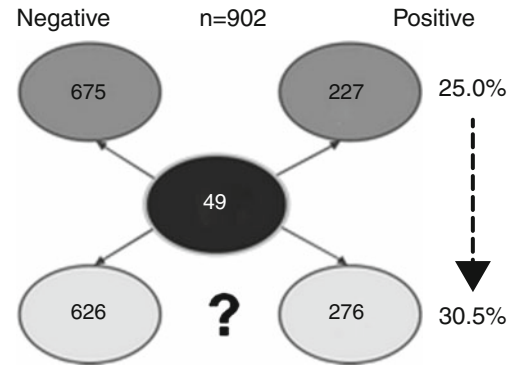

Fig. 13.2 Latent bronchospasm found in bronchoprovocation tests increases the true number of patients with bronchial hyperreactivity and thus with a suspicion of early stage of asthma

found an immediate significant increase of FEV_1 by 28%, i.e., which overpassed the baseline value; suggesting the elimination of bronchospasm provoked not only by inhalation of methacholine but also of its latent component present during the control conditions. In this patient, PEF was on the lower side of normal values, with occasional variable decreases below the normal level. Fiberoptic bronchoscopy was performed in the patient, with excision and subsequent histological examination. Severe inflammatory changes were found in histological specimens, with numerous eosinophilic leukocytes, focal signs of squamous metaplasia, and mild dysplasia, which all indicate the presence of chronic inflammation. In this patient, a history of dyspnea with chest wheezing and a negative bronchoprovocation test, with a decrease of FEV_1 only by 14%, indicate a preexisting latent bronchospasm. On the other hand, a positive bronchodilatory effect (increase of FEV_1 by 28%), significant variability in PEF monitoring, measured four times daily, the presence of eosinophils in induced sputum, and histological examinations of bronchial mucosa, confirmed the diagnosis of pesticide induced bronchial asthma.

13.4 Discussion

The major finding of the present study was that in a group of subjects with negative results of a bronchoprovocation test, there were a number of them with a significant bronchodilatory effect of a β-adrenergic agent, overshooting the baseline level of FEV_1. This result points to the possible presence of a latent bronchospasm, which confirms bronchial hyperreactivity and supports the diagnosis of bronchial asthma despite the negative bronchoprovocation test. This reasoning was confirmed by a bronchoscopy and bronchial biopsy with eosinophilic infiltration in the presented patient case. Therefore, the authors of the present article submit that such latent bronchospasm, present already during the control conditions, causes that the bronchi are not no longer able to react in a constrictive way to subsequent bronchoconstrictor challenge. The observed reactions of FEV_1 consisting of a slight decrease at the highest concentrations of histamin or methacholine and then a bronchodilating effect of salbutamol after the end of a bronchoprovocation test may in fact detect the presence of a latent bronchial hyperreactivity. Such patients may have a high potential for later development of typical bronchial hyperreactivity with asthma and inflammation. Therefore, lung function in such deserves to be carefully followed.

We conclude that a low, gradual decrease of FEV_1 in response to bronchoprovocation with histamin or methacholine, and particularly an appreciable bronchodilatory rebound of FEV_1 of >20% after the use of a β_2-adrenergic agent toward the end of a bronchoprovocation test, indicate a latent bronchospasm which is suggestive of an early stage of bronchial asthma. The results of this study

point to the importance of performing a bronchodilation trial at the end of bronchoprovocation test also in patients who have normal results of dynamic lung functional parameters. A bronchodilation trial in patients suspected of having asthma may allow detecting latent bronchospasm, a feature of early asthma, and may help manage the disease.

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

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Chapter 14
Impact of Daytime Sleepiness on Rehabilitation Outcome in the Elderly

H. Frohnhofen, R. Popp, K. Frohnhofen, and S. Fulda

Abstract Daytime sleepiness (DS) is associated with poor health, impaired physical functioning, as well as somatic and psychiatric morbidity. The impact of DS on functional outcome in the elderly is unknown. We investigated whether observed daytime sleepiness in geriatric patients with moderate to severe functional impairment was associated with functional clinical outcomes. We addressed the issue by determining the impact of observed daytime sleepiness, by means of the Essener Questionnaire of Age and Sleepiness (EQAS), on improvement in functional status – measured by the Barthel ADL Index – among disabled geriatric in-patients. We included 129 patients, 28 (22%) were male and 101 (78%) were female. Sleepiness according to EQAS scale was absent in 27 (21%) patients, mild in 71 (55%) patients and moderate to severe in 31 (24%) patients. The three patient groups did not differ in the Barthel ADL Index (BI) on admission or co-morbid conditions. Geriatric treatment was comparable across groups. Improvement in the BI of at least 1 standard deviation (SD) occurred in 23/27 (85%) of subjects without sleepiness, in 53/71 (75%) of subjects with mild to moderate sleepiness and in 15/31 (44%) of subject with severe sleepiness ($p < 0.01$). BI increased at least 2 SD in 20/27 (74%), 38/71 (54%) and 11/31 (35%) individuals, respectively ($p<0.02$). We conclude that the daytime sleepiness predicts a poorer functional recovery rate in older patients during geriatric in-hospital rehabilitation. Furthermore, we found a significant association and a dose response relationship between severity of daytime sleepiness and improvement in Barthel ADL Index.

Keywords Barthel index • Daytime sleepiness • Elderly • Essener questionnaire of age and sleepiness • Geriatrics

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14.1 Introduction

Functional and cognitive decline is emerging as one of the great health threats in aging Western society (Bergman et al. 2007; Bortz 2002). Life expectancy has significantly increased over time but concurrently the rate of functional impairment has increased in the older population. In this context, functional impairment and disability can be seen as a limitation due to an illness resulting in decrements in the area of cognition, communication, mobility, self care, and activities of daily living (ADL) (Avlund et al. 2004; Chasens et al. 2007). Importantly, subjects with functional impairment are at high risk for negative health outcomes such as falls, dependency in daily living, nursing home placement, and mortality (Dam et al. 2008; Luppa et al. 2010). Today, one of the pivotal goals of geriatric medicine is to ensure daytime functioning and to rehabilitate daytime functioning in older subjects with disability or dependency (Judge et al. 1996).

Therefore, it is crucial to identify modifiable factors that have a negative impact on daytime functioning. Daytime sleepiness is such a factor (Asplund 1966; Goldman et al. 2008; Gooneratne et al. 2003, 2011; Onen and Onen 2010; Üstün and Kennedy 2009), as adequate alertness is necessary for well-being and performance (Cluydts et al. 2002). Depending on the definition, epidemiologic studies have shown that the prevalence of daytime sleepiness varies from 10% to over 30% in the adult population and increases with age (Foley et al. 2007; Ohayon and Vecchierini 2002; Tsuno et al. 2007; Whitney et al. 1998).

Daytime sleepiness is currently defined as "the inability to stay awake and alert during the major waking episodes of the day, resulting in unintended lapses into drowsiness or sleep" (American Academy of Sleep Medicine 2005). Daytime sleepiness varies in severity but becomes pathological when sleepiness occurs at inappropriate times or in atypical situations. Excessive daytime sleepiness (EDS) refers to severe sleepiness for at least 3 month. Several subjective tools like questionnaires and objective tools such as physiological measures and performance tests are available (Johns 1991). However, no single gold standard for assessing sleepiness is established at present (Cluydts et al. 2002; American Academy of Sleep Medicine 2005).

Most tools used for the assessment of EDS focus on middle aged groups, lack normative data for the elderly population, and are not elderly-specific. In particular, they do not account for cognitive decline or the specific needs and life conditions of elderly people (Frohnhofen et al. 2009; Fulda and Popp 2011). Of note, the evaluation of EDS in older subjects is additionally compromised, as the relationship between daytime sleepiness and low daily activity due to physical impairment is mutual. A low level of daily activity predisposes to daytime sleepiness, since physical activity is a factor that enhances alertness and vice versa (Cluydts et al. 2002).

Epidemiological studies are not able to unravel this issue. So far, there are no prospective studies available with interventions and functional outcome measures in older subjects with sleepiness. The few studies that have been conducted in stroke victims with sleep disordered breathing found a negative impact of prevalent sleep apnea on rehabilitation outcomes (Good et al. 1996; Cherkassky et al. 2003). However, sleepiness was not a major focus in those studies.

The aim of the present study was to determine prospectively whether observed daytime sleepiness is associated with an unfavourable functional outcome in a large sample of carefully characterized geriatric in-patients. To that end, we used the Barthel ADL Index (BI) to assess geriatric patients with moderate to severe functional impairment in basic activities of daily living (ADL) at admission and measured improvement in functional outcome by a gain in BI after standard care.

14.2 Methods

14.2.1 Subjects

The subjects for this study were recruited consecutively during a time period of 7 months in the year 2010 from patients admitted for geriatric rehabilitation. Patients with permanent confinement to bed, inability to cooperate or communicate, patients permanently dependent on a wheel chair, and patients who refused to participate were not included into the study. Patients were eligible, if they had a moderate to severe impairment of the activities of daily living and were able to communicate sufficiently. Individuals or next-of-kin had to give written informed consent. The protocol documents were approved by the institutional review board.

Data on age, gender, smoking, co-morbidities, and geriatric assessment were collected. We recorded arterial hypertension, heart failure, atrial fibrillation, previous stroke or cancer, chronic obstructive pulmonary disease (COPD), dementia, and diabetes mellitus as important co-morbidities. Cognitive status was assessed by means of the mini-mental-state-examination (MMSE), a cut-off value of 24 or less was regarded as indicative of cognitive impairment (Folstein et al. 1975). Overall muscle strength was measured through handgrip strength (Roberts et al. 2011). Depressed mood was assessed by the WHO-5 Scale, a valid tool that comprises a range from 5 to 25. A cut-off value of less than 12 indicates emotional impairment (Diener 2000). The instrumental activities of daily living were assessed by means of an IADL scale (Lawton and Brody 1969) that has a range from 0 to 8. A cut-off value of 6 indicates problems in living independently.

14.2.2 Assessment of Daytime Sleepiness

Daytime sleepiness was evaluated by means of the Essener Questionnaire of Age and Sleepiness (EQAS). The EQAS is a newly developed and validated observational tool (Frohnhofen et al. 2010). It overcomes limitations of other standard sleepiness scales like the Epworth Sleepiness Scale (ESS) (Frohnhofen et al. 2009) that do not take into account the specific needs, cognitive decline or life conditions of elderly people (Fulda and Popp 2011). The questionnaire and user scoring instructions are freely available and can be downloaded on the homepage of the German Sleep Society (DGSM; www.charite.de/dgsm/dgsm/fachinformationen_frageboegen_efas.php). Subjects are observed by caregivers for at least 1 week. In short, the observer notes periods of sleepiness during the day and rates frequency and severity according to the instructions provided with the EQAS. The overall EQAS score is based on the frequency and severity of sleepiness symptoms. The score varies between 0 and 12 points. Zero points represent no daytime sleepiness and a score above 4 indicates severe daytime sleepiness (Frohnhofen et al. 2010). The personnel evaluating daytime sleepiness of the participants were unaware of the aim of the study.

14.2.3 Assessment of Functional Outcome

We used the Barthel ADL Index (BI) for the assessment of functional status and rehabilitation outcome. Measurements were undertaken on admission and prior to discharge by nurses unaware of the aim of this study. The BI is an ordinal scale that measures performance in basic activities of daily living (ADLs) and mobility (Mahony and Barthel 1965). It measures independence and help needed with the following ten activities: bowel control, bladder control, personal hygiene, toilet transfer,

bathtub transfer, feeding, and dressing, wheelchair transfer, walking as well as ascending and descending stairs. BI scores range from zero to 100 points. A higher score is associated with a greater likelihood of being able to live at home with a certain degree of independence. The BI has demonstrated high test re-test reliability (0.89) and inter-rater reliability (0.95). There is also a high correlation (0.74–0.8) with other measures of physical disability (O'Sullivan and Schmitz 2007). In order to avoid floor and ceiling effects of the BI that could obscure changes of the BI (van der Putten et al. 1999), only subjects with a BI score between 10 and 35 at the time of admission were eligible.

14.2.4 Statistical Methods

Variables were checked regarding assumptions underlying the use of parametric and non-parametric statistics, and analyzed accordingly. Measures were summarized as means ± SD. The alpha-level of significance was set at 0.05 (two-tailed). Analyses were performed using SPSS version 15.0 statistical software (SPSS Inc., Chicago, IL, USA).

14.3 Results

From a total of 145 eligible patients, 129 (89%) could be included. Six patients or their relatives did not agree to participate and ten patients had missing data. Twenty eight (22%) individuals were male and 101 (78%) individuals were female. Table 14.1 describes the main characteristics of the whole study population and of the three subgroups with different degrees of daytime sleepiness defined by means of the EQAS.

As can be seen from Table 14.1, patients were very old, had only mild cognitive impairment, and had moderate to severe disability according to the selection criteria. The prevalence of mild to moderate sleepiness was 55% and 24% of patients showed severe sleepiness. The three groups did not differ in the results of the geriatric assessment except for IADL scores. BI on discharge was significantly lower in patients with severe sleepiness as compared to patients without sleepiness.

Table 14.1 Basic data and geriatric assessment results for the complete sample and for each of the three subgroups stratified by the level of daytime sleepiness

	Total sample (n = 129)	EQAS 0 (n = 27)	EQAS 1–4 (n = 71)	EQAS > 4 (n = 31)	p
Age (year)	84 ± 7	83 ± 6	84 ± 7	84 ± 7	n.s.
Male (n/%_)	28/22	3/11	14/20	11/35	n.s.
Height (cm)	166 ± 9	169 ± 9	165 ± 9	170 ± 9	n.s.
Body weight (kg)	68 ± 16	67 ± 15	64 ± 14	66 ± 14	n.s.
BMI (kg/m^2)	24 ± 8	27 ± 7	24 ± 7	24 ± 8	n.s.
Handgrip Strength (kg)	11 ± 8	15 ± 10	11 ± 7	10 ± 7	n.s.
BI Admission (0–100)	33 ± 8	35 ± 7	32 ± 8	34 ± 9	n.s.
BI Discharge (0–100)	54 ± 23	68 ± 21	52 ± 21	45 ± 22	<0.001
IADL (0–8)	2 ± 2	3 ± 3	2 ± 2	1 ± 1	<0.02
MMSE (0–30)	24 ± 6	25 ± 5	24 ± 6	22 ± 6	n.s.
WHO-5-Q (5–25)	9 ± 7	6 ± 5	11 ± 7	8 ± 5	n.s.
Hospital stay (days)	32 ± 20	26 ± 17	33 ± 19	34 ± 26	n.s.

Data are means ± SD; p refers to between-group comparison.
EQAS Essen Questionnaire of Age and Sleepiness, *BMI* Body Mass Index, *BI* Barthel ADL Index, *IADL* Instrumental Activities of Daily Living, *MMSE* Mini-Mental-State Examination, *WHO-5-Q* World Health Organisation-5-Questionnaire

Table 14.2 Co-morbid conditions according to presence and severity of observed daytime sleepiness

	Total sample (n = 129 n/%)	EQAS 0 (n = 27 n/%)	EQAS 1–4 (n = 71 n/%)	EQAS >4 (n = 31 n/%)	p
Hypertension	106/82	20/74	61/86	25/81	n.s.
Heart failure NYHA III-IV	17/13	1/4	11/15	5/16	n.s.
Atrial fibrillation	33/26	6/22	17/24	10/32	n.s.
Previous myocardial Infarction	21/16	1/4	3/4	3/10	n.s.
Previous stroke	3/2	0/0	3/4	1 3	n.s.
Dementia	34/26	6/22	21/30	7/23	n.s.
COPD	23/18	2/7	16/23	5/16	n.s.
Diabetes mellitus	25/19	6/22	14/20	5/16	n.s.
Previous cancer	16/12	2/7	9/13	5/16	n.s.

NYHA New York Heart Association clinical scale for the assessment of the severity of heart failure, *COPD* Chronic obstructive pulmonary disease

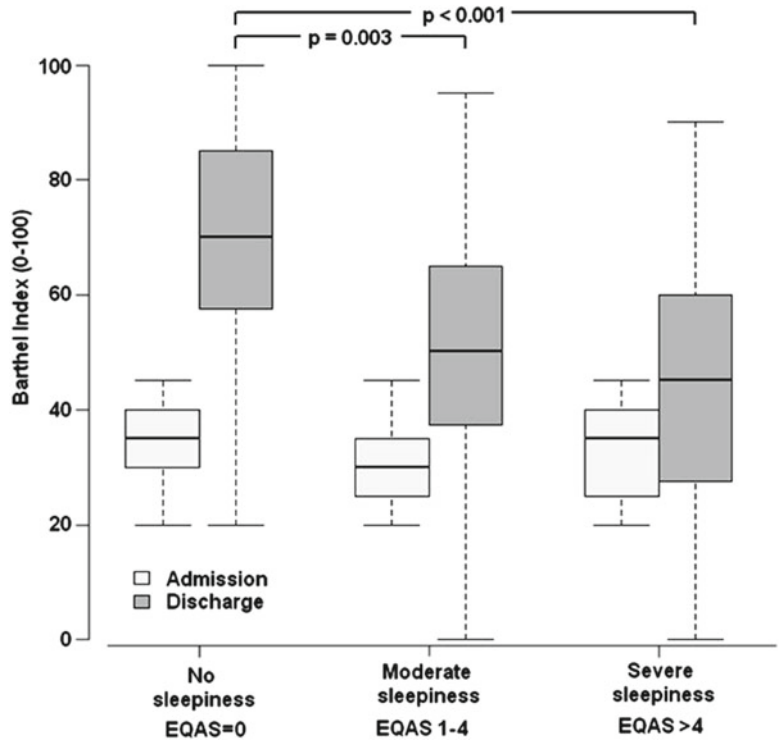

Fig. 14.1 Barthel ADL Index on admission and discharge according to the presence of daytime sleepiness as measured by the Essener Questionnaire of Age and Sleepiness (EQAS)

Table 14.2 presents co-morbid conditions of the complete sample and the three subgroups differing in daytime sleepiness. Overall, there was a high frequency of co-morbidities, typical for such a sample of geriatric in-patients. Subgroups did not differ significantly with regard to the frequency of single co-morbid conditions. All participants received the same amount of physiotherapy and occupational therapy with at least two treatment units of 30 min each per day. Intensity of treatment did not differ between groups.

Figure 14.1 shows the BI measurement on admission and discharge. BI measurements did not differ significantly on admission because of the inclusion criteria. However, the gain in BI differed

significantly between groups. Increases in BI were substantial in individuals without observed daytime sleepiness (EQAS 0) and lowest in those with severe sleepiness (EQAS >4). The proportion of subjects with a gain in BI of at least 1 SD (based on the total sample) of BI on admission was 23/27 (85%) in subjects without sleepiness, 53/71 (75%) in subjects with mild to moderate sleepiness and 15/31 (44%) in subject with severe sleepiness ($p<0.01$). A gain of the BI of at least 2 SD was observed in 20/27 (74%), 38/71 (54%) and 11/31 (35%) individuals, respectively ($p<0.02$).

14.4 Discussion

Our major finding was that the observation of daytime sleepiness predicted a poorer functional recovery rate for older patients during geriatric in-hospital rehabilitation. We found a significant negative association between the severity of daytime sleepiness and the improvement in Barthel ADL Index. Importantly, the subjects with different degrees of daytime sleepiness did not differ according to functional impairment on admission, co-morbid conditions, and intensity of treatment. This considerably strengthens the assumption that the observed changes in the BI are attributable to daytime sleepiness.

Furthermore, we also found a dose-response relationship between daytime sleepiness and the improvement in BI. These findings give some evidence towards the speculation of a causal link between sleepiness and improvement in daytime functioning. However, prospective randomized interventional studies are required to explore this question.

Our results correspond to the findings in the literature. In a cardiovascular health study, Whitney et al. (1998) showed that daytime sleepiness correlated with sedentary lifestyle and limitations in activity in the 4,578 participants. Likewise, Stenholm et al. (2010) demonstrated that excessive tiredness influenced measured and self reported mobility outcomes in 2,825 participants. Gooneratne et al. (2003) found that in elderly subjects (>65 years) functional status was significantly impaired in subjects with daytime sleepiness. However, assessments were done by self reports and analysis was conducted retrospectively.

In addition, several studies by Avlund and colleagues found consistent associations between tiredness and daytime functioning (Avlund et al. 2001, 2002, 2003, 2004). However, their definition of tiredness in these studies was more similar to exhaustion. Since exhaustion is a core criterion of frailty (Fried et al. 2001; Schultz-Larsen and Avlund 2007) those studies may have included frail rather than sleepy subjects. In contrast to the above mentioned studies, Hoch et al. (1992) could not demonstrate that sleepiness had an impact on functional status, when younger and older healthy subjects were compared. Of note, in that small study self reported sleepiness was rather mild.

Our study has several strengths. First, the analyses included the objective measurements of functional status (Mahony and Barthel 1965) and daytime sleepiness (Frohnhofen et al. 2010). The application of such a validated observational scale for the measurement of sleepiness overcomes the problems of misperception and misreporting of symptoms, well known obstacles in geriatrics (Frohnhofen et al. 2009). Second, the measures were carried out by different members of the staff, who were all unaware of the aim of this study. Therefore, bias should be minor. Third, the patients did not differ in co-morbidities and functional status on admission. Thus, the differences in improvement of functional outcome can be attributed to differences in sleepiness. Forth, we included only patients with moderate to severe functional impairment on admission. This inclusion criterion obviated ceiling and floor effects of functional measures and allowed us to show clinically significant differences in outcome.

The study has also some limitations that warrant discussion. First, by definition the EQAS requires that patients must be observed for at least 1 week. Therefore, appraisal of sleepiness is not possible in subjects who live alone or who do stay shorter periods of time. Second, the definition of sleepiness

through the EQAS may differ from that used in other studies (Cluydts et al. 2002). Therefore, results cannot be compared directly. However, the tool we used is validated for older subjects and captures trait-sleepiness objectively. Furthermore, it precludes the problems resulting from misunderstanding of a questionnaire or misperception of symptoms that can be found in older persons (Fulda and Popp 2011). Third, we included only very old in-hospital patients. Therefore, results only apply to such a subgroup of older individuals and cannot be generalized to the community-dwelling elderly. Forth, we did not search for the causes of daytime sleepiness. Several diseases like sleep apnea or restless legs syndrome must be considered. However, such an approach was beyond the scope of this study.

In summary, we have shown that in a carefully characterized sample of geriatric patients the presence of daytime sleepiness predicted a poorer recovery. Further studies with a larger number of patients are warranted to substantiate these findings. Future research will need to place a greater emphasis on elucidating the risk factors and the causes of daytime sleepiness in the elderly in order to determine whether therapy directed at these factors can improve sleepiness and the resulting functional consequences.

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

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Chapter 15
Pulmonary Physiotherapy in Patients with Bronchial Asthma

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Abstract In the present study we investigated the effectiveness of a 3-month breathing exercise program in patients with mild-to-moderate asthma, as assessed from spirometric indices. The study group consisted of 28 asthma patients (mean age of 43 years). The physiotherapy program consisted of 45-min exercise sessions, performed twice a week for 3 months. We measured the flow-volume indices (FEV_1, FVC, PEF, MEF_{50}) before and after the exercise sessions at the beginning and end of the physiotherapy program. In addition, the patients measured their personal best peak expiratory flow (PEF). We found no significant changes in spirometric indices before and after an exercise session either at the beginning or end of the physiotherapy program, although there was a tendency for lower values after the exercise sessions at both beginning and end of the physiotherapy program. There was a significant decrease in PEF after an exercise session at the beginning of the physiotherapy program; this decrease lost significance after completion of the physiotherapy program. However, PEF values were greater both before and after the exercise sessions at the end of the physiotherapy program compared with the corresponding sessions before the program. We conclude that the breathing exercise program employed in the study failed to appreciably improve lung function in asthmatic patients. However, there was no asthma exacerbations observed during the conduction of breathing exercise program, which underscores the need for pulmonary rehabilitation in asthma treatment.

Keywords Breathing exercise • Bronchial asthma • Peak expiratory flow • Pulmonary rehabilitation • Spirometry

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15.1 Introduction

Bronchial asthma is one of the most frequent chronic inflammatory disorders of airways and constitutes a major social problem, since it increases healthcare cost and limits patients' quality of life (Accordini et al. 2006; Lindberg et al. 2002). The incidence and prevalence of asthma varies even within the same country and it depends on the age of the population studied, ethnicity, financial status, and on the criteria used for diagnosis. There has been an increase in the number of atopic asthma cases over the last century. At the beginning of twentieth century less than 1% of population had allergic diseases, whereas in the 1950s that rate increased to 3–5% and in the 1960s it reached 5–10% (Rabe et al. 2000).

Bronchial asthma is characterized by increased hyperresponsiveness of airways to various stimuli, which causes relapsing episodes of shortness of breath, wheezing and coughing, mainly at night time and in the early morning hours. Bronchial tree hyperactivity is more common in winter (14.8%) than in summer (5.9%). There are risk factors facilitating asthma development, mainly coming from the environment, such as exposure to aeroallergens, air pollutants, nicotine smoke, and air conditioning, but also deficiency of vitamins, high protein diet, or diet containing inadequate amounts of omega-3 fatty acids may foster asthma. The airflow limitation observed in asthma is associated with an exacerbation of the underlying, symptom-free chronic inflammation of bronchioles, leading to remodeling of airway walls. The resulting structural changes seem to affect sensory information from nerve endings in the airways, which may constitute motor hyperactivity of bronchial smooth muscles (Bousquet et al. 2001; GINA 2002, 2010; Vilsvik et al. 2001; Yeatts et al. 2003). Consequences of bronchial narrowing and obstruction include impaired respiratory function. The disturbance in gas exchange resulting from unfavorable conditions of ventilation and its neural regulation leads to oxygen deficit, which, in turn, limits the patients' physical capacity and quality of life (Groneberg et al. 2004; Menz et al. 2007; Stanton et al. 2008).

The main aim of pulmonary rehabilitation in asthma is to improve the patients' quality of life and to lower the intensity of fear and anxiety associated with breathlessness. Pulmonary physiotherapy, along with pharmacological treatment, comprises the essential element of medical care for bronchial asthma and it helps to alleviate the intensity of symptoms and to reduce the consequences of the disease. The primary focus of physiotherapy is to teach patients effective expiration techniques, diaphragmatic breathing, and to strengthen abdominal muscles (Burianova et al. 2008; Menz et al. 2007). In the present study we set out to verify the effectiveness of a 3-month program of breathing exercise in improving lung function, assessed from spirometry, in patients with mild-to-moderate asthma.

15.2 Methods

The study was performed in accordance with the Helsinki Declaration for Human Experimentation and the protocol was approved by a local Ethics Committee. The study group consisted of 28 bronchial asthma patients (F/M-3/25; mean age of 43 years, mean body mass of 62.5 kg, mean body height of 164.2 cm, mean BMI of 23.1 kg/m^2). The patients were treated at the outpatient Regional Ambulatory of the Allergy Clinic in Katowice, Poland. The physiotherapy program consisted of 45-min exercise sessions, performed twice a week for the duration of 3 months under the supervision of a physiotherapist, with a recommendation of continual home breathing exercise. The program consisted of breathing exercises of moderate intensity, teaching of expiration techniques such as 'pursed lip breathing' and diaphragmatic breathing in various body positions with progression to walking. The exercises aimed at relaxation of accessory inspiratory muscles, enhancing the removal of air from lungs and the work

of the diaphragm, increase in abdominal muscles strength, and improvement of coughing effectiveness. Special attention was paid to teaching the proper breathing rhythm (relaxed inspiration and prolonged expiration). Throughout the physiotherapy program, the patients were taking their regular medications as prescribed by physicians.

At the beginning and end of the 3-month physiotherapy program, before and after the 45-min exercise sessions, we measured the flow-volume-loop indices: FEV_1, FVC, PEF, and MEF_{50} (where FEV_1 - forced expiratory volume in 1 s, FVC-forced vital capacity, PEF-peak expiratory flow, MEF_{50} - mid expiratory flow at 50% of FVC), with the use of a Lung Test-1000 spirometer. The patients were told to perform maximal forced expiration through a mouthpiece with nose clip in place, immediately after performing maximal inspiration. The test was done in the resting sitting position. The data were in the absolute values and as the percentage of predicted values for subjects of similar anthropometric characteristics. Additionally, the patients were instructed to measure their personal best PEF, with the use of their personal peak flow meters. The PEF measurement was performed before spirometry tests to avoid intensification of airway obstruction caused by forced exhalations. For all measurements, three trials were performed and the best of the three was selected to further analysis.

Data are given as means ± SD. Normality of data distribution was checked with the Wilk-Shapiro test. A *t*-test for dependent variables was used to compare differences between the values of individual indices before and after an exercise session and at the beginning and end of the physiotherapy program. A $p<0.05$ was considered to represent statistical significance. All statistical analyses were performed using a commercial Statistica package (v. 6.0).

15.3 Results

The results of lung function indices are presented in Table 15.1. We observed no significant changes in spirometric indices recorded before and after an exercise session either at the beginning or end of the 3-month physiotherapy program, although there was a consistent tendency for lower values after the exercise sessions at both beginning and end of the physiotherapy program.

There was a significant decrease in the PEF value after an exercise session at the beginning of the physiotherapy program; the decrease became insignificant after completion of the physiotherapy program (Table 15.2). However, PEF values were greater both before and after the 45-min exercise sessions at the end of the 3-month physiotherapy program compared with the corresponding sessions before the physiotherapy program.

Table 15.1 Lung function indices in 28 asthmatic patients before and after a single 45-min breathing exercise session at the beginning and end of 3-month physiotherapy program

	Beginning 45-min exercise			End 45-min exercise	
	Before	After	% Predicted	Before	After
FEV_1 (l)	2.6 ± 0.7	2.5 ± 0.7	81.9 ± 14.9	2.6 ± 0.7	2.5 ± 0.7
FVC (l)	3.2 ± 0.7	3.1 ± 0.7	85.8 ± 13.6	3.2 ± 0.7	3.1 ± 0.6
PEF (l/s)	6.1 ± 1.8	5.9 ± 1.9	85.7 ± 14.7	6.1 ± 1.9	6.0 ± 1.7
MEF_{50} (l/s)	3.0 ± 1.5	2.9 ± 1.4	68.9 ± 26.8	3.0 ± 1.5	2.9 ± 1.4

Values are means ± SD
There were no significant differences noted

Table 15.2 Peak expiratory flow (PEF) in 28 asthmatic patients before and after a single 45-min breathing exercise session at the beginning and end of 3-month physiotherapy program

	Beginning		End	
	45-min exercise		45-min exercise	
	Before	After	Before	After
PEF (l/min)	355.6 ± 76.1	335.2 ± 89.6*	399.3 ± 91.6**	392.6 ± 81.2**

Values are means ± SD
*p < 0.001 for the difference before and after the 45-min exercise session; **p < 0.001 for the difference before the corresponding exercise sessions at the beginning and end of the 3-month breathing exercise program

15.4 Discussion

The present study failed to demonstrate appreciable effects on lung function, assessed from spirometric indices, of a 3-month physiotherapy program in patients suffering from asthma. Spirometry constitutes an essential tool in diagnosis, treatment, and monitoring of bronchial asthma (Petty 2001). Although the results of spirometry may be affected by the patient's attitude, the extent of airway narrowing, exposure to aeroallergens, and the severity of the disease related to daily changes and seasonal exacerbations (Bousquet et al. 2001; Burianova et al. 2008; GINA 2010), the lack of improvement in spirometric indices after the long-term breathing exercise program, overall, speaks against an essential role of such exercise in asthma treatment. That, however, does not exclude an ancillary role of breathing exercise in asthma. Breathing exercise we employed apparently led to disease stabilization, as we did not observe any exacerbations throughout the time of physiotherapy. This observation may be taken as verification of the need for physiotherapeutic approaches in asthma treatment.

The tendency for a decrease in spirometric indices we observed just after completion of a 45-min exercise session was most likely a result of the after-exercise fatigue of respiratory muscles; the phenomenon also reported in other studies (Vilsvik et al. 2001). In the longer run, however, we observed an increase in PEF values recorded before and after an exercise session after completion of physiotherapy compared with the corresponding recordings taken before physiotherapy. These increases may be a sign of benefits acquired from physiotherapy. Alternatively, these increases may reflect the comfort of the patient's use of a peak flow meter at home, with no distress stemming from repeated lung function tests always performed at a physician's office. Personal peak flow meters are a conveniently accessible means of monitoring asthma, whereas such devices are not commonly used in diagnosis of asthma (Petty 2001). Regardless of the underlying cause of PEF increase after breathing exercises, it should be underscored that pulmonary physiotherapy may only be adjunctive, and not substitutive, to pharmacological treatment in helping alleviate symptoms.

15.5 Conclusions

- Physiotherapy outcomes after the completion of a 3-month breathing exercise program were not satisfactory. On the other hand, however, we did not observe any exacerbation of asthma throughout the physiotherapy program, which positively verifies the need for physiotherapeutic interventions in asthma treatment.
- It may be assumed that effects of physiotherapy treatment in asthma are affected by the patient's attitude and the severity of the disease, as expressed by daily changes and seasonal exacerbations.

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

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Chapter 16
Hypoxemia During Bilevel Positive Airway Pressure Treatment in Patients with Obstructive Sleep Apnea Syndrome and Chronic Respiratory Insufficiency

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Abstract In patients with obstructive sleep apnea (OSA) syndrome and chronic respiratory insufficiency one of the options of treatment is bilevel positive airway pressure (BPAP) during sleep. The aim of the study was to find out what are the factors influencing the early results of BPAP treatment in such OSA patients. The study was carried out in 55 adult obese patients (mean body mass index 45 ± 7 kg/m^2), severe OSA syndrome (mean apnea/hypopnea index 62 ± 19), and chronic respiratory insufficiency (mean $PaCO_2$ 54 ± 5.7 torr) who underwent polysomnography during BPAP treatment. In 31 patients (56%) the mean SaO_2 during sleep was <88% despite the optimal BPAP and oxygen titration: 83 ± 4% during NREM and 81 ± 7% during REM sleep *vs.* 91 ± 2% and 90 ± 3%, respectively, in the remaining 24 patients ($p<0.001$). The patients with advanced hypoxemia during sleep and BPAP treatment had lower forced vital capacity (2.2 ± 0.9 *vs.* 2.7 ± 0.8 l, $p<0.05$), lower diurnal PaO_2 (49 ± 8 *vs.* 54 ± 7 torr), higher diurnal $PaCO_2$ (57 ± 5 *vs.* 52 ± 5 torr, $p<0.01$), and higher $PaCO_2$ during sleep (75 ± 13 *vs.* 59.5 ± 7.5 torr). In conclusion, in obese patients with severe OSA syndrome and chronic alveolar hypoventilation there is a risk of sleep hypoxemia during BPAP treatment, despite optimal pressure titration.

Keywords Alveolar hypoventilation • Bilevel positive airway pressure • Chronic alveolar hypoventilation • Hypoxemia • Obstructive sleep apnea

16.1 Introduction

Obstructive sleep apnea (OSA) syndrome develops as a consequence of repeated apneas and hypopneas during sleep, caused by intermittent complete or partial upper airway obstruction (Guilleminault et al. 1976). OSA is strongly related to obesity. The prevalence of OSA syndrome in the obese persons is 25–30%, and in the morbidly obese may reach up to 40–65% (Laaban 2004; Maalej et al. 2010). In a varying proportion of OSA patients, mostly often in massively obese patients, chronic respiratory insufficiency develops which manifests as chronic alveolar hypoventilation (Mokhlesi 2010; Rabec et al. 2011).

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The treatment of choice in OSA patients is continuous positive airway pressure – CPAP (Sullivan et al. 1981; Kushida et al. 2008). However, in some patients bilevel positive airway pressure (BPAP) may be needed (Kushida et al. 2008). BPAP permits an independent adjustment of inspiratory and expiratory positive airway pressures: IPAP and EPAP, respectively (Sanders and Kern 1990). BPAP treatment is reserved for those OSA patients who either cannot tolerate high pressures of CPAP or cannot use this device because of persistent nocturnal hypoxemia during CPAP application (Sanders and Kern 1990; Resta et al. 1998; Schäfer et al. 1998; Weitzenblum et al. 2008; Ozsancak et al. 2009; Mokhlesi 2010; Rabec et al. 2011).

In some patients with OSA and chronic alveolar hypoventilation, nocturnal hypoxemia and hypercapnia may persist, despite the abolishment of apneas and hypopneas with the use of BPAP treatment (Mokhlesi 2010; Rabec et al. 2011). Thus, the aim of this study was to find out if based on clinical picture, including nocturnal sleep assessment, it would be possible to sort out OSA patients with chronic alveolar hypoventilation who, with high probability, would continue to hypoventilate during BPAP treatment.

16.2 Methods

The study was performed in accordance with the Declaration of Helsinki for Human Experimentation and was approved by a local Ethics Committee. The study group consisted of 55 patients (43 men, 12 women), who were obese (body mass index – BMI >30 kg/m^2), had severe OSA syndrome (AHI >30/h), and had chronic respiratory insufficiency, i.e., chronic alveolar hypoventilation with diurnal $PaCO_2$ >45 torr. Twenty seven patients underwent full polysomnography (PSG). In the remaining patients the diagnosis of OSA was based on nocturnal polygraphic respiratory studies which included continuous registration of respiratory flow, chest and abdominal movements, and arterial oxygen saturation (SaO_2) by pulsoximetry. During the full PSG assessment, the following variables were recorded for sleep stage identification: electroencephalography (three channels), electrooculography (two channels), and electromyography (two channels). Stages N1, N2 and N3 of the NREM (non-rapid-eye-movements) and stage REM (rapid-eye-movements) were distinguished. Sleep was scored manually in 30 s epochs according to the criteria of Rechtschaffen and Kales (1973), with corrections introduced by the American Academy of Sleep Medicine in 2007 (Iber et al. 2007). Sleep breathing disorders were assessed in PSG from the following variables: respiratory flow, chest and abdominal movements, and pulsoximetry. Apnea-hypopnea index (AHI) has been calculated as a mean number of obstructive apneas and hypopneas per hour of sleep during both polygraphic respiratory and full PSG studies.

The diagnosis of chronic alveolar hypoventilation was based on the results of arterialized capillary blood gases obtained during wakefulness at rest and in a stable phase of the disease, showing a $PaCO_2$ >45 torr. Additionally, arterialized capillary blood gas content was measured at midnight while the patient was asleep.

In the morning preceding a full PSG study, BPAP was used during wakefulness for approximately 1 h in the presence of a doctor; both low and high pressures of EPAP and IPAP were demonstrated to the patients and the best fitting nasal or facial masks were tested. During the PSG study, titration of BPAP was performed and the optimal levels of EPAP, IPAP, and pressure support were adjusted by an experienced technician, according to the guidelines of the American Academy of Sleep Medicine (Kushida et al. 2008) and were verified by the disappearance of apneas, hypopneas, oxygen desaturations, reductions of electroencephalographic arousals, and tolerability by patient. BPAP (VP II ST-A, ResMed or Bilevel Tranquility, Healthdyne Technologies) was used in spontaneous or spontaneous/timed mode. Supplemental oxygen was added to BPAP treatment (1–7 l/min) when SaO_2 during sleep was continuously <88%.

Data were given as means ± SD. Comparisons of the study groups patients were performed with a *t*-test. A $p < 0.05$ was used as a threshold value for statistical significance.

16.3 Results

The mean age of the patients was 49 ± 11.5 years and the mean BMI of 45 ± 7.1 kg/m^2 indicated massive obesity in the majority of the patients. Despite an increased daytime $PaCO_2$ of 54 ± 5.7 torr, the mean pH was in the normal range of 7.38 ± 0.04 due likely to a compensatory increase in HCO_3^- concentration which amounted to 31.5 ± 2.7 mmol/l. The mean daytime PaO_2 of 52 ± 8 torr indicated hypoxemia.

The mean forced vital capacity (FVC) was slightly diminished; 2.5 ± 0.85 l, i.e., 64 ± 15.5% of predicted, suggesting some restrictive pattern of ventilatory function. The mean forced expiratory volume in 1 s (FEV_1) was 1.8 ± 0.65 l, i.e., 55 ± 16% predicted, and the mean FEV_1/FVC ratio (FEV_1/FVC × 100%), was in the normal range, 76 ± 14%. However, there were 13 patients (24%) with FEV_1/FVC ratio below 70%, indicating chronic obstructive pulmonary disease (COPD) coexisting with OSA.

Sleep breathing studies indicated severe OSA syndrome in all patients – AHI 62 ± 19/h, with marked arterial oxygen desaturations during sleep apneas and hypopneas – mean SaO_2 at the end of apneas and hypopneas of 70 ± 10% and minimal SaO_2 of 51 ± 14%.

The results of PSG studies during BPAP treatment have shown stage N1: 4 ± 3% of total sleep time (TST), stage N2: 35 ± 19% of TST, stage N3: 29 ± 19% of TST, stage REM 26 ± 19% of TST, mean SaO_2 during NREM and REM sleep: 87% ± 5% and 85% ± 8%, respectively, minimal SaO_2 during NREM and REM sleep: 79 ± 1.6% and 76 ± 13.6%, respectively.

The mean values of IPAP and EPAP after the titration were 16 ± 3 hPa and 10 ± 3 hPa, respectively. Supplemental oxygen was added during BPAP titration in all patients with persistent sleep hypoxemia and in 14 (45%) of the remaining patients. In 31 patients (56%), the mean SaO_2 during sleep was <88% despite optimal BPAP and oxygen titration: 83 ± 4% during NREM sleep and 81 ± 7% during REM sleep *vs.* 91 ± 2% and 90 ± 3%, respectively, in the remaining 24 patients ($p < 0.001$). In the patients with sleep hypoxemia during BPAP, arterial blood gas content before treatment showed significantly higher nocturnal and diurnal $PaCO_2$ and HCO_3^- and lower nocturnal and diurnal pH and PaO_2 than in the remaining patients (Table 16.1).

The mean increase in $PaCO_2$ from wakefulness to sleep was 18 ± 12 torr in the group of the patients who subsequently appeared hypoxemic during BPAP treatment and 8 ± 6 torr in the patients who were not hypoxemic during BPAP treatment ($p < 0.01$). Among 42 patients without coexisting COPD, there

Table 16.1 Arterial blood gas content during wakefulness and nocturnal sleep before treatment in patients with hypoxemia during BPAP treatment (Group A) and without hypoxemia during BPAP treatment (Group B)

	Group A	Group B	p
Nocturnal $PaCO_2$ (torr)	75 ± 13	60 ± 8	<0.001
Nocturnal PaO_2 (torr)	45 ± 10	51 ± 10	NS
Nocturnal HCO_3^- (mmol/l)	35.8 ± 3.8	31.8 ± 1.5	<0.01
Nocturnal pH	7.30 ± 0.03	7.34 ± 0.04	<0.05
Diurnal $PaCO_2$ (torr)	57 ± 5	52 ± 5	<0.01
Diurnal PaO_2 (torr)	49 ± 8	55 ± 7	<0.01
Diurnal HCO_3^- (mmol/l)	32.6 ± 2.6	30.6 ± 2.5	<0.05
Diurnal pH	7.37 ± 0.04	7.39 ± 0.03	<0.05

Table 16.2 Comparison of patients with hypoxemia during BPAP treatment (Group A) and without hypoxemia during BPAP treatment (Group B)

	Group A	Group B	p
Age (year)	48 ± 15	49 ± 8	NS
Height (cm)	165 ± 10	171 ± 6	<0.05
Weight (kg)	122 ± 18	133 ± 25	NS
BMI	45 ± 6	45 ± 8	NS
ESS	16 ± 7	18 ± 4	NS
FVC (l)	2.2 ± 0.9	2.7 ± 0.8	<0.05
FVC (% predicted)	64 ± 15	63 ± 16	NS
FEV_1 (l)	1.6 ± 0.6	1.9 ± 0.1	NS
FEV_1 (% predicted)	56 ± 16	55 ± 17	NS
FEV_1/FVC%	77 ± 14	75 ± 14	NS

ESS epworth sleepiness scale

Table 16.3 Results of diagnostic polysomnography in patients with hypoxemia during BPAP treatment (Group A) and without hypoxemia during BPAP treatment (Group B)

	Group A	Group B	p
AHI (n/h)	59 ± 18	65 ± 20	NS
Mean SaO_2 in NREM sleep (%)[a]	66 ± 11	73 ± 11	NS
Minimal SaO_2 in NREM sleep (%)[a]	44 ± 17	61 ± 12	<0.01
Mean SaO_2 in REM sleep (%)[a]	41 ± 12	55 ± 9	NS
Minimal SaO_2 in REM sleep (%)[a]	34 ± 16	51 ± 12	NS

[a]Denotes the measurement at the end of apneas and hypopneas

were 18 (43%) who appeared hypoxemic during BPAP and among 13 patients with coexisting COPD syndrome there were 6 (46%) who appeared hypoxemic during BPAP treatment. Among 12 women, there were 10 patients (83%) with hypoxemia during BPAP and among 43 men there were 13 patients (30%) with hypoxemia during BPAP.

In 18 patients (33%), there was severe sustained hypoxemia (mean SaO_2 ≤85%) during BPAP treatment: 81 ± 4% in NREM sleep and 72 ± 10% in REM sleep. Such a severe sleep hypoxemia during BPAP treatment occurred in two patients (15%) with coexisting COPD and in 5 patients without COPD (36%).

The patients with sleep hypoxemia during BPAP treatment (SaO_2 <88%), as compared with the patients without sleep hypoxemia during BPAP treatment, had smaller height and lower FVC (but not expressed as the percent of predicted values) (Table 16.2). There were no significant differences in the AHI and in the mean SaO_2 at the end of sleep apneas and hypopneas both in NREM and in REM sleep, but the minimal SaO_2 during NREM sleep was lower in those patients who during BPAP treatment had sustained hypoxemia (Table 16.3).

16.4 Discussion

This study shows that the risk of persistent sleep hypoxemia during BPAP treatment is relatively high in the patients with OSA syndrome and chronic alveolar hypoventilation. More than half of the patients were non-responders to BPAP treatment and continued to hypoventilate during sleep while using BPAP, i.e., maintained the SaO_2 during sleep with BPAP persistently below 88%. In these patients sleep hypoxemia persisted, despite optimal titration of BPAP, i.e., after elimination of apneas

and hypopneas, and despite providing the patients with the optimal pressure support and supplemental oxygen. In about one third of the patients, the SaO_2 during sleep and during BPAP treatment was very severe, i.e., below 85%.

The risk of persistent hypoventilation during BPAP treatment has been noted by other authors, but the reason of this phenomenon is not fully understood (Rabec et al. 2011; Mokhlesi 2010; Schönhofer et al. 1997). A high percentage of patients who appeared non-responders to BPAP treatment in the present study could be a result of the fact that the population of our patients was highly selected; we studied exclusively the patients who were obese (BMI > 30) and most of them were massively obese, the mean BMI was 45, and all the patients had chronic alveolar hypoventilation with marked diurnal hypercapnia, the mean $PaCO_2$ during wakefulness was as high as 54 torr.

It is not quite clear why some of the obese patients with OSA syndrome develop chronic alveolar hypoventilation (Rabec et al. 2011). The most important reason is probably a change in the central regulation of ventilation (Krachman and Criner 1998), with decreased ventilatory response to hypercapnia (Sampson and Grassino 1983), or hypoxemia (Zwillich et al. 1975). The other causes include increased work of breathing, decreased lung volumes, decreased chest wall and lung parenchymal compliances, and reduced inspiratory muscle strength (Sharp et al. 1964; Thomas et al. 1989).

In the majority of our patients (76%) chronic alveolar hypoventilation developed in the course of the obesity-hypoventilation syndrome. Obesity-hypoventilation syndrome means the coexistence of obesity, daytime hypoventilation, and sleep-disordered breathing in the absence of an alternative neuromuscular, mechanical or metabolic explanation for hypoventilation (Mokhlesi 2010).

In approximately 1/3 of our patients, chronic hypercapnia and hypoxemia developed in the course of coexisting COPD. The coexistence of OSA syndrome and COPD used to be termed the overlap syndrome (Flenley 1985). Most of the obese patients with the overlap syndrome present with chronic alveolar hypoventilation (Brzecka et al. 2011; de Miguel et al. 2002). It has to be underlined that in the majority of our patients with the overlap syndrome the level of chronic lower airway obstruction was not severe enough to explain chronic respiratory insufficiency. Thus, the mechanisms leading to chronic alveolar hypoventilation in the overlap syndrome in most patients were similar to those in the obesity-hypoventilation syndrome. The percentage of OSA patients who were non-responders to BPAP treatment was similar in the obesity-hypoventilation and overlap patients.

The minority of our patients were women and this is typical for the OSA patients' populations (Laaban et al. 2010). Surprisingly, the majority of women belonged to the group of the non-responders to BPAP treatment. One of the reasons could be that women had lower height and in consequence lower FVC, leading to smaller reservoirs of oxygen in the lungs. A decrease in lung volumes constitutes an important factor contributing to the severity of arterial oxygen desaturation during sleep apneas (Phillipson 1985; Sands et al. 2009).

The patients who appeared to be at risk of sustained hypoxemia during BPAP treatment had more severe chronic alveolar hypoventilation – both during wakefulness and during sleep, as expressed by higher values of $PaCO_2$. Additionally, the patients who were at risk of being hypoxemic during BPAP treatment had higher increase of $PaCO_2$ from wakefulness to sleep than the patients who responded properly to BPAP treatment.

The weakness of these findings is that the blood was taken only once while the patient was asleep and there were no continuous CO_2 measurements during nocturnal hours. However, a concomitant increase of HCO_3^- and a fall of pH confirmed the conclusion that severe alveolar hypoventilation during sleep could be considered a reliable factor indicating the risk of inadequate arterial blood oxygenation during BPAP treatment, even after elimination of obstructive sleep breathing disorders. To our best knowledge these findings have not been published before.

Interestingly, there were no important differences in the severity of sleep apnea between the responders and non-responders to BPAP treatment, as expressed by similar in both groups AHI, mean SaO_2 at the end of the apneas and hypopneas in NREM sleep, and mean and minimal SaO_2 at the end of sleep apneas and hypopneas in REM sleep, with the exception of the lower minimal SaO_2 at the end

of sleep apneas and hypopneas in NREM sleep in non-responders to BPAP treatment. This difference could be explained by more severe daytime and nocturnal hypoxemia in these patients. It has been shown in mathematical models that low pre-apneic alveolar level of oxygen, as well as reduced lung volume, cause an early onset of desaturation during apnea (Sands et al. 2009).

We used BPAP with simple technical resolutions, i.e., the mode of ventilation was spontaneous or spontaneous/timed in all patients and we did not use the option of providing the patient with adequate tidal volume. Thus, in patients who experienced prolonged sleep hypoxemia during BPAP treatment, a further step of treatment should be noninvasive positive pressure ventilation. The patients who continue to hypoventilate during treatment with pressure support – as during BPAP treatment – are the candidates for treatment with the use of volumetric respirators (Ambrogio et al. 2009; Rabec et al. 2011).

16.5 Conclusions

In the obese patients with severe OSA syndrome and chronic alveolar hypoventilation, there is a high risk of sleep hypoxemia during BPAP treatment despite optimal inspiratory and expiratory positive airway pressure titration, especially in the patients with high diurnal $PaCO_2$ and marked increase of $PaCO_2$ during sleep. The other risk factors of the failure of BPAP treatment in preventing sleep hypoxemia in the obese patients with severe OSA syndrome and chronic alveolar hypoventilation are female gender, low vital capacity, and marked hypoxemia during wakefulness.

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Chapter 17
Validation of the Essener Questionnaire of Age and Sleepiness in the Elderly Using Pupillometry

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Abstract In the elderly population, daytime sleepiness (DS) is a burden that affects quality of life, cognitive and physical functioning as well as health status and morbidity. The measurement of DS in older subjects continues to be a challenge, as there are only few elderly-specific assessment tools available. Therefore, we compared the newly developed Essener Questionnaire of Age and Sleepiness (EQAS) with pupillography, a physiological measure of sleepiness. The aim was to identify EQAS cut-off values for increased daytime sleepiness. For the validation study, we determined EQAS scores and the pupillary unrest index (PUI) of the pupillographic sleepiness test (PST) in 88 geriatric in-patients. We also collected data on age, gender, co-morbidities, and geriatric assessment in these subjects. Of all included patients 37 (42%) completed the PST. Fourteen (16%) subjects refused to participate and 37 (42%) subjects could not complete 11 min required for a valid PUI. Subjects with complete and incomplete pupillometry did not differ in basic assessment parameters of health status or cognitive functioning. EQAS scores correlated significantly with PUI values ($r=0.70$; $p<0.001$) demonstrating a dose–response relationship. Based on ROC analysis, an EQAS score above 3 was optimal to distinguished sleepy from non-sleepy participants with sensitivity of 67%, specificity of 93% and positive and negative predictive values of 75% and 90%, respectively. In conclusion, the high negative and positive predictive values of the EQAS indicate that this instrument is a useful and valid assessment tool for daytime sleepiness in the elderly. The easy administration of this observational instrument favors its adoption in geriatric medicine.

Keywords Daytime sleepiness • Elderly • Essener questionnaire of age and sleepiness • Pupillographic sleepiness test • Pupillography • Geriatrics

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17.1 Introduction

Epidemiological studies have shown that daytime sleepiness (DS) is a frequent finding in older people (Ohayon and Vecchierini 2002; Whitney et al. 1998). Prevalence of DS ranges from 10% to over 30% depending on the method used for measurement (Cluydts et al. 2002; Ohayon and Vecchierini 2002; Whitney et al. 1998; Young 2004). Importantly, in the elderly DS is a burden that affects quality of life (Asplund 1996; Ohayon and Vecchierini 2002; Onen and Onen 2010), emotional well being (Chasens et al. 2007), social and daytime functioning (Avlund et al. 2001, 2002; Dam et al. 2008; Gooneratne et al. 2003), and survival (Empana et al. 2009; Gooneratne et al. 2011; Hays et al. 1996). Furthermore, elderly subjects suffering from DS are prone to falls (Avlund et al. 2003, 2004) and to nursing home placement (Luppa et al. 2010).

In the aging society, there is a need for evaluating and assessing daytime sleepiness in older subjects given the high prevalence, its negative outcomes, and the availability of treatments for daytime sleepiness. However, the evaluation of daytime sleepiness in older subjects remains a challenge (Fulda and Popp 2011). Recently, we developed a new tool for the evaluation of DS in elderly people, the Essener Questionnaire of Age and Sleepiness (EQAS) (Frohnhofen et al. 2010). This tool is an observer-rated scale, where the frequency and severity of observed sleepiness are evaluated over a period of at least 1 week. The scale can be used by staff or relatives. The EQAS performed well with regard to re-test reliability ($r=0.98$), internal consistency (Cronbach's Alpha from 0.88 to 0.92), and inter-rater reliability ($r=0.79$). So far, the EQAS has only been validated against self-report measures (Frohnhofen et al. 2010).

We therefore conducted a study to compare EQAS scores to pupillometry results, a physiological measure of sleepiness (Lowenstein et al. 1963; Wilhelm et al. 2001a; Yoss et al. 1970). We choose the pupillary unrest index (PUI) of the pupillometry as the measurement parameter, because the PUI is an accepted and validated measure of sleepiness (Avlund et al. 2001). In sleep deprivation paradigms, there is an increase of the PUI after sleep loss (Wilhelm et al. 1998b, 2001a) and a good correlation with other physiological measure of sleepiness (i.e., The Multiple Sleep Latency Test) with respect to time-of-day variations (Danker-Hopfe et al. 2001). An enhancement of the pupil unrest was also observed in patients with narcolepsy (O'Neill et al. 1998) as well as in hypersomniac patients (Wilhelm et al. 1998a).

The aim of this study was to determine the relationship between EQAS scores and PUI that could help identify EQAS cut-off values for increased daytime sleepiness.

17.2 Methods

17.2.1 Subjects

Subjects for this study were recruited in 2010 from patients admitted for geriatric rehabilitation. Patients were eligible, if they had no major impairment in the activities of daily living (ADLs), had no dementia, and no eye disease. Subjects with medication that could affect reactivity of the pupils were also excluded. Individuals had to give written informed consent. The protocol was approved by the institutional review board.

17.2.2 Measures of Daytime Sleepiness

We measured daytime sleepiness in all individuals by means of two different methods, the pupillographic sleepiness test (PST) (Wilhelm et al. 2001a, b) and the Essen Questionnaire of Age and Sleepiness (EQAS) (Frohnhofen et al. 2010). The infrared video pupillography (AMTech

Pupilknowlogy GmbH, Dossenheim, Germany) captures low frequency oscillations (fatigue waves) of the pupillary diameter at complete darkness and quiet. Spontaneous and involuntary pupillary behavior was recorded continuously over a period of 11 min. The pupil's instability in darkness is measured by the pupillary unrest index (PUI) given in mm/s. High fluctuations in pupil size due to sleepiness produce high PUI values. Recording methods and data management followed standard procedures (Danker-Hopfe et al. 2001; Lüdtke et al. 1998; Wilhelm et al. 1998b). A cut-off value above 6.64 mm/min for the PUI indicates increased sleepiness (one standard deviation above the mean of 4.5 mm/min of a normative sample (Wilhelm et al. 1998b)). However, the PUI lacks reference values for the elderly, as normative data are only available for the age period 20–60 years. For these age decades, the PUI was independent of age and gender (Wilhelm et al. 1998b).

The Essen Questionnaire of Age and Sleepiness (EQAS) is a recently developed observational tool for the measurement of daytime sleepiness in the elderly (Frohnhofen et al. 2010). The questionnaire and user scoring instructions can be downloaded for free on the homepage of the German Sleep Society (DGSM; www.charite.de/dgsm/dgsm/fachinformationen_frageboegen_efas.php). Subjects must be observed by caregivers for at least 1 week. The observer notes periods of sleepiness during the day and the frequency and severity is rated according to the user instructions of the EQAS (Frohnhofen et al. 2010). Predefined anchor points for frequency and severity are used to create a summary score. The score ranges from 0 to 12 points. Both measurements of sleepiness were undertaken by different members of the staff who were all unaware of the aim of the study.

17.2.3 Age, Gender, Co-morbidities, and Geriatric Assessment

Data on age, gender, co-morbidities, and geriatric assessment were collected. We recorded arterial hypertension, heart failure, atrial fibrillation, previous stroke or cancer, chronic obstructive pulmonary disease (COPD), cognitive impairment, and diabetes mellitus as co-morbidities. We used Barthel ADL Index (BI) (Mahony and Barthel 1965) for the assessment of the activities of daily living (ADLs). Cognitive impairment was assessed by means of the Mini-Mental-State-Examination (MMSE), a widely used and valid tool encompassing a score of 0–30. A cut-off value of 24 or less is regarded as indicating cognitive impairment (Folstein et al. 1975).

17.2.4 Statistical Methods

Variables were checked regarding assumptions underlying the use of parametric and non-parametric statistics, and analyzed accordingly. Measures were summarized as means ± SD. The alpha-level of significance was set at 0.05 (two-tailed). Receiver operation curves (ROC) were used to compare diagnostic performance of the EQAS in comparison to pupillography. The optimal cut-off value for the EQAS as well as sensitivity, specificity, positive and negative predictive values were determined. All analyses were performed using SPSS version 15.0 statistical software (SPSS Inc., Chicago, IL, USA).

17.3 Results

Of the 88 patients who were eligible for participation, 37 (42%) completed the pupillometry. Fourteen (16%) subjects refused to participate and 37 (42%) subjects could not complete 11 min required for valid pupillometry. There was no difference in BI on admission and discharge, age, MMSE, and

Table 17.1 Basic description of participants with complete or incomplete pupillographic sleepiness test (PST)

	Complete PST (n = 37)	Incomplete PST (n = 37)	p
Age (year)	80.5 ± 6.7	82.4 ± 6.4	n.s
BI on admission (0–100)	60.9 ± 21.0	64.3 ± 26.5	n.s.
BI on discharge (0–100)	80.0 ± 13.4	73.4 ± 24.9	n.s.
MMSE (0–30)	23 ± 6	–	
EQAS (0–12)	2.1 ± 2.5	2.0 ± 2.7	n.s.
PUI (mm/min)	5.1 ± 2.9	–	n.s.
Pupil size (mm)	4.7 ± 0.7	5.0 ± 1.5	n.s.

Data are means ± SD
BI barthel ADL index, *MMSE* mini-mental-state-examination, *EQAS* essen questionnaire of age and sleepiness, *PUI* pupillary unrest index

Table 17.2 Presence of co-morbid conditions in the sample (n = 37)

Co-morbid conditions	n/%
Mild cognitive impairment	6/16
Heart failure	2/5
Hypertension	32/86
Diabetes	5/14
COPD	3/8
Atria fibrillation	6/16
History of Stroke	0/0
History of Cancer	1/3

COPD chronic obstructive pulmonary disease

EQAS scores between participants with complete and incomplete pupillometry (Table 17.1). The final sample consisted of 37 elderly subjects. A distribution of basic characteristics and co-morbidities is given in Tables 17.1 and 17.2. As expected, there was a female preponderance (n = 29; 78%). Summaries for ADL status on admission and discharge, EQAS scores and pupillary unrest index (PUI) are given in Table 17.1.

The observed EQAS scale values were 0 in 12 (32%) subjects, 1 or 2 in 14 (38%) subjects, 3 or 4 in 5 (13%) subjects and above 4 in 6 (17%) subjects. 9 (24%) subjects had a PUI value higher than 6.64, the cut-off value that indicates sleepiness. Figure 17.1 shows the relationship between EQAS scale values and the PUI values. EQAS scores correlated significantly with PUI values ($r = 0.70$; $p < 0.001$). Of the nine patients with a PUI value above 6.64, six had EQAS scale values of at least 4 and 26 of the 28 patients with a PUI value below 6.64 had an EQAS scale value below 4. Sensitivity and specificity in regard to sleepiness, defined as a PUI value above 6.64, was 67% and 82% for an EQAS scale value above 2.67 and 93% for an EQAS scale value above 3, and 44% and 96% for an EQAS scale value above 4, respectively. The positive (PPV) and the negative predictive values (NPV) for sleepiness determined with pupillography were 55% and 88% for an EQAS scale value above 2, 75% and 90% for an EQAS scale value above 3, and 80% and 84% for an EQAS scale value above 4.

ROC analysis was carried out to further investigate the relationship between EQAS scale values and the PUI. Sensitivity, specificity, and cut-off values were determined considering a cut-off value of 6.64 for the PUI. Figure 17.2 gives the results of the ROC analysis. An EQUAS score above 3 was optimal to distinguish sleepy from non-sleepy participants with sensitivity of 67%, specificity of 93% and positive and negative predictive values of 75% and 90%, respectively.

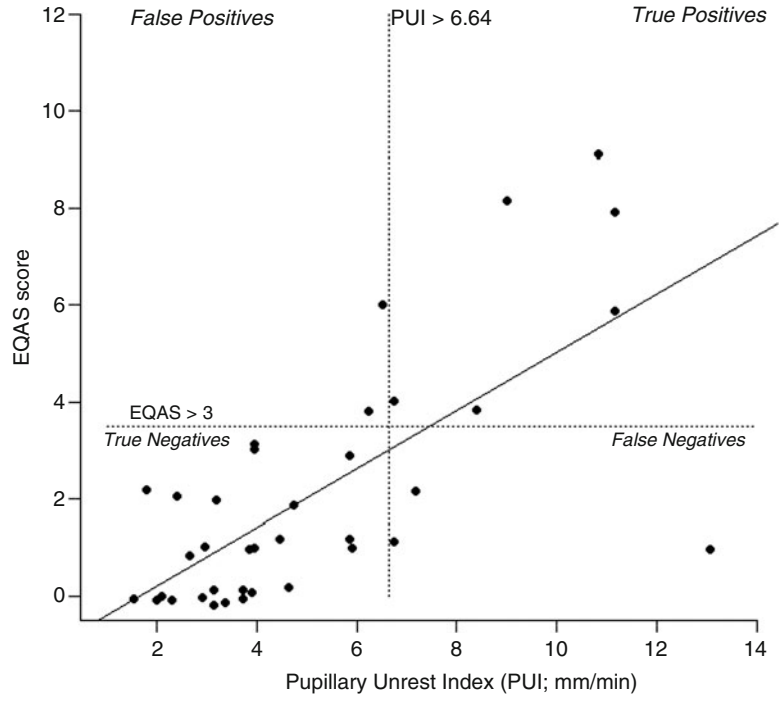

Fig. 17.1 Relationship between Essen Questionnaire of Age and Sleepiness (*EQAS*) scores and Pupillary Unrest Index (*PUI*)

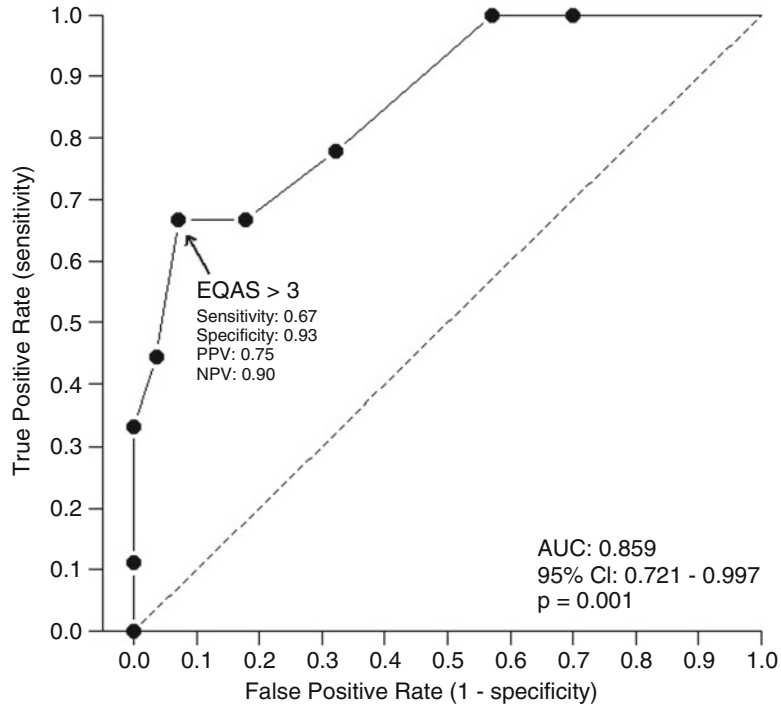

Fig. 17.2 ROC curve for the Essen Questionnaire of Age and Sleepiness (EQAS) score *vs.* sleepy (n = 9) *vs.* non-sleepy (n = 28) subjects based on the Pupillary Unrest Index (*PUI*)

17.4 Discussion

Our study demonstrates that the EQAS scores correlate significantly with the PUI, a physiological measure of sleepiness. Furthermore, the dose response relationship we observed emphasized a close relationship between both measures.

The area under the curve (AUC) is a reasonable summary of the overall diagnostic accuracy of a test. According to published benchmarks, an area of 0.9–1.0 represents an excellent test and an area of 0.8–0.9 represents a good test (Akobeng 2007). The result of an AUC of 0.859 (95% CI 0.721–0.997) and the high negative and positive predictive values indicate, that the EQAS is a useful tool for the measurement of sleepiness. In addition, our previous work has shown that the EQAS has adequate inter-rater and test-retest reliability (Frohnhofen et al. 2010). Together with the ease of administration, this supports the EQAS as a useful measure of daytime sleepiness in the elderly population.

We identified an EQAS scale value above 3 as differentiating sleepy from non-sleepy subjects according to PUI criteria of sleepiness. The high negative (90%) and positive (75%) predictive value of this cut-off score indicate that the EQAS may be an adequate substitute for the pupillometry in the measurement of sleepiness in the elderly. This is auspicious since only half of all study subjects were able to perform the pupillometry even though participants had no major limitations in activities of daily living. Furthermore, both groups (i.e., elderly subjects who were able or failed to perform the pupillographic sleepiness test for 11 min) did not differ in respect do basic variables as age, pupil size, functional ADL status, or degree of sleepiness as measured by the EQAS. It therefore adds to the strength of the EQAS that it is applicable in a far larger group of elderly subjects compared to the pupillometry. This finding also underlines the need for normative PUI data in the elderly population and for exploration of age specific constraints in performing the pupillographic sleepiness test in more detail. In this context, the relationship between the PUI and the gradual decrease of pupil with age also has to be considered, as mean pupil size in our elderly population was quite lower (4.7 ± 0.7 SD mm respective 5.0 ± 1.5SD mm) than in the normative sample for the age period 20–60 years (6.5 ± 0.9 mm) (Wilhelm et al. 1998b).

The measurement of daytime sleepiness is a challenge in older subjects (Fulda and Popp 2011). Despite the documented high frequency of DS, the EQAS is the only tool that has been validated specifically for use in the elderly. The most frequently applied tool for assessment of daytime sleepiness is the Epworth Sleepiness Scale (ESS). This self report scale is easy to use but has only been validated in middle aged subjects (Johns 1991). Normative data are missing for older subjects. Importantly, a study that included geriatric patients showed that only about one third of patients were able to fill in the ESS (Frohnhofen et al. 2009). One of the reasons for incompleteness that emerged from this study was that items related to mobility and activities outside the house were frequently omitted by the participants (Frohnhofen et al. 2009). This underlines the need for tools that are tailored to the experiences and needs of the elderly population.

A strength of this study is that the EQAS has been compared to the PUI, a physiological measure of sleepiness. Additionally, nurses who undertook EQAS evaluation were unaware of the results in the pupillographic sleepiness test. Therefore, bias should be minor. The small sample size and the restriction to in-patients is a limitation of the study. Therefore, results cannot be applied to older subjects in general. Further studies are needed to determine its usability and relevance in other subgroups of older subjects such as community-dwelling elderly and nursing home residents.

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

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Chapter 18
Lung Function at Age 18–25 Years: A Comparison of Different Reference Value Systems

E. Marek, J. Volke, H.-J. Smith, B. Serbetci, H. Kalhoff, N. Kotschy-Lang, R. Merget, and W. Marek

Abstract The anthropometrical data of the Caucasian population have significantly changed within the last five decades. The European Community for Coal and Steel (ECCS) assumes a plateau phase and recommends the entry of 25 years old for calculation of reference values in this age range. The question arises if the commonly used reference recommendations for lung function of the ECCS can still be accepted. In the present study standardized spirometric lung function tests were performed by pneumotachography, recording lung volumes and flows (MasterScreen Pneumo, CareFusion, Höchberg) in asymptomatic nonsmoking subjects (202 females, 201 males), aged between 18 and 26, according to the ATS/ERS criteria. The results were compared with the reference recommendations of ECCS, SAPALDIA, LuftiBus, and Bochum (only males). All absolute lung function values showed a correlation ($p < 0.05$) with height. With respect to FVC and FEV_1, SAPALDIA and Bochum reference values were comparable and close to a 100 (range 97.6–101.4) %pred, whereas both ECCS and LuftiBus showed higher values (range 103.6–109.9%pred). The FEV_1/FVC ratio was close to a 100 (range 97.6–101.7) %pred in all reference systems, whereas flows showed a wide variability between the reference systems (77.1–114.6%pred), single flows (e.g., 96.9–114.2%pred for MEF_{50}) and males/females (males: 93.6–114.6%pred; females: 77.1–107.9%pred). We conclude that SAPALDIA reference values for FVC and FEV_1 should be used, as they better represent lung function in the age group. ECCS and LuftiBus reference values are appreciably (4–10%) lower. Differences between reference systems were less important for the FEV_1/FVC ratio and lung flows.

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18.1 Introduction

The anthropometrical data of young adults have significantly changed within the last five decades, with increasing body height and body mass index. Therefore, the question arises whether the commonly used reference values of ventilatory lung function testing of the European Community for Coal and Steel (ECCS) (Quanjer 1983; Quanjer et al. 1993), or reference values from other studies are still valid today. ECCS values were erected by consensus in the 1960s and 1970s by local reference values from subjects with a limited range of age and body height. In practice, the measured values of young adults are classified by relating them to references, which are calculated for the age of 25 years in subjects aged 18–25, based on the assumption of a plateau phase of lung function in young adults (Sherrill et al. 1989; Robbins et al. 1995). In the last decades, several new reference studies were published, finding higher values for lung function parameters (ATS 1991, 1995; Brandli et al. 1996; Hankinson et al. 1999; Kuster et al. 2008; Roca et al. 1986), but could not commonly replace the former recommendations (Crapo et al. 1981; Enright et al. 1993; Knudson et al. 1983). Concerning the present reference values, the issue of alterations in lung function during the transition from childhood to adolescence and adulthood is an unsolved problem and needs to be studied further. The question if there is a plateau phase in lung function parameters is discussed controversially in the literature (Sherrill et al. 1989, 1992; Enjeti et al. 1978; Robbins et al. 1995; van Pelt et al. 1994). Difficulties arise from the fact that in adolescence height as the main parameter is changing (age or weight are potentially secondary parameters), later on height is nearly fixed and only age is changing. Furthermore, there are reasons to assume different variability in lung function parameters due to height in adolescence or later on, and in age with growing height and BMI. ECCS acts on the assumption of a plateau phase between 18 and 25 years of age. A complete set of parameters is available only from the 'historic' ECCS recommendations (Quanjer 1983; Quanjer et al. 1993).

The European Task Force on standardization of lung function testing has recently published a series of comprehensive recommendations for lung function testing and interpretation (Miller et al. 2005a, b; Pellegrino et al. 2005). However, the problems in evaluating the lower limit of normal (LLN), the limited age range and the concept in handling the transition from adolescence to adults were not addressed. Current investigations try to describe lung function parameters from preschool children to senescence in one continuous formula taking into account a peak value in early adolescents (Stanojevic et al. 2008). In a group of healthy young adults, 18–26 years of age, we examined if the ECCS reference recommendations still can be accepted in daily routine measurements in that special age group. Furthermore, we compared the results to the references values of the SAPALDIA and LuftiBus studies (Brandli et al. 1996; Kuster et al. 2008), and the set of 'Bochum reference values' for healthy non-smoking males (Marek et al. 2009).

18.2 Methods

The study was performed in conformity with the Declaration of Helsinki of the World Medical Association and the protocol was approved by a local Ethics Committee. Lung function was examined using pneumotachography for recording static lung volumes and parameters from the forced flow-volume-loops in 403 asymptomatic non-smoking Caucasian females and males, aged 18–26 years. Subjects were without diseases of the lung, heart or other organs with influence on lung function.

18.2.1 References for Lung Function in Children and Adults

The commonly accepted reference values for children were published in 1987 by Zapletal et al. (1987) for 3–16 years old boys and girls. In Europe reference values of the ECCS were published in 1983, and in 1993 in revised version (Quanjer 1983; Quanjer et al. 1993). In the 1990s, the SAPALDIA study was published by Brandli et al. (1996 and 2000), and recently in the LuftiBus study by Kuster et al. (2008). Reference value for FEV_1 for males of 180 cm body height and children and adolescents between 3 and 18 years of age with a final height of 180 cm along with the corresponding lower limit of normal (LLN) and the differences between predicted values and LLN are graphically presented in Fig. 18.1. The differences between Zapletal et al. (1987) reference values for an 18 years old adolescent of 180 cm height and other reference definitions for adults of 180 cm height range from 100 to 400 ml.

18.2.2 Anthropometric Data

The body height of males, recruited in the cross sectional study did not correlate with age, height = 0.126·age + 185.3 cm ($r^2 = 0.001$). As observed in males, body height did not correlate with age in females, height = 0.113·age + 166.7 cm ($r^2 = 0.001$) either. In both males and females, BMI showed a tendency to increase with age, BMI = 0.307·age + 16.8 ($r^2 = 0.036$) and BMI = 0.452·height + 11.5 ($r^2 = 0.097$), respectively (Table 18.1).

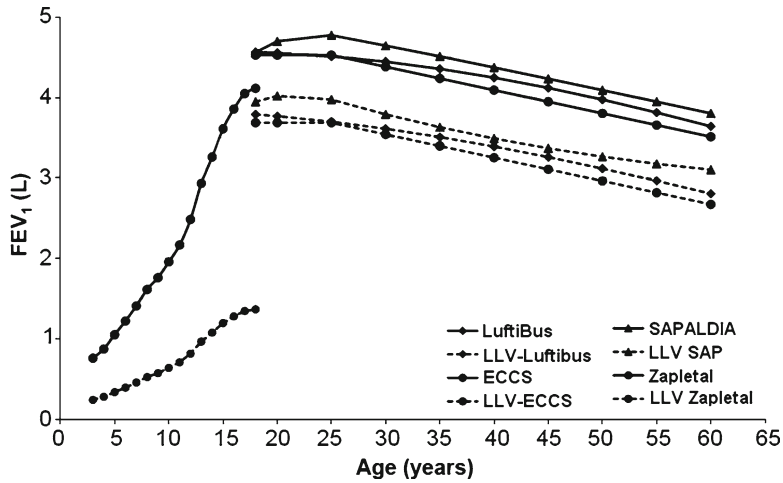

Fig. 18.1 Correlation of reference values for FEV_1 with age from Zapletal for boys and adolescents and from ECCS, SAPALDIA, and LuftiBus study for males of 180 cm in height

Table 18.1 Anthropometrical data for the male and female participants

	Males (n = 201)		Females (n = 202)	
	Mean ± SD	Min-Max	Mean ± SD	Min-Max
Age (yr)	22.9 ± 2.0	20.1–26.2	21.7 ± 1.9	21.1–26.2
Height (cm)	182.0 ± 6.9	164.2–206.1	169.0 ± 6.8	152.2–187.3
Weight (kg)	78.8 ± 11.1	55.3–110.6	61.8 ± 8.9	48.3–107.4
BMI (kg/m²)	23.8 ± 2.1	20.4–32.7	21.7 ± 2.8	16.2–37.0

18.2.3 Lung Function Measurements

A minimum of three lung function measurements were recorded. The investigations included static and dynamic lung volumes and maximal expiratory flows, using MasterScreen Pneumo systems (CareFusion, Höchberg). All tests were performed according to the recommendations of the ATS/ERS Task Force on lung function testing (Wanger et al. 2005) and compared with the reference formulas of the ECCS (Quanjer et al. 1993). Only those measurements were accepted where the expiratory time (TE) exceeded 4 s, the variation of end-expiratory flow was below 25 ml/s and no cough disturbed the expiratory phase.

18.2.4 Data Analysis

The results were presented as means ± SD. Using Fisher's paired *t*-test, mean values were proofed to be significantly different from the reference values of ECCS, SAPALDIA- or LuftiBus values. A $p < 0.05$ was considered statistically significant. Linear regression analysis was performed for age, body height and BMI. Exponential or logarithmic functions did not show a close correlation to age. Therefore, the results from the simple linear regression analysis were presented. The mean values in %predicted according to the ECCS, SAPALDIA, LuftiBus and the Bochum reference formulas of spirometric parameters were compared.

18.3 Results

18.3.1 Correlations of Lung Function Parameters with Age and Height

No noticeable correlation between age and investigated respiratory parameters (VC, FVC, FEV_1, FEV_1%FVC, PEF, $MEF_{75,50,25}$) was found in the investigated age range of 18–26 years (Table 18.2, Fig. 18.2). Lung function parameter values increased with body height (Table 18.3). The most important parameters VC_{IN}, FVC, and FEV_1 were significantly correlated in both gender groups (Fig. 18.3).

18.3.2 Lung Function Parameters Compared with ECCS, LuftiBus, SAPALDIA, and Bochum Reference Values in Males

Values of lung function parameters in the group of young adult males were higher than predicted (Table 18.4). Most of them were 104.0 ± 7.4% of the reference values predicted by ECCS, 106.2 ± 8.6% by LuftiBus, and 106.1 ± 8.2% by SAPALDIA references. Lung function parameters of young adult males closely correlated with Bochum reference values. The mean value obtained from all parameters investigated was 98.0 ± 7.8%pred. The lowest values were obtained according to Bochum values for PEF (93.6 ± 15.7%pred), and the highest for MEF_{25} (103.5 ± 30.1%pred).

Table 18.2 Correlation of lung function parameters and age

	Males (n = 201)		Females (n = 202)	
	Regression equations	Coefficient of determination	Regression equations	Coefficient of determination
$\mathbf{VC_{IN}}$ (%pred)	y = −0.002x + 5.987	$r^2 < 0.011^{n.s.}$	y = −0.009x + 4.329	$r^2 < 0.011^{n.s.}$
FVC (%pred)	y = 0.007x + 5.663	$r^2 < 0.021^{n.s.}$	y = −0.006x + 4.276	$r^2 < 0.011^{n.s.}$
$\mathbf{FEV_1}$ (%pred)	y = 0.001x + 4.936	$r^2 < 0.011^{n.s.}$	y = −0.024x + 4.086	$r^2 = 0.028^{n.s.}$
$\mathbf{FEV_1\%VC_{IN}}$	y = −0.243x + 112.9	$r^2 = 0.021^{n.s.}$	y = −0.699x + 118.8	$r^2 = 0.011^{n.s.}$
PEF (%pred)	y = 0.159x + 7.102	$r^2 = 0.028^{n.s.}$	y = −0.057x + 8.491	$r^2 = 0.008^{n.s.}$
$\mathbf{MEF_{75}}$ (%pred)	y = 0.217x + 4.281	$r^2 = 0.050^{n.s.}$	y = −0.076x + 7.999	$r^2 = 0.014^{n.s.}$
$\mathbf{MEF_{50}}$ (%pred)	y = −0.003x + 6.230	$r^2 < 0.021^{n.s.}$	y = −0.039x + 5.370	$r^2 = 0.006^{n.s.}$
$\mathbf{MEF_{25}}$ (%pred)	y = 0.004x + 3.619	$r^2 = 0.007^{n.s.}$	y = −0.066x + 3.634	$r^2 = 0.042^{n.s.}$

n.s. non-significant

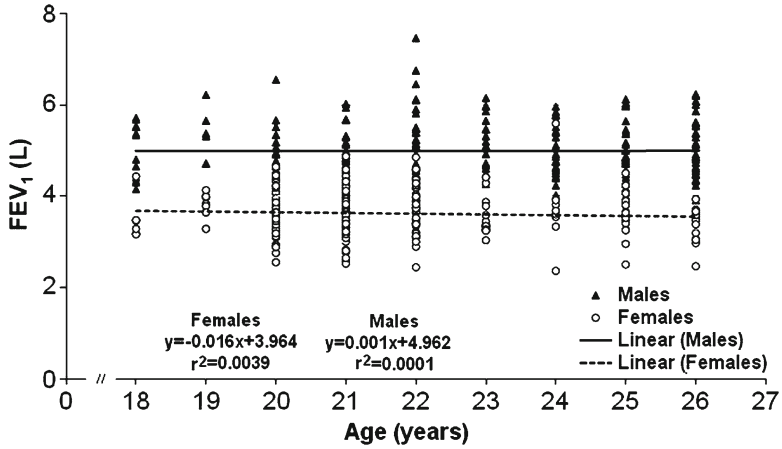

Fig. 18.2 Correlation of body height with age for non-smoking males (▲) and females (o)

Table 18.3 Correlation of lung function parameters and body height

	Males (n = 201)		Females (n = 202)	
	Regression equations	Coefficient of determination	Regression equations	Coefficient of determination
$\mathbf{VC_{IN}}$ (%pred)	y = 0.073x − 7.428	$r^2 = 0.382^{**}$	y = 0.052x − 4.633	$r^2 = 0.356^{**}$
FVC (%pred)	y = 0.071x − 7.136	$r^2 = 0.379^{***}$	y = 0.056x − 5.250	$r^2 = 0.369^{**}$
$\mathbf{FEV_1}$ (%pred)	y = 0.048x − 3.835	$r^2 = 0.224^{***}$	y = 0.039x − 3.054,	$r^2 = 0.2778^{**}$
$\mathbf{FEV_1\%VC_{IN}}$	y = 0.055x + 97.3	$r^2 > 0.021^{n.s.}$	y = −0.055x + 112.9	$r^2 < 0.021^{n.s.}$
PEF (%pred)	y = 0.047x − 0.614	$r^2 = 0.074^{n.s.}$	y = 0.072x − 2.321	$r^2 = 0.072^{n.s.}$
$\mathbf{MEF_{75}}$ (%pred)	y = 0.018x + 3.316	$r^2 = 0.011^{n.s.}$	y = 0.068x − 3.092	$r^2 = 0.062^{n.s.}$
$\mathbf{MEF_{50}}$ (%pred)	y = 0.021x + 1.014	$r^2 = 0.024^{n.s.}$	y = 0.023x + 2.019	$r^2 = 0.012^{n.s.}$
$\mathbf{MEF_{25}}$ (%pred)	y = 0.020x − 1.124	$r^2 = 0.053^{n.s.}$	y = 0.014x + 0.192	$r^2 = 0.014^{n.s.}$

n.s. non-significant

$^{**}p < 0.01$, $^{***}p < 0.001$

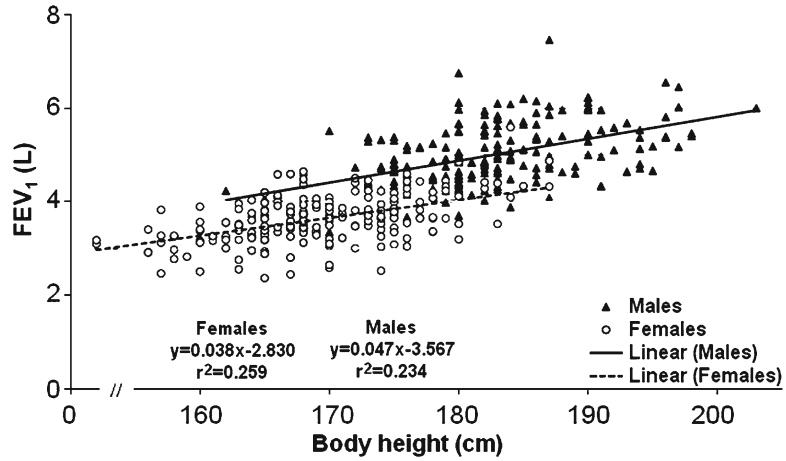

Fig. 18.3 Correlation of FEV_1 with body height for non-smoking males (▲) and females (o)

18.3.3 Lung Function Parameters Compared with ECCS, LuftiBus, and SAPALDIA Reference Values in Females

The values of spirometric lung function parameters in the group of younger females were up to 9.9% higher compared with the ECCS reference values in males, seen in Table 18.4. On average, the mean lung function parameters were 101.5 ± 3.64% of the reference values predicted by ECCS, 101.7 ± 6.1% by LuftiBus, and 98.5 ± 4.5% by SAPALDIA references.

18.3.4 Lung Function Parameters Compared with ECCS, LuftiBus, and SAPALDIA Reference Values for Both Genders

With respect to FVC and FEV_1, SAPALDIA and Bochum reference values were comparable and close to a 100 (range 97.6–101.4) %pred, whereas both ECCS and LuftiBus showed considerably higher values (range 103.6–109.9%pred). There was no main difference between males and females (Table 18.4). The FEV_1/FVC ratio was close to a 100 (range 97.6–101.7) %pred in all reference systems, whereas flows showed a wide variability between reference systems (77.1–114.6%pred), single flows (e.g., 96.9–114.2%pred for MEF_{50}) and males/females (males: 93.6–114.6%pred; females: 77.1–107.9%pred).

18.4 Discussion

The commonly accepted reference formulas of the ECCS (Quanjer 1983; Quanjer et al. 1993) for the assessment of ventilatory lung function measurements of Caucasians are limited in fulfilling the current requirements of lung function testing. As for all other reference recommendations, the handling of the transition from adolescence to adults is an unsolved problem. The formulas were compiled by the ECCS experts from different investigations and subsets of individuals in the 1970s and earlier. Meanwhile, anthropometrical parameters significantly altered, the population is getting higher especially in young adults, and technology has improved. The stringent definition of the lower limits of normal by subtracting 1.64·RSD with over age constant RSD has significant drawbacks for older and

Table 18.4 Lung function parameters in %pred of ECCS, LuftiBus, SAPALDIA, and Bochum in young adult males (n = 201)

	ECCS		LuftiBus		SAPALDIA		Bochum	
	Males	Females	Males	Females	Males	Females	Males	Females
VC_{IN} (%pred)	101.5 ± 11.1$^{n.s.}$	104.8 ± 12.2***	–	–	–	–	97.7 ± 11.0$^{n.s.}$	–
FVC (%pred)	105.8 ± 11.4***	109.9 ± 13.3***	106.5 ± 11.4***	105.7 ± 12.8***	99.5 ± 10.7$^{n.s.}$	99.1 ± 12.1$^{n.s.}$	97.6 ± 10.3$^{n.s.}$	–
FEV_1 (%pred)	107.4 ± 13.5***	103.6 ± 12.5***	106.9 ± 13.4***	105.1 ± 12.7***	101.9 ± 12.8**	99.8 ± 12.0$^{n.s.}$	99.5 ± 10.7$^{n.s.}$	–
FEV_1 % VC_{IN}	101.4 ± 7.4$^{n.s.}$.	101.7 ± 7.8**	100.4 ± 7.2***	98.5 ± 7.72***	101.4 ± 7.23*	99.3 ± 7.77n.s.	97.6 ± 3.3*	–
PEF (%pred)	104.8 ± 17.3**	97.8 ± 15.1$^{n.s.}$	94.4 ± 15.6***	89.9 ± 13.9***	110.6 ± 18.1***	108.0 ± 16.7***	93.6 ± 15.6***	–
MEF_{75} (%pred)	105.0 ± 22.6**	99.3 ± 18.0$^{n.s.}$	106.7 ± 22.9***	97.8 ± 17.8$^{n.s.}$	107.3 ± 22.8***	101.4 ± 18.5$^{n.s.}$	97.5 ± 15.3$^{n.s.}$	–
MEF_{50} (%pred)	106.7 ± 24.9**	96.9 ± 19.6*	114.2 ± 26.6***	107.9 ± 21.8***	112.6 ± 26.2***	104.1 ± 21.1*	99.1 ± 23.1$^{n.s.}$	–
MEF_{25} (%pred)	101.6 ± 30.1$^{n.s.}$	98.0 ± 25.4$^{n.s.}$	114.6 ± 33.4***	107.2 ± 27.5***	109.1 ± 31.8***	77.1 ± 19.7$^{n.s.}$	103.1 ± 30.1$^{n.s.}$	–
Mean ± SD	**104.3 ± 7.4**	**101.5** ± 3.4	**106.2 ± 8.6**	**101.7** ± 6.1	**106.1 ± 8.2**	**98.4** ± 4.4	**98.0 ± 7.2**	–

n.s. non significant

*p < 0.05, **p < 0.01, ***p < 0.001

smaller subjects. The most frequently used reference values in Europe include a plateau phase, which would be appropriate for only 63% of the subjects according to the data of Robbins et al. (1995) and Roca et al. (1986). Prediction equations with no plateau, as used by most pulmonary function laboratories in the USA, are only appropriate for 22% of the men aged 18–33 years in this study. Van Pelt et al. (1994) studying FEV_1 in a cross-sectional and longitudinal study in young adults, found a plateau phase or a period of continued lung growth when data were correlated to age. Today there is a consensus that FEV_1 in smokers declines earlier in smoking young adults, compared with non-smoking young adults (Robbins et al. 1995; van Pelt et al. 1994). Until now, we cannot conclude, that pulmonary function development in young adults reaches a plateau phase since we have performed a cross sectional study. In the relevant age range of 18 to about 33 years, longitudinal studies have shown either an ongoing lung growth or a decline in lung function parameters. Taking the mean values into account, the different slopes may compensate each other and result in a plateau, but this is only one explanation. Follow-up periods of 10 years, reported in the literature, are quite a long time, but do not cover the period from 17 to 45 years. More research is needed to get a final conclusion.

18.4.1 ECCS Reference Values Compared with LuftiBus and SAPALDIA Predictions

ECCS predicted values for FEV_1 in comparison to the LuftiBus-Study differ by about 200 ml in young adult males. For middle aged and older subjects differences are even smaller. The reference values of the SAPALDIA-Study are about 200 ml higher for young and middle aged males and about 300 ml for subjects older than 65 years. Values of LLN are largely similar in young subjects by ECCS and LuftiBus, LLN values for middle aged subjects are about 200 ml higher in the LuftiBus study. Despite the decrease of more than 1.5 l from 25 to 80 years of age, the difference between the predicted value and the 5th percentile is nearly constant over the whole range of age. In the original version of the SAPALDIA-Study, the value of the lower limit of normal approximates the predicted values with increasing age (Brandli et al. 1996). Due to a simplified mathematical model, with respect to the small number of older subjects, the authors newly computed the equations for the LLN (Brandli et al. 2000). Now the reference values and their LLN are almost parallel in the SAPALDIA-Study as we know from ECCS formulas.

18.4.2 Multicenter Study for New European Lung Function Recommendations

The need for a complete set of reference values, replacing the ECCS recommendations due to the altered structures of our population can be realized only with a great financial, material and personal engagement in a multi centre European research project. At least, 20,000 subjects have to be recruited from local registration offices. Only subjects with verified heath status and non-restricted cooperation in the measurement are allowed to be selected, whereas smokers and diseased subjects carefully have to be excluded from evaluation. In a comprehensive reference value project not only static and dynamic lung volumes and maximal flows should be studied, but also parameters of body plethysmography, diffusion testing and blood gas analysis should be studied with standardized and well calibrated devices. Recently, the European Respiratory Society established a task force for generation of new reference values of lung function with the aim of compiling current normals from early childhood to senescence. A set of sustained references across all ages will be derived from their investigations, solving the problems of overlaps from adolescence to adults. But for statistical reasons this procedure is highly problematic. In childhood the independent variables for lung function parameters are mainly height and weight, however, for adolescents and adults height, age and sex are determining. So, there is a discontinuity in the underlying mathematical models. Stanojevic et al. (2007, 2008) have published

a reference values spanning from early childhood to senescence. This new approach should provides an elegant solution to a complex and longstanding problem of fitting age and height trends to all-age lung function data. These equations provide smoothly changing reference curves during periods of rapid growth and transition to produce a single reference across a wide age range (5–80 years) in Caucasians.

18.5 Conclusions

No correlation between age and body height was found in the age range of 18–26 years in males and females, whereas BMI slightly increases with age. However, in the small age range of investigation, lung function parameters did not correlate with age or BMI but the expected correlation to body height could be confirmed. According to our limited data, the recommendation of a plateau phase from ECCS entering an age of 25 years for calculation of reference values in the age range between 18 and 25 years can be supported. Static and dynamic parameters of younger adults were significantly higher than predicted by ECCS, SAPALDIA and LuftiBus study reference values. Between Zapletal references for adolescents and ECCS, SAPALDIA, and LuftiBus predictions a difference of 300–500 ml was found, which is not acceptable. Considering the increasing age and height of our population and the changes in working conditions, a comprehensive multi center study on lung function of Caucasians should be initiated by the international respiratory societies.

Conflicts of Interest: No conflicts of interest were declared in relation to this article.

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Chapter 19
Pulmonary Function Impairment in Patients Undergoing Allogeneic Hematopoietic Cell Transplantation

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Abstract Deterioration of pulmonary function can be the sole symptom of early stages of pulmonary complications following allogeneic hematopoietic cells transplantation (alloHCT). The aim of the study was to evaluate the prevalence and types of pulmonary function abnormalities in allogeneic cells recipients. Twenty three (5 children and 18 adults) allogeneic hematopoietic cells recipients who underwent pulmonary function assessment before and 6–12 months after alloHCT were included in the study. Forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), total lung capacity (TLC), and lung diffusion capacity for carbon dioxide (D_LCO) were determined. Values <80% of predicted were considered abnormal. We found significant reductions of FVC, D_LCO, and TLC after alloHCT. The most important reduction was noted in D_LCO (pre-alloHCT of 85% ± 15% *vs.* post- alloHCT of 60% ± 21%, $p < 0.05$). Six patients (26%) presented with lung function impairment before alloHCT: obstructive lung disease (4%), restrictive lung disease (13%), and decreased D_LCO (17%). In 19 patients (83%) pulmonary function abnormalities were demonstrated after alloHCT. The most common disturbance was a D_LCO decrease that occurred in 16 patients (70%). In conclusion, frequency of pulmonary function abnormalities in patients after alloHCT is high. A diffusion capacity decrease and restrictive pattern of ventilation insufficiency develop in the majority of patients after alloHCT. It would be reasonable to include pulmonary function testing to standard periodic examination in patients qualified for, and after, alloHCT procedure.

Keywords Allogeneic hematopoietic cell transplantation • Diffusion capacity • Lung disease • Pulmonary function tests • Ventilation insufficiency

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19.1 Introduction

Allogeneic hematopoietic cell transplantation (alloHCT) has been a widely applied treatment approach for high-risk malignant diseases and bone marrow failure, resistant to conventional therapy. However, agents used for conditioning (high dose chemotherapy and total body irradiation) as well as immunosuppressant administered in the post-transplant period along with graft *vs.* host disease (GvHD) may profoundly impair the function of different organs, the lungs inclusive (Quabeck 1994; Kotloff et al. 2004; Michelson et al. 2007). Pulmonary complications have been reported in 40–60% of adult allogeneic hematopoietic cells recipients, and may contribute to death in over one-third of these cases; similar data in children are limited and natural history of pulmonary complications remains incompletely understood (Soubani et al. 1996; Griese et al. 2000; Eikenberry et al. 2005; Roychowdhury et al. 2005). Deterioration of pulmonary function after alloHCT can be the sole symptom of early stages of pulmonary complications. There are few data that show that pulmonary function tests may play an essential role in early diagnosis of pulmonary complications after alloHCT. Many studies have been conducted to determine the risk factors for post transplant pulmonary complications, some of which have included an analysis of pretransplant pulmonary function as a potential risk factor (Clark et al. 1987; Ghalie et al. 1992; Chien et al. 2003, 2004). However, the predictive value of pretransplant pulmonary function tests is still controversial. In the present study, we aimed to evaluate the prevalence and types of pulmonary function impairment in patients undergoing allogeneic hematopoietic cell transplantation.

19.2 Methods

19.2.1 Patient Population

The study was performed in accordance with the Declaration of Helsinki for Human Experimentation and was approved by a local Ethics Committee. Twenty three (5 children and 18 adults) allogeneic hematopoietic cells recipients seen in an outpatient clinic of the Department of Pulmonology and Lung Cancer of Wroclaw Medical University in Wroclaw, Poland in the period 2007–2010 were included in the study. None of the patients had a prior history of chronic lung disease. The clinical characteristics of patients are summarized in Table 19.1.

19.2.2 Lung Function Measurements

Pulmonary function tests were performed before alloHCT (pre-HCT) and 6–12 month (median 9.0 ± 1.7 months) after alloHCT (post-HCT). The test included spirometry, body plethysmography and gas diffusion capacity. Gas transfer was measured by a single breath technique. All measurements were performed with a Lung test 1000 system (MES, Cracow, Poland) according to the guidelines recommended by the American Thoracic Society (American Thoracic Society 1987). The variables recorded were forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1), FEV_1/FVC $\times$ 100% (FEV_1/FVC ratio), total lung capacity (TLC), residual volume (RV), and the diffusion capacity of the lung for carbon monoxide (D_LCO). The lung function variables were expressed in the absolute values and as the percentage of predicted (Quanjer et al. 1983). Obstructive lung disease was defined as a value for FEV_1/FVC of less than fifth percentile of predicted. Restrictive lung disease was defined

Table 19.1 Clinical characteristics of 23 patients who underwent pulmonary function tests before and after alloHCT

Sex (M/F)	14/9
Median age at alloHCT, years (range)	25 (9–33)
Underlying disease	
ALL	14
CML	3
MDS	4
SAA	2
GvHD	12

ALL acute lymphoblastic leukemia, *CML* chronic myelogenous leukemia, *MDS* myelodysplastic syndrome, *SAA* severe aplastic anemia, *GvHD* graft *vs.* host disease

as a TLC of less than 80% of predicted. Diffusion capacity was considered abnormal if D_LCO was less than 80% of predicted.

19.2.3 Data Analysis

Data were presented as means ±SD. The prevalence of pulmonary function abnormalities was expressed as the percentage of patients with an abnormal FEV_1/FVC, TLC, or D_LCO for each time period. Significance of differences in the pulmonary function variables between pre-HCT and post-HCT was assessed with a paired *t*-test.

19.3 Results

The results of pulmonary function tests before alloHCT (pre-HCT) and after alloHCT (post-HCT) in 23 consecutive patients are shown in Table 19.2. The prevalence of different lung function abnormalities in our patients is presented in Fig. 19.1a.

Before alloHCT, 6 patients out of the 23 (26%) had pathologic lung function. When lung function abnormalities were grouped according to the previously defined patterns, the most common disturbance in pre-HCT PFT was a D_LCO decrease. It occurred in four patients (17%). In all of them, the abnormalities were still present post-HCT. Obstructive lung disease was found in one out of the 23 patients (4%) before alloHCT and in three patients (13%) restrictive lung disease was found.

After bone marrow transplantation, the number of patients with lung function abnormalities increased. The abnormalities were demonstrated in 19 patients (83%), as shown in Table 19.2. Again, the most common disturbance was a D_LCO decrease that occurred in 16 patients (70%). Four patients (17%) presented obstructive and eight patients (35%) restrictive disturbances.

After alloHCT, we observed significant reductions of FVC, D_LCO, and TLC percent predicted values. The highest reduction was noted in D_LCO values (pre-HCT of 85 ± 15%pred *vs.* post-HCT of 60 ± 21%pred, $p < 0.05$).

We analyzed the distribution of different respiratory function patterns after alloHCT in patients with graft *vs.* host disease (GvHD+) and without it (GvHD−) (Fig. 19.1b). All patients in the group with GvHD after alloHCT had pulmonary function impairment in comparison with the GvHD− group where four patients (36%) had normal pulmonary function tests. D_LCO decrease was the most common disturbance in pulmonary function in the GvHD+ group, occurring in 10 out of the 12 (83%) GvHD+ patients.

Table 19.2 Lung volumes and lung diffusing capacity before and after alloHCT in 23 consecutive patients

	Pre- HCT	Post- HCT
FVC %pred	87 ± 12	76 ± 11*
FEV_1 %pred	81 ± 11	75 ± 10
FEV_1/FVC %	84 ± 7	82 ± 8
DLCO %pred	85 ± 15	60 ± 21*
TLC %pred	91 ± 11	76 ± 17*
RV %pred	121 ± 32	150 ± 43

Data are means ± SD
Statistical comparisons: values post-HCT are compared with values pre-HCT
FVC forced vital capacity, *%pred* percent predicted, FEV_1 forced expiratory volume in 1 s, D_LCO lung diffusing capacity for carbon monoxide, *TLC* total lung capacity, *RV* residual volume, *pre-HCT* before allogeneic hematopoietic cell transplantation, *post-HCT* after allogeneic hematopoietic cell transplantation
*p < 0.05

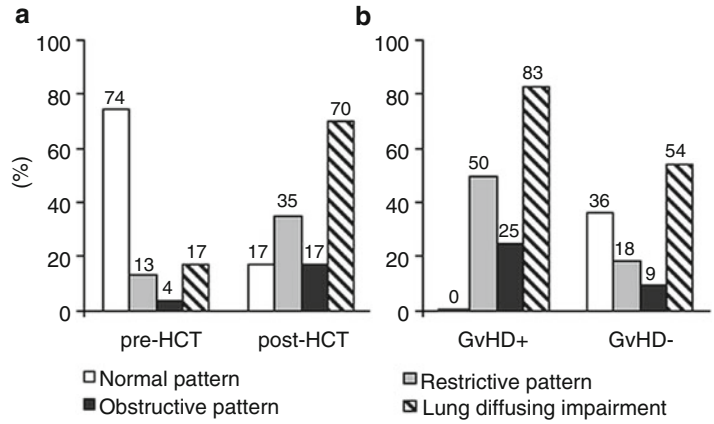

Fig. 19.1 Distribution of different respiratory function patterns in all patients (**a**) before and after allogeneic hematopoietic cell transplantation (pre-HCT and post-HCT) and (**b**) in patients with graft *vs.* host disease (GvHD+) and without it (GvHD–)

19.4 Discussion

The majority of patients evaluated in this study presented with pulmonary function abnormalities after alloHCT. A diffusion disorder was the most frequently observed disturbance in the first year of follow-up after HCT. Restrictive lung disease was also common and was found in one third of patients within the first year post alloHCT. Obstructive disorder was far less common. In fact, only four patients showed a pronounced deterioration of FEV_1/FVC.

Interestingly, the present study shows that before alloHCT restrictive and diffusion abnormalities were found in 4% and 17% of patients, respectively. This was probably due to the prior use of pulmotoxic cytotoxic drugs in the treatment of malignant disease (patients with severe aplastic anemia who had not been treated by chemotherapy prior alloHCT had normal pulmonary function). Since multiple chemotherapy protocols were used before the transplantation, it was not possible to identify which drugs were responsible for pre-HCT abnormalities documented in this study.

Our findings are in agreement with data recently published by other groups. The diffusion disorder was the most frequently described lung function abnormality after alloHCT. In a study conducted by Quigly et al. (1994), in which PFT were evaluated in 25 children after bone marrow transplantation, only a temporary decrease of D_LCO was seen at 6 months post- alloHCT, with improvement to a subnormal level (mean percentage predicted D_LCO was 69) 15 months after alloHCT. Restrictive or

obstructive abnormalities were not identified in this study. In other studies, both significant decreases of TLC and D_LCO have been reported after alloHCT (Nysom et al. 1996; Cerveri et al. 1999). Frisk et al. (2004) found that restrictive and diffusion abnormalities were present in 20% and 35% of patients, respectively, at 60 months post-alloHCT. Other studies also found a significant decrease in D_LCO 8–12 months after alloHCT, followed by partial recovery (Depledge et al. 1983; Rodriguez-Roisin et al. 1989; Sutedja et al. 1988). This transient decrease in diffusing capacity after alloHCT may reflect transient interstitial lung disease. In a recent study, Kaya et al. (2009) show that the most common pulmonary function abnormality before alloHCT is isolated reduction in D_LCO which has been observed in 18 (36%) out of the 50 patients. The authors observed significant reductions in FEV_1, FVC, TLC, and D_LCO at 3 months post-alloHCT and similar reductions at 6 months post-alloHCT, except for D_LCO (not significant). In a group of 14 children treated for acute leukemia or lymphoma, Kaplan et al. (1994) found that the percentage predicted FVC and FEV_1 values decreased significantly during the first 18–24 months after alloHCT, with a greater decline in FVC than in FEV_1, suggesting restrictive disease. Cerveri et al. (1999) reported that 12 out of the 52 children presented with restrictive pattern of pulmonary function disturbances (defined as a decrease in FVC and an increase in FEV_1/FVC) at least 2 years after alloHCT. Griese et al. (2000) observed mild restriction in 83 out of the 138 children with a median follow-up of 7 years after alloHCT. In the study of 27 children, Fanfulla et al. (1997) showed a significant FVC decline 18 months after alloHCT. All these studies and the present study provide convincing evidence that lung function deteriorates after alloHCT in both children and adults. The data from the literature support a restrictive process.

19.5 Conclusion

The study demonstrates that the prevalence of pulmonary function abnormalities in patients undergoing allogeneic hematopoietic cell transplantation is high, especially in those who develop GvHD. A decline in diffusion capacity and restrictive pattern of ventilation develop in the majority of patients after alloHCT. It is reasonable to include pulmonary function testing into standard periodic examination of patients undergoing alloHCT.

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

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Chapter 20
Lung Impairment in Scleroderma

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Abstract Scleroderma typically manifests as fibrosis of the skin, but may also involve other organs, particularly the lungs. Interstitial lung disease and functional abnormalities are observed in the majority of patients. The aim of this study was to evaluate radiological changes in the lungs and their correlation with functional disorders in scleroderma patients. The study was conducted in 37 scleroderma patients (F/M-31/6). High resolution computed tomography (HRCT), Warrick score system and spirometry, body plethysmography, and lung diffusion examinations (DLco) were performed. The HRCT showed septal and subpleural lines in 70%, ground-glass opacities in 51%, and honeycomb lungs in 30% of the cases. The DLco values were decreased in 92% of the patients. Total lung capacity (TLC) showed a restrictive pattern in 24% of the patients, and only in 11% of them obstruction predominated. The Warrick score correlated inversely with both DLco ($r=0.36$; $p>0.05$). Interstitial lung disease often coexists with scleroderma and is accompanied by functional lung abnormalities.

Keywords Scleroderma • Lung • Lung diffusion capacity • Spirometry • Warrick score

20.1 Introduction

Scleroderma or systemic sclerosis (SSc) is a chronic connective tissue disease of unknown etiology, typically manifested as fibrosis of the skin. The disease may be classified as diffuse systemic sclerosis (dSSc) and limited systemic sclerosis (lSSc). The first type characterized by fast progress, extensive

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skin changes and early organ complications is often connected with the presence of anti-topoisomerase I antibodies (Scl-70 antibodies). Clinical course of lSSc is slow, skin changes are localized in distant parts of the body, and serious organ complications appear late. Patients suffering from limited systemic sclerosis are usually positive for anticentromere antibodies. Autoimmunological processes, microcirculatory changes, and abnormal production of collagen by fibroblasts lead to skin and internal organs fibrosis. Lung fibrosis in systemic sclerosis is typically connected with Scl-70 antibodies, therefore is often observed in dSSc (Kowal-Bielecka et al. 2009).

Lung involvement is observed in 70–90% of patients suffering from SSc, when alive, and up to a 100% of cases at autopsy (Bellia et al. 2009). Interstitial lung disease associated with SSc is a well recognized cause of premature death in the group of these patients (Ioannidis et al. 2005). Some SSc patients can be asymptomatic or remain stable in the course of the disease for years (Launay et al. 2006). The most sensitive and reproducible method for detection and staging of interstitial lung changes is high resolution computed tomography (HRCT) and the Warrick score system helps evaluate the severity of lung disease (Warrick et al. 1991).

The aim of the present study was to evaluate radiological changes in the lungs and their correlation with functional impairments in scleroderma patients.

20.2 Methods

The study was performed in accordance with the Declaration of Helsinki for Human Experimentation and was approved by a local Ethics Committee. Thirty seven scleroderma patients (F/M-31/6), mean age 43.2 ± 13.9 years were enrolled into the study. The diagnosis was established on the basis of recommendations from the European League against Rheumatism (EULAR) of 2009 (Kowal-Bielecka et al. 2009). HRCT was performed with a GE Light Speed VCT 64-row CT scanner. Five essential abnormalities were distinguished and their severity assessed with the Warrick score: ground glass opacities (score 1), irregularities in the pleural margins (score 2), septal and subpleural lines (score 3), honeycomb lung (score 4), and subpleural cysts (score 5). To each severity score, the extent score was added. Abnormality involving 1–3 segments constituted the extent score 1, 4–9 segments – extent score 2, and more than 9 segments – extent score 3. A total score range was 0–30. The higher the Warrick score, the more advanced were radiological changes in the lungs.

Functional evaluation of the lung included spirometry, body plethysmography, and single-breath carbon monoxide (CO) diffusion measurements. Forced expiratory volume in 1 s (FEV1), forced vital capacity (FVC), and FEV1/FVC ratio were assessed in spirometry (Flowscreen, Jaeger) and total lung capacity (TLC) was measured in a body plethysmograph (Jaeger). Measurements and evaluation was conducted according to European Respiratory Society (ERS) and American Thoracic Society (ATS) recommendations (Pellegrino et al. 2005; Hansen et al. 2007; MacIntyre et al. 2005; Miller et al. 2005; Wagner et al. 2005).

Continuous variables were expressed as means ± SD and minimum and maximum values. Correlation between parameters was assessed with Pearson's correlation. A p-value of <0.05 was considered as statistically significant. Statistical analysis was performed using Statistica software package version 6.0.

20.3 Results

In the examined group of 37 patients, scleroderma duration ranged from 1 to 20 years. Antinuclear antibodies (ANA) were positive in 9%, antiScl-70 (antitopoisomerase) antibodies in 59%, and anticentromere antibodies in 37% of the patients. Sixty two percent of the patients had diffuse systemic

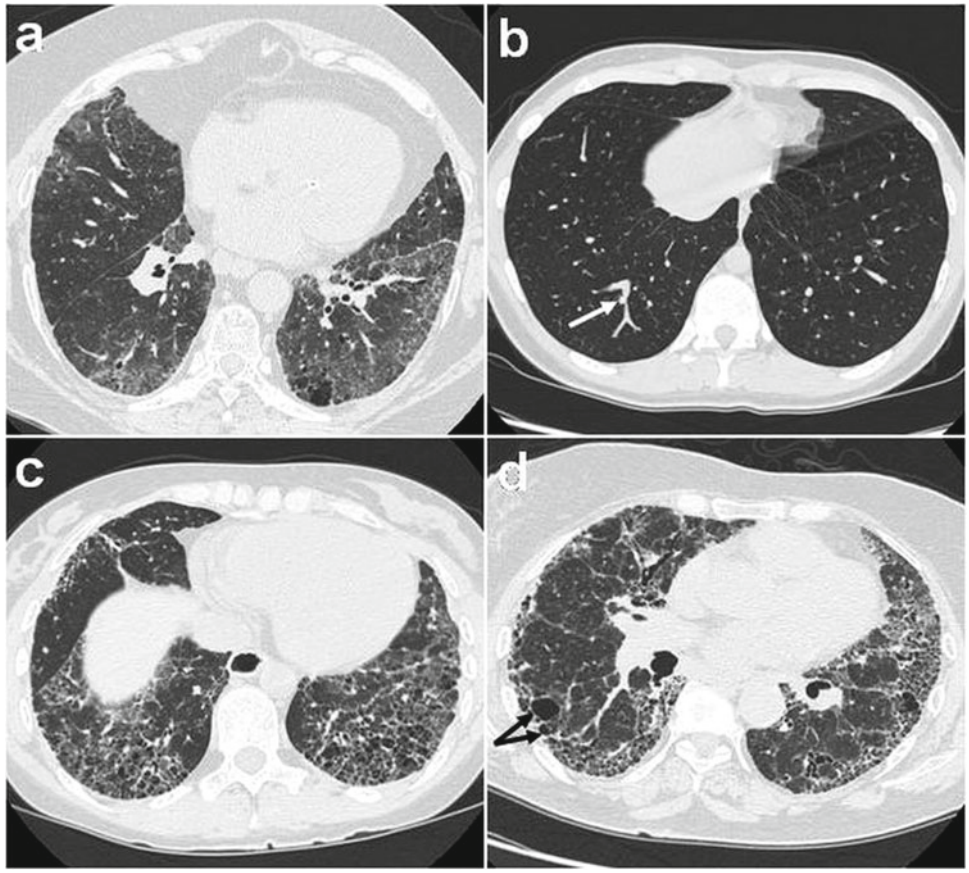

Fig. 20.1 HRCT scans. (**a**) Both-sided ground glass opacities; (**b**) Septal and subpleural lines (*arrow*); (**c**) Areas with honeycomb in the lower lobes; (**d**) Subpleural cysts at the basal segment level (*arrows*)

Table 20.1 Radiological lung abnormalities in scleroderma

	%
Ground-glass opacities	51
Linear septal and subpleural thickening	70
Irregularities in pleural margins	70
Thin-walled subpleural cysts	9
Honeycomb lung	30

sclerosis (dSSc) with extensive, advanced skin changes and the remaining 38% had limited disease (lSSc). The treatment involved azathioprine, cyclophosphamide, d-penicylamine, and low dose corticosteroids. The patients received medicines in various combinations for about a 12-month period. Asymptomatic lung patients constituted 11% of all cases. Twenty four (65%) patients presented exertion dyspnea, 11 (29%) dry cough, and 2 (5%) patients had dyspnea at rest. Physical examination revealed crackles in 23 (62%) patients with SSc.

HRCT showed differentiated lung abnormalities in 32 (87%) of the patients with SSc, with the presence of both-sided interstitial lung changes localized usually to the lower lobes. The Warrick score ranged from 0 to 26, with the mean of 9.6 ± 7.6. Linear septal and subpleural thickening, irregularities in the pleural margins and ground-glass opacities were predominant. About 1/3 of the patients had honeycomb lung and 1/10 had thin-walled subpleural cysts (Fig. 20.1, Table 20.1).

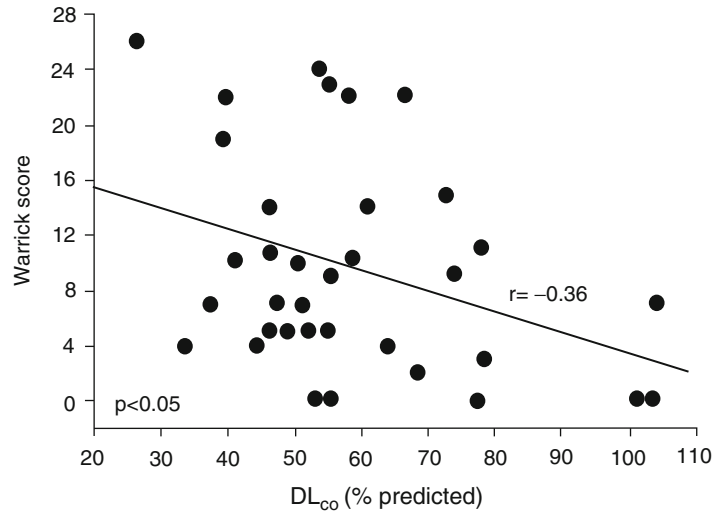

Fig. 20.2 The Warrick score plotted against lung diffusing capacity (DLco) ($r = 0.36$, $p < 0.05$)

Functional lung evaluation showed mild obstruction in 4 (11%) patients. The mean FEV1 value was 2.41 ± 0.69 L or 85.6% predicted. The patients with a normal TLC value and the Warrick score 0 had obstruction. One patient in this group revealed a slightly decreased DLco. Restriction was confirmed in 9 (24%) patients. The mean TLC value was 4.76 ± 1.21 L or 95.3% predicted. The DLco was decreased in 34 (92%) patients, with the mean of 4.40 ± 1.35 mL/min/mmHg or 58.2% predicted. Decreased DLco values coexisted with restriction in all cases. Mild functional impairments were revealed in 19%, moderate in 57%, and severe in 16% of the patients. The Warrick score correlated inversely with DLco ($p < 0.05$, $r = 0.36$), but failed to correlate significantly with TLC (Fig. 20.2). There were no appreciable differences in the frequency of symptoms, HRCT findings, and functional abnormalities between the lSSc and dSSc patients.

20.4 Discussion

Interstitial lung disease (ILD) is a leading cause of mortality and morbidity in scleroderma. ILD develops in up to 75% of patients with SSc, but clinically significant ILD occurs in just 25% of them. Non-specific interstitial pneumonia predominates in the course of the disease (Cottin 2007; Bussone and Mouthon 2011). Lung involvement frequently complicates SSc and causes loss of quality of life. Coughing and breathlessness on exertion can be the earliest symptoms of ILD (Kaloudi et al. 2007). The present study revealed these symptoms in 65% of patients. Crackles were present in 62% of patients on physical examination.

HRCT is a leading examination for the detection and evaluation of ILD in SSc, with sensitivity for recognition of abnormalities of up to 60% of patients. Pulmonary involvement may be limited in extent and involve just 10% of lung parenchyma. Ground-glass opacities concern about 50% of cases and probably represent the first stage of lung fibrosis. An initial HRCT examination may be normal in 36% cases, while progression is observed in the course of SSc or the disease remains stable for years (Launay et al. 2006). The results of our study confirmed the presence of interstitial abnormalities in 87% of patients. The percentage of ground-glass opacities was 51% and was similar to that reported by Wells (2008). The presence of honeycomb was revealed in 30% of the patients examined, which is close to the 37% reported by Goldin et al. (2008). HRCT also revealed linear septal or subpleural

thickening and irregularities in the pleural margins. In the present study we confirmed the findings of Warrick et al. (1991) and Bellia et al. (2009) showing that the Warrick score inversely correlates with diffusing lung capacity for CO. However, we did not confirm a similar inverse relationship regarding the TLC as reported by those authors. The interstitial abnormalities were present with various intensity and combinations, but we did not find any consistent differences in the intensity of HRCT changes and functional abnormalities between lSSc and dSSc patients.

More than 90% of the SSc patients have lung function abnormalities, particularly regarding lung diffusing capacity. Therefore, lung function assessment should be performed in every newly diagnosed patient with SSc and once yearly during follow-up (Behr and Furst 2008). Respiratory system involvement is often the cause of death in systemic sclerosis patients. Therapeutic approach is limited in advanced lung fibrosis and treatment is most effective at early stages of disease when systemic sclerosis is difficult to diagnose. There are no early markers of SSc and typical antibodies are not present in all patients thus, radiological and functional evaluation of lung abnormalities in SSc may be considered as a useful diagnostic tool (Dougados et al. 2004; Avouac et al. 2009).

20.5 Conclusions

Interstitial lung disease in patients with scleroderma may coexist with functional abnormalities. The Warrick score based on HRCT, accompanied by lung diffusing capacity and total lung capacity tests could be recommended for the evaluation of lung damage and monitoring its progress in the course of scleroderma.

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

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Chapter 21
Severity of Nocturnal Cardiac Arrhythmias Correlates with Intensity of Sleep Apnea in Men

E. Szaboova, D. Holoubek, Z. Tomori, P. Szabo, V. Donic, and B. Stancak

Abstract Various cardiac arrhythmias frequently occur in patients with sleep apnea, but complex analysis of the relationship between their severity and the probable arrhythmogenic risk factors is conflicting. The question is what cardiovascular risk factors and how strongly they are associated with the severity of cardiac arrhythmias in sleep apnea. Adult males (33 with and 16 without sleep apnea), matched for cardiovascular co-morbidity were studied by polysomnography with simultaneous ECG monitoring. Arrhythmia severity was evaluated for each subject by a special 7-degree scoring system. Laboratory, clinical, echocardiographic, carotid ultrasonographic, ambulatory blood pressure, and baroreflex sensitivity values were also assessed. Moderate sleep apnea patients had benign, but more exaggerated cardiac arrhythmias than control subjects (2.53 ± 2.49 *vs.* 1.13 ± 1.64 degrees of cumulative severity, $p < 0.05$). We confirmed strong correlations between the arrhythmia severity and known arrhythmogenic risk factors (left ventricular ejection fraction and dimensions, right ventricular diameter, baroreflex sensitivity, carotid intima-media thickness, age, previous myocardial infarction, and also apnea-hypopnea index). In multivariate modelling only the apnea-hypopnea index indicating the sleep apnea intensity remained highly significantly correlated with the cumulative arrhythmia severity ($\text{beta} = 0.548$, $p < 0.005$). In conclusion, sleep apnea modifying cardiovascular risk factors and structures or functions provoked various nocturnal arrhythmias. The proposed scoring system allowed a complex analysis of the contribution of various triggers to arrhythmogenesis and confirmed the apnea-hypopnea index as an independent risk for nocturnal cardiac arrhythmia severity in sleep apnea.

Keywords Arrhythmia scoring • Cardiovascular risk factors • Hypoxemia • Nocturnal cardiac arrhythmias • Obstructive sleep apnea

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21.1 Introduction

Cardiac arrhythmias are frequent in patients with sleep apnea-hypopnea syndrome (SAHS) and represent a potential risk for increased cardiovascular (CV) morbidity and mortality. Data analyzing the prevalence and severity of cardiac arrhythmias in sleep apnea patients are discrepant. It is mainly due to the separate analysis of various arrhythmias and lack of standardized complex scoring design (Ryan et al. 2005; Mehra et al. 2009). Various arrhythmia classifications have been employed (Lown and Wolf 1971; Morganroth 1984; Zoni Berisso et al. 1996), but they are being continuously modified (Brusoni et al. 1983; Harbison et al. 2000) to meet a scoring system suitable for healthy and pathological heart with respect to frequency and complexity of arrhythmias. The genesis of cardiac arrhythmias in SAHS is complex and is supported by the presence of arrhythmogenic substrate and mechanisms and of modulating factors. Marked neuro-humoral and hemodynamic changes develop during apnea/hyperventilation episodes, especially obstructive ones. Upper airway obstruction, hypoventilation, exaggerated intrathoracic pressure oscillations with increased cardiac wall stress (Hall et al. 1998; Schafer et al. 1998), hypoxemia, and acidosis can all elicit various reflex and humoral mechanisms, resulting in arousal, hyperventilation, hyperoxia, and activation of autonomic nervous system (Hedner and Grote 1998; Mehra et al. 2009). As a result of such an apneic milieu, electrophysiological changes of cardiac tissue may occur triggering various dysrhythmias by one or more mechanisms (Szaboova et al. 1997; Blomström-Lundqvist et al. 2003). The appearance of different categories of complex dysrhythmias in the same patient may constitute a higher risk for fatal arrhythmias.

The aim of the present study was to compare the occurrence and severity of nocturnal cardiac arrhythmias (NCA) in subjects with/without SAHS matched for CV pathology and risk factors (RF) for atherosclerosis (AS), and to assess the association between the severity of NCA and various arrhythmogenic risk factors. A complex statistical analysis of such a relationship is conflicting while dichotomous approach is used. For the purpose of our study we constructed a special empirical 7-degree scoring system, allowing a new approach with a non-dichotomous evaluation of the cumulative severity of various cardiac arrhythmias and statistical analysis.

21.2 Methods

21.2.1 Laboratory and Clinical Characteristics of the Subjects

A local Ethics Committee approved the investigation and informed consent was obtained from all study participants. Adult males (33 with and 16 without SAHS) matched for specific CV RF and co-morbidity were studied using standard overnight polysomnography in a sleep laboratory of P.J. Safarik University in Kosice, Slovakia, between January and July 2002. The subjects underwent standardized laboratory and clinical examination. Resting ECG, echocardiographic (ECHOCG), ambulatory blood pressure (ABPM), carotid ultrasound (USG), and baroreflex sensitivity (BRS) data were collected. The patients were selected into the SAHS and non-SAHS groups, each consisting of three subgroups (apparently healthy subjects, patients with arterial hypertension – AH and coronary artery disease – CAD). The study design required rigorous group matching. Polysomnography and patient selection were provided by a sleep specialist. ECG data (resting and polysomnographic) were reviewed by a single certified cardiologist. ECHOCG, BRS testing and ABPM were managed by another cardiologist, carotid arteries were studied by an angiologist, each of them blinded to

polysomnographic data. Inclusion criteria were: excellent polysomnographic data quality, baseline ECG without dysrhythmias, male gender, 20–80 years of age, and presence of determined CV pathology. Exclusion criteria included insufficiency of vital organs, known cardiac arrhythmias including life-threatening ones, acute coronary syndrome and coronary interventions within previous 3 months, treatment of OSAHS, bronchial asthma, abnormal electrolyte status, apparent acute and chronic inflammatory diseases, complicated haematological disorders, endocrinopathy, diabetes mellitus (DM) with chronic complications or treated with insulin, malignancy, alcohol or drug abuse and non-compliance. RF for AS, hyperlipoproteinaemia (HLP), DM, AH and obesity were evaluated according to international guidelines (Mancia et al. 2007). CAD was based on the history of previous myocardial infarction (MI) or coronary revascularization, presence of typical clinical symptoms confirmed with positive exercise testing with ECG or myocardial perfusion scintigraphy or the finding of significant (>50%) stenosis on coronarography (Fox et al. 2006).

21.2.2 ECG Analysis of Arrhythmia Severity

Baseline ECG and ECG from a complete overnight polysomnography were scored manually. For statistical analysis we used polysomnographic ECG (single-channel ECG with modified lead I; sample rate 100 Hz). Baseline ECG served for comparison and identification of any daytime resting ECG pathology. Firstly, the occurrence, type, and frequency of arrhythmias were assessed in each subject. The severity was calculated separately for three arrhythmia types: supraventricular, ventricular ectopy and conduction blocks, and had a value of the most severe documented arrhythmia. The cumulative degree of arrhythmia severity for each subject was the sum of the highest calculated severity for supraventricular, ventricular arrhythmias and blocks (Table 21.1).

ECG recognition of arrhythmias was compatible with the latest ESC guidelines (Blomström-Lundqvist et al. 2003; Zipes et al. 2006; Camm et al. 2010). Premature beats (either supraventricular – SVES or ventricular – VES) were defined as single, frequent, unifocal/multifocal and repetitive (≥2 premature successive beats: couplet, triplet, non-sustained tachycardia). Supraventricular tachycardia (SVT) was presented with narrow QRS (<120 ms) and heart rate ≥100 beats/min. A QRS width of >0.14 s favored ventricular tachycardia (VT). Non-sustained ventricular tachycardia (NVT) was defined as ≥3 consecutive VES with a mean rate of ≥100 beats/min, lasting <30 s, sustained VT lasting >30 s. Conduction delay arrhythmias documented in our study included sinus arrest, sino-atrial exit block – SAB, atrio-ventricular block – AVB, bifascicular or trifascicular block and were classified according to standard ECG patterns.

To distinguish between benign, potentially malignant and malignant (fatal) type of arrhythmias we used Morganroth's classification (1984), modified by the latest ACC/AHA/ESC guidelines (Zipes et al. 2006). This rating was adapted for the purpose of our study (Table 21.1) to reach a special 7-degree scale of severity. Potentially life-threatening ventricular arrhythmias were defined as frequent (VES > 10/h) and repetitive and/or complex forms (≥3 Lown's scoring). Inclusion of complex supraventricular (atrial fibrillation, flutter, tachycardias) and severe bradycardic arrhythmias/asystolia (sinus arrest with asystolia 2–4 s, type 2 2nd degree SAB and AVB, 3rd degree SAB, 3rd degree AVB with narrow QRS, bi-fascicular and tri-fascicular block) (Vardas et al. 2007) into the potentially lethal arrhythmia group reflects the multitude of combination possibilities for initiation of a re-entrant pathway. As lethal arrhythmias were signed: ventricular fibrillation/flutter, sustained VT, torsades de pointes, brady-arrhythmic and asystolic arrest (asystolia >4 s, 3rd degree AVB with wide QRS and electromechanical dissociation).

Table 21.1 Scoring scale of various types and frequency of arrhythmia cumulative severity

	Degree of severity						
Type of arrhythmias	1	2	3	4	5	6	7
Supraventricular							
SVES <100/h	+						
SVES >100/h			+				
Couplet, triplet, bigeminy, salvos		+					
Paroxysmal SVT				+			
Atrial flutter					+		
Atrial fibrillation, WPW syndrome						+	
Ventricular							
VES ≤10/h	+						
VES 10–100>/h			+				
VES 100–200>/h				+			
VES >200/h					+		
Polymorphic, bigeminy				+			
Couplet, triplet, salvos					+		
R/T, non-sustained VT						+	
Torsades de pointes, sustained VT, VF							+
Blocks							
Sinus arrest with asystole <2 s			+				
Sinus arrest with asystole 2–4 s					+		
Sinus arrest with asystole >4 s							+
2nd SAB Wenckebach			+				
2nd SAB Mobitz 2						+	
3rd SAB						+	
1st AVB		+					
2nd AVB Wenckebach			+				
2nd AVB Mobitz 2						+	
3rd AVB with narrow QRS						+	
3rd AVB with wide QRS							+
Bundle branch block (monofascicular)							
RBBB (incomplete, complete)		+					
LAHB, LPHB		+					
Bifascicular block							
LBBB, RBBB + LAHB/LPHB (norm PR)				+			
Trifascicular block							
LBBB, RBBB + LAHB/LPHB (long PR)						+	
LBBB/RBBB alternans						+	

Cumulative severity of nocturnal cardiac arrhythmias. Arrhythmias with 1–3 severity were defined as benign, 4–6 as potentially fatal, 7 as fatal

Example: the overall arrhythmia severity for patient revealed SVES < 100/h + 1x run of SVT + VES <10/h + ventricular bigeminy='8'

SVES supraventricular extrasystoles, *SVT* supraventricular tachycardia, *WPW* Wolff-Parkinson-White syndrome, *VES* ventricular extrasystoles, *VT* ventricular tachycardia, *VF* ventricular fibrillation, *SAB* sinoatrial-exit block, *AVB* atrioventricular block, *RBBB* right bundle branch block, *LBBB* left bundle branch block, *LAHB* left anterior hemiblock, *LPHB* left posterior hemiblock

21.2.3 Assessment of Arrhythmia-Related Predictors

21.2.3.1 Trans-thoracic Echocardiography

An ultrasonograph with 2.5 MHz probe (AU4 Idea, Esaote Biomedica), parasternal and apical views were used to acquire information on structural and functional parameters of the heart: end-diastolic dimensions of left atrium (LA), left and right ventricles (LV, RV), interventricular septum (IVS) and LV posterior wall thickness (LVPW) and LV ejection fraction (LVEF).

21.2.3.2 Ambulatory Blood Pressure Monitoring

ABPM was performed by a device Meditech ABPM 03, occasionally Cardiotens 01 (Meditech, Budapest) according to current guidelines. Parameters evaluated in our study were: average 24-h, daytime and night-time values of systolic and diastolic blood pressure (BP) in mmHg and the diurnal index (DI). Thresholds for confirmation of AH with different types of BP measurement are generally known (Mancia et al. 2007).

21.2.3.3 Ultrasonographic Investigation of the Carotid Arteries

The carotid arteries were examined in a supine position with a real-time triplex, high-resolution B-mode ultrasonograph (AU4 Idea, Esaote Biomedica, 7.5 MHz probe). The largest value of intima-media thickness (IMTmax) and the occurrence of IMT ≥ 0.85 mm, were used to detect the earliest signs of AS, as described previously (Szaboova et al. 2007).

21.2.3.4 Baroreflex Sensitivity

Spontaneous BRS was tested using the method of controlled breathing (6 breathing cycles/min) by an oscillometer Colin-CBM 7000. Data were evaluated using a special software (Scope Win 95) as spectral and sequence analysis. All measurements were performed under standard conditions (La Rovere et al. 1998). The sequence method identifies the time sequence of >4 consecutive heart beats with a progressive increase/reduction of systolic BP (SBP) and RR interval prolongation/shortening. Spectral analysis allows evaluation of the measured values of SBP and RR intervals in short sections using Fast Fourier transformation. 3 × 5-min periods were tested and the final result was the average of three measurements. The values <6 ms/mmHg were pathological.

21.2.3.5 Sleep Studies

Polysomnographic monitoring was performed with Alice 3 device (Respironics). Recordings were performed overnight, with continuous ECG monitoring. Technical parameters of the device have been described elsewhere (Szaboova et al. 2007). All records were scored manually. Apnea was identified as a cessation of airflow or <20% of baseline. Hypopnea was scored if airflow signal were reduced of >30% with >3% oxygen desaturation, lasting ≥10 s. Obstructive apnea (OA) was identified if airflow was absent for ≥10 s with paradoxical thoraco-abdominal motion, central apnea if there was no

thoraco-abdominal excursion. Mixed apnea was associated with absent inspiratory effort initially, followed by resumption of inspiratory effort. The presence of ≥10 apneas-hypopneas/h of sleep of mostly (>50%) obstructive type were classified as OSAH (ASDA Report 1999). Indices calculated per hour of sleep were as follows: apnea-hypopnea index (AHI), arousal index (ArI), minimal and average nocturnal oxygen saturation ($MinSaO_2$, $AvgSaO_2$), mean saturation after oxyhemoglobin desaturations by >3% ($DeSaO_2$) and the percent of time spent with $SaO_2 < 90\%$. Total sleep time was defined as hours of actual REM and non-REM phase of sleep during an individual sleep-time period (ASDA Report 1999, Szaboova et al. 2007).

21.2.4 Statistical Methods

The results were expressed as means ± SD and analyzed using a statistical package STATISTICA 1999. The non-parametric Mann Whitney U test was used for continuous parameters, chi-squared test or Fischer's exact test were calculated in the assessment of proportions. Spearman's correlation coefficient was assessed between arrhythmia severity and each potential risk factors (age, body mass index – BMI, waist-to-hip ratio – WHR, relevant co-morbidities: positive family history, AH, CAD, previous MI, smoking habit, DM, respiratory variables: AHI, $MinSaO_2$, $AvgSaO_2$, $DeSaO_2$ and $SaO_2 < 90\%$, ECHOCG findings: LVEF, dimensions of LA, RV, LV, LVPW, IVS, carotid IMTmax, BP characteristics: pulse pressure, DI, nocturnal mean systolic and diastolic BP and parameters of BRS). Backward-selection stepwise regression was used to evaluate the relation of arrhythmia severity and those potential arrhythmogenic variables, which showed a significant association in the univariate model (age, WHR, LVEF, dimensions of LA and LV, thickness of IVS, LVPW and BRS). We also included respiratory parameters as potential predictors in this model (AHI, $MinSaO_2$, $AvgSaO_2$, $DeSaO_2$). Firstly all independent variables were entered into the model with $p < 0.05$, finally the non-significant variables $p > 0.1$ were removed sequentially.

21.3 Results

21.3.1 Subject Characteristics

Baseline, anthropometric, laboratory, clinico-physiological and respiratory characteristics in subjects with and without SAHS, matched for AS risk factors and CV co-morbidity are shown in Table 21.2. Obstructive dominant apnea was evident in 76% of the SAHS patients, in the remaining ones no dominant apnea type was determined. The prevalence of main CV risk factors was similar in both groups. There were non-significantly more elderly, hypertensive patients with positive family history in the SAHS group, whereas the non-SAHS group revealed a higher occurrence of obesity, DM, HLP, smoking, established CAD, and previous MI. The mean age was at a risk level in both groups. No antiarrhythmic/potentially pro-arrhythmic medication was given. Hypertension was optimally controlled in 2/3 of patients in both groups. The management of metabolic risk factors and CAD was satisfactory and up-to date in all patients. Baseline ECG abnormalities included incomplete RBBB, left anterior and posterior hemi block, left ventricular strain and post-infarctional changes (pathologic Q waves) in CAD patients. Ischemia-related patterns were not recognized.

Table 21.2 Baseline, anthropometric, laboratory, clinical characteristics, and atherosclerotic risk factors in subjects with and without SAHS

	SAHS	Non-SAHS	
Parameters	n = 33	n = 16	p
Age (year)	52 ± 8	48 ± 11	NS
BMI (kg/m^2)	28.9 ± 4.4	29.7 ± 4.4	NS
Waist circumference (cm)	101.8 ± 9.9	100.2 ± 11.5	NS
Total cholesterol (mmol/l)	5.5 ± 1.1	5.1 ± 0.8	NS
Triglycerides (mmol/l)	2.6 ± 3.9	2.0 ± 0.9	NS
HDL-cholesterol (mmol/l)	1.2 ± 0.3	1.2 ± 0.3	NS
LDL-cholesterol (mmol/l)	3.7 ± 1.2	3.1 ± 0.7	NS
Glycaemia (mmol/l)	5.6 ± 0.8	5.6 ± 1.2	NS
Age risk (≥45 years) (n/%)	28/84.8	9/56.2	NS
Positive family history (n/%)	7/21.2	2/12.5	NS
AH (n/%)	21/63.6	7/43.7	NS
DM (n/%)	2/6.1	3/18.7	NS
HLP (n/%)	18/54.5	9/56.2	NS
Obesity (BMI) (n/%)	9/27.3	6/37.5	NS
Central obesity (waist) (n/%)	14/42.4	7/43.7	NS
Smoking (n/%)	19/57.6	10/62.5	NS
CAD (n/%)	8/24.2	5/31.2	NS
Previous MI (n/%)	5/15.1	3/18.7	NS
AHI (n/h)	26.5 ± 15.8	4.1 ± 2.6	$<10^{-11}$
Arousal index (n/h)	22.2 ± 13.7	14.9 ± 13.3	0.06
$MinSaO_2$ (%)	76.7 ± 10.5	87.0 ± 6.5	0.0002
$AvgSaO_2$ (%)	90.5 ± 4.8	91.8 ± 2.4	NS
$DeSaO_2$ (%)	85.7 ± 4.9	88.4 ± 4.8	0.048
Total sleep time (h)	5.4 ± 1.98	5.7 ± 2.0	NS
$SaO_2 < 90$ % (%)	18.8 ± 19.5	13.5 ± 21.9	NS

Data are as means ± SD, unless otherwise stated

SAHS sleep apnea-hypopnea syndrome, *BMI* body mass index, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *AH* arterial hypertension, *DM* diabetes mellitus, *HLP* hyperlipoproteinemia, *CAD* coronary artery disease, *MI* myocardial infarction, *AHI* apnea-hypopnea index, *$MinSaO_2$* minimal, *$AvgSaO_2$* average nocturnal oxygen saturation, *$DeSaO_2$* mean saturation after oxyhemoglobin desaturations by >3%, *$SaO_2 < 90\%$* %-percent time of sleep spent with oxygen saturation <90%, *n/h* number per hour of sleep

21.3.2 Arrhythmia-Related Predictors

Table 21.3 shows a comparison of main arrhythmia-related predictors. No significant hypertension-related structural changes, or differences in blood pressure values measured during 24-h ambulatory monitoring were documented between both groups. Sonographic parameters indicated significantly more severe AS lesions in the SAHS group confirmed by carotid artery maximal wall thickness and the occurrence of IMT > 0.85 mm. It suggests an additional atherogenic effect of SAHS (Szaboova et al. 2007; Sorajja et al. 2008). We documented significantly decreased BRS in the SAHS compared with non-SAHS subjects, but values remained physiological in both groups.

21.3.3 Arrhythmia Severity

The SAHS patients had significantly more frequent and exaggerated cardiac arrhythmias *vs.* non-SAHS subjects (2.53 ± 2.49 *vs.* 1.13 ± 1.64, $p < 0.05$), but the mean value of cumulative arrhythmia

Table 21.3 Cardiovascular (structural and functional) characteristics of subjects with and without SAHS

Parameters	SAHS	Non-SAHS	p
Cumulative arrhythmia severity	2.5 ± 2.5	1.1 ± 1.6	0.02
Grade of arrhythmia	(0–9)	(0–6)	
LVEF (%)	57.2 ± 5.0	60.1 ± 7.4	NS
LA (mm)	38.2 ± 2.8	38.1 ± 3.9	NS
LV (mm)	47.6 ± 3.8	46.2 ± 5.2	NS
IVS (mm)	11.9 ± 1.6	11.1 ± 1.3	NS
LVPW (mm)	10.4 ± 1.6	9.7 ± 1.8	NS
RV (mm)	28.1 ± 2.4	26.5 ± 2.3	0.02
BRS (spectral)	12.7 ± 8.2	19.8 ± 10.6	0.01
BRS (slope)	12.8 ± 9.9	20.0 ± 11.6	0.02
24-h SBP (mmHg)	127 ± 12	122 ± 11	NS
24-h DBP (mmHg)	77 ± 8	71 ± 14	NS
D SBP (mmHg)	131 ± 12	129 ± 11	NS
D DBP (mmHg)	82 ± 9	79 ± 8	NS
N SBP (mmHg)	119 ± 12	117 ± 11	NS
N DBP (mmHg)	70 ± 8	69 ± 7	NS
Diurnal index	8.3 ± 6.3	8.3 ± 8.6	NS
PP (mmHg)	49 ± 7	51 ± 11	NS
IMTmax (mm)	0.9 ± 0.2	0.8 ± 0.2	0.02
IMT > 0.85 mm (n/%)	18/54.5	4/25	0.05
Stenosis <40% (n/%)	10/30.3	4/25	NS
Stenosis 40–60% (n/%)	2/6.1	0/0	NS

Data are means ± SD, unless otherwise stated

n number, *LVEF* left ventricular ejection fraction, *LA* left atrium, *LV* left ventricle, *IVS* inter-ventricular septum, *LVPW* left ventricular posterior wall, *RV* right ventricle, *BRS* baroreflex sensitivity, *24-h SBP/DBP* mean value of 24-h systolic/diastolic blood pressure, *D SBP/DBP* mean value of daytime systolic/diastolic blood pressure, *N SBP/DBP* mean value of night-time systolic/diastolic blood pressure, *PP* pulse pressure, *IMTmax* maximal value of intima-media thickness, *IMT > 0.85 mm* occurrence of IMT > 0.85 mm

severity on a 7-degree scale remained low. Benign types predominated and no fatal arrhythmias were found. The most severe arrhythmias were complex forms: short run of SVT and ventricular bigeminia, but their prevalence was also low. The occurrence of potentially lethal arrhythmias, either complex (ventricular, supraventricular, bradycardic forms) or frequent ones (VES > 100/h) was 21.2% in the SAHS *vs.* 6.3% in the non-SAHS group ($p = 0.245$). Univariate analysis in the whole group showed significant correlations of the cumulative severity of cardiac arrhythmias with such well-known predisposing factors, as: hemodynamic status, structural changes of the heart, neurogenic influence on the heart rhythm and structural changes of the arterial wall and clinical conditions (Table 21.4). The strongest correlations were found between the cumulative arrhythmia severity and LVEF, dimension of LV and BRS. Sleep apnea-related factors were in tight positive correlation with the severity of arrhythmias (AHI, ArI, REM stage sleep) (Table 21.3). In multivariate modelling the AHI very significantly correlated with the cumulative arrhythmia severity (beta = 0.548, $p = 0.0045$) (Fig. 21.1).

Table 21.4 Univariate analysis of the contribution of potential risk factors to cumulative arrhythmia severity in subjects with and without SAHS

Parameters	Spearman's R	p
LVEF	–0.53	0.0001
LA	0.35	0.016
RV	0.46	0.001
LV	0.52	0.0002
LVPW	0.42	0.03
IVS	0.43	0.003
IMTmax	0.46	0.001
BRS (slope)	–0.51	0.0004
BRS (spectral)	–0.52	0.0002
Arterial hypertension	0.33	0.02
Previous MI	0.41	0.004
Age	0.46	0.003
Waist-to-hip ratio	0.31	0.03
Apnea-hypopnoea-index	0.46	0.002
Arousal index	0.33	0.04
REM sleep	0.32	0.03

LVEF left ventricular ejection fraction, *LA* left atrium, *RV* right ventricle, *LV* left ventricle, *LVPW* left ventricular posterior wall, *IVS* inter-ventricular septum, *IMTmax* maximal value of intima-media thickness, *BRS* baroreflex sensitivity, *MI* myocardial infarction.

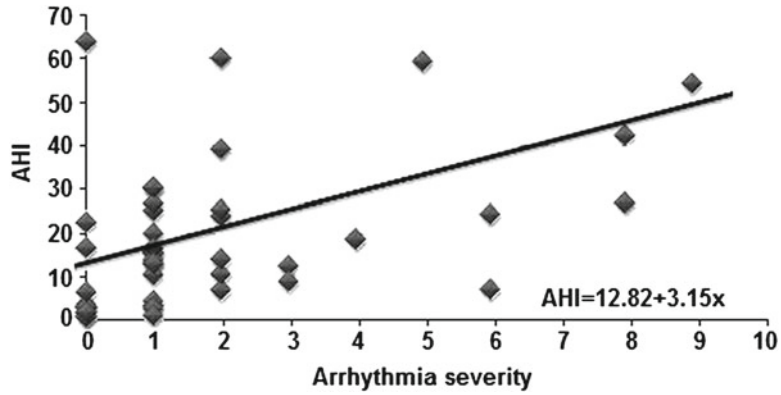

Fig. 21.1 Linear regression between cumulative arrhythmia severity and apnea-hypopnea index (*AHI*)

21.4 Discussion

The results of our cross-sectional study clearly demonstrate that despite a more risky CV profile and a higher prevalence of CAD and previous MI in the non-SAHS group, the subjects presenting moderate SAHS have more exaggerated NCA compared with the subjects without SAHS. The severity of arrhythmias shows a strong association with left ventricular systolic function and structural changes of the heart as a possible consequence of remodelling, following long-term hypertension, multifocal AS and MI, age >45 years and obesity. Functional triggers such as chronic intermittent nocturnal

hypoxemia expressed by AHI, and marked autonomic imbalance, manifesting either by AHI, ArI, BRS or duration of REM sleep stage were also identified. However, only AHI was confirmed as an 'independent predictor' influencing the cumulative arrhythmia severity. AHI seems to be an expression of multiple interactions of various triggers acting during sleep apnea. The rationale for the use of the original scoring scale is required by the fact that different categories of potentially malignant arrhythmias may occur in the same patients; thus their whole arrhythmia-related risks should be summarized. No uniform hypothesis is established regarding the mechanisms by which structural and functional factors interact to lead to the occurrence of lethal arrhythmias. Often times, it is difficult to determine with certainty the initiating event in a patient (brady-arrhythmia, or tachyarrhythmia) (Sovari et al. 2010). A clear reconfirmation of such a wide spectrum of previously established pathogenetic factors (MI, AH, low LVEF, LV hypertrophy, dilated LA, LV, blunted BRS, and sympathetic hyperactivity) (Zipes et al. 2006) in the relationship with the cumulative arrhythmia severity presented in this study underlines the suitability and validity of our scoring scale.

21.4.1 Association of NCA with Sleep-Related Breathing Disorders (SRBD)

This study confirms the previous findings showing a higher prevalence, benign, but more complex character of NCA in moderate apneic patients even with normal LV function than in controls (Grimm et al. 1996; Harbison et al. 2000; Gula et al. 2004; Alfonso-Fernandez et al. 2005; Koshino et al. 2008). However, our SAHS patients had a three times higher occurrence of complex arrhythmias during sleep in comparison with controls. More severe arrhythmias seem more likely to occur in the setting of pre-existing structural heart disease and more severe SAHS (Javaheri 2000; Quan and Gersh 2004; Ryan et al. 2005). Some studies (Harbison et al. 2000; Javaheri 2000; Kohler et al. 2008) have demonstrated benefits of nasal continuous positive airway pressure (nCPAP) on arrhythmias including potentially fatal ones occurring during sleep in patients with SAHS (Grimm et al. 1996; Harbison et al. 2000; Marin et al. 2005). No fixed or structural conduction system abnormalities were apparent in most of these patients (Grimm et al. 1996).

21.4.2 Risk of Arrhythmogenesis in SRBD

The risk of arrhythmogenesis in patients appears to be directly related to sleep apnea severity and hypoxemia (Harbison et al. 2000; Roche et al. 2003; Porthan et al. 2004; Gami et al. 2005; Mehra et al. 2006), which was confirmed also in our study. Most of rhythm disturbances in patients with SAHS showed a significant correlation in univariate analysis with nocturnal $MinSaO_2$, manifesting commonly during REM sleep (Kanagala et al. 2003), sleep fragmentation, urinary catecholamine excretion, and arousal (Gami et al. 2004; Alonso-Fernandez et al. 2005). Harbison et al. (2000) demonstrated a low occurrence of potentially malignant arrhythmias in moderate SAHS patients, showing significant relationship with AHI in a univariate model. We provided a whole-night polysomnography in sleep apneic patients and strictly matched control subjects. Using our plausible arrhythmia severity scale, in univariate analysis we confirmed a significant association of arrhythmia severity with various known triggers, but only with AHI in multivariate analysis. An independent prediction of incidental fibrillation/flutter by obesity and SAHS, reported in a retrospective large cohort study of individuals <65 years of age (Gami et al. 2007), differed from our analysis in population sample, design, lack of control group, and in the scoring method for arrhythmia evaluation. Interestingly, another study also confirmed a higher arrhythmia risk in younger (with less severe cardiac pathology) than older SAHS subjects (Mehra et al. 2006). Higher prevalence of nocturnal paroxysmal asystolia was detected as a

consequence of nocturnal sinus dysfunction and blunted diurnal parasympathetic modulation of the sinus node (Roche et al. 2003). Decreased vagal tone and increased sympathetic activity may lead to arrhythmias culminating with sudden cardiac death during the sleeping hours in patients with SAHS (Gami et al. 2005). Daytime BRS increased after 4 weeks of nCPAP therapy, indicating that the beneficial effect of treatment on the cardiac sympatho-vagal balance is not limited to the sleep period (Kohler et al. 2008). These findings illustrate that NCA in many patients with SAHS are directly related to apneic events and their autonomic effects, and are not likely caused by structural heart disease alone. This statement seems to be underlined in our study indirectly, confirming AHI as the only predictor of arrhythmia severity in the multivariate analysis.

21.4.3 Mechanisms of NCA Provocation in SRBD

A primary consequence of apnea is hypoxemia promoting sympathetic activation, ischemia of various tissues, blood-pressure elevations, systemic inflammation, and a tendency to coagulation, vascular oxidative stress and endothelial dysfunction, which may all contribute directly or indirectly to CV complications (Gami et al. 2007). Intermittent hypoxemia, hypercapnia, and hyperventilation-induced hypocapnia may trigger arrhythmias (Javaheri 2000; Koshino et al. 2008). While a bradycardic response to OA is related to hypoxia and parasympathetic hyperactivity, intrathoracic pressure swings connected with reversal of breathing and postapneic tachycardia could be an effect of hypoxia and sympathetic discharge due to arousal reaction. Chemoreceptor excitation may persist also during wakefulness in SAHS (Narkiewicz et al. 1998). In addition to these autonomic abnormalities, electrophysiological changes are responsible for arrhythmogenic mechanisms in SAHS (Gami et al. 2005). Abnormal automatism may occur due to hypoxemia and respiratory acidosis, triggered automatism may arise due to enhanced sympathetic nervous system activity associated with respiratory-related hypoxemia and arousal *via* atrial catecholamine-sensitive ion channels (Roche et al. 2003). Re-entry mechanisms may occur at the end of apneas, resulting from increased ventilatory efforts, which may lead to bradycardia-dependent increased dispersion of atrial repolarization (Franz and Bode 2003; Roche et al. 2003). Stimulation of rapidly adapting receptors, particularly in the nasopharyngeal region by strong pressure changes, activate the brainstem inspiratory center to provoke the sniff- and gasp-like aspiration reflex, characterized by rapid and strong inspiratory effort accompanied by powerful sympathetic activation, providing revitalization effects similar to autoresuscitation by gasping (Tomori et al. 2010). This may also elicit changes in cardiac transmural pressure and increase cardiac wall stress, causing diastolic dysfunction and later left atrial volume enlargement. By this way, SAHS may contribute to the cardiac remodeling (Hall et al. 1998). Our study has limitation in a relatively small sample of subjects, lack of females, and severe SAHS patients.

21.5 Conclusions

SAHS proved to be a unique condition to generate sometimes severe arrhythmias by modifying the heart function or structure mediated by chronic intermittent nocturnal hypoxemia and marked autonomic imbalance, both associated with AHI. Our study demonstrated a greater burden of cardiac arrhythmias during sleep assessed by an empirical severity scoring scale even in mild- to moderate SAHS patients. The documented association between AHI and arrhythmia severity underlines the necessity to treat SAHS in order to prevent arrhythmias. More material collected from strictly selected subjects in a proof-of-concept study with the evaluation of a large number of pathogenetic factors is needed for further analysis of the causal relationships between SAHS and arrhythmias during sleep.

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Chapter 22
β2-Adrenergic Receptor Gene Polymorphism and Response to Bronchodilating Treatment Evaluated by Spirometry

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Abstract β2-adrenergic receptors re abundantly expressed in airways, which explains the role of β2 agonists, the strongest bronchodilators, in treatment of bronchial constriction. There may be a relation between β2ADR gene polymorphism and the response to treatment with β2 agonists. In the present study we attempted to study these relationship *in vivo*, estimating spirometric values before and after the use of salbutamol in reference to variant of β2ADR gene polymorphisms. The study involved 148 healthy male volunteers. After the examination of the gene polymorphism of the β2-adrenergic receptor (β2-ADR) at nucleotide positions 46 and 79 (g.46 and g.79) we performed spirometry testing in all subjects. The pulmonary function was checked twice a day; before and 15 min after the administration of salbutamol. All subjects had normal basic values of spirometry. The use of salbutamol significantly increased spirometric values in all groups determined by β2ADR gene polymorphisms. Analysis of the spirometric values in individual groups showed a significant increase only in peak expiratory flow (g.46AA and g.79CC). The results of this study give an insight into a possibly important mechanism of the response to treatment with β2-agonists.

Keywords β2-adrenergic gene • β2-adrenergic receptor • β2-agonists • Gene polymorphism • Spirometry • Bronchodilators • Pulmonary function

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22.1 Introduction

β2-adrenergic receptors (β2ADR) (McGraw and Liggett 1999; Panebra et al. 2010; Taylor et al. 2000) are found in myocytes of smooth muscles in bronchi, respiratory tract epithelium, submucosal glands, type II pneumocytes, and cholinergic ganglion cells. They are also present in blood vessels, eosinophils, T lymphocytes, and macrophages (Liggett 1998, 2000). Stimulation of β2ADR results in the relaxation of large and small bronchi, inhibited release of mediators in allergic reaction, stimulation of mucociliary transport, and dilation of vessels supplying blood to bronchi. Reactions resulting from the stimulation of β2-adrenergic receptors are associated with the delivery of catecholamines (adrenalin and noradrenalin synthesized in adrenal glands) to the lungs. Their blood level rapidly increases as a result of increased activity of the sympathetic system during physical effort or in stressful situations, which substantially improves air flow in airways. Under physiological conditions a tonic contraction of bronchial smooth muscles occurs, resulting from the activity of vagus nerves and the non-adrenergic and non-cholinergic systems (NANC), may be reduced through administration of an agonist of the β2-adrenergic receptor.

The β2-adrenergic receptor is classified to the group of metabotropic membrane receptors interacting with the Gs protein (Liggett 2000; McGraw and Liggett 1999). The receptor is made up of a chain of 413 amino acids; it forms seven intramembrane spiral hydrophobic domains alternately linked with extracellular and intracellular loops (Cho 2010; Liggett 1997). The proper function of β2ADR depends on the receptor structures, determined by β2ADR gene polymorphism, translocation from the site of synthesis to the cellular membrane, anchoring to it, coupling with Gs protein, and the interaction with a ligand.

The β2ADR gene, cloned by Lefkowitz et al. (1990) resides on a long arm of chromosome 5 (5q31-32) and is intronless (Drysdale et al. 2000; Kotani et al. 1999; Liggett 1998; Ramsay et al. 1999; Scott et al. 1999). Up to the present time, 9 gene mutations have been identified in nucleotides. Four polymorphic positions, located in nucleotides 46, 79, 100, and 491 are responsible for the modification of amino acids in respective positions of the receptor polypeptide chain (Hein 2001; Liggett 2000; Scott et al. 1999). The most common polymorphism of β2ADR gene concerns codons 16 and 27. Polymorphism at codon 16 is associated with the potential replacement of adenine with guanine (g.46A → G) in nucleotide 46 of the gene (g.46), which results in the replacement of arginine with glycine at position 16 of the receptor polypeptide chain. The receptor with arginine at position 16 was the first cloned isoform of β2ADR, and its frequency in the Caucasian population is 15% (Small et al. 2003). A more common polymorphism at codon 27 of β2ADR, caused by the replacement of cytosine with guanine at position g.79 (g.79C → G), results in the replacement of glutamine with glutamate acid at position 27 of the receptor chain.

Spirometry is the most common of the pulmonary function tests used for the diagnosis and assessment of pulmonary conditions, monitoring their course, and evaluation of the treatment outcomes. Due to the presence of basic tonus in smooth bronchial muscles, healthy subjects may be given a fast and short-acting agonist of the β2 receptor (recommended for the bronchodilators test). Salbutamol is the most popular preparation meeting these requirements (American Thoracic Society 1995; Santus et al. 2003). In population studies, a bronchodilator test is based on the determination of difference in FEV_1 after *vs*. before the administration of a bronchodilator (Brand et al. 1992).

The objective of this study was to evaluate the reaction of bronchi to inhaled salbutamol in relation to the polymorphism of the β2ADR encoding gene at nucleotide positions 46 and 79. The results presented in this paper are a continuation of a previously published study which mostly concerned the β2ADR polymorphism (Poziomkowska-Gesicka et al. 2010). The present study combines the aspects of polymorphism with the bronchodilating effects of salbutamol, which is considered a separate ramification of the study.

22.2 Methods

The study was performed at in conformity with the Declaration of Helsinki (1989) for Human Experimentation and the protocol was approved by a local Ethics Committee. A 148 male subjects were enrolled into the study group.

Polymorphism of the β2ADR encoding gene was evaluated preliminarily at nucleotide positions 46 and 79. The material for genetic analysis was sampled from the subjects (buccal mucosa smear and oral cavity smear taken 30 min after of food or drink intake). Genomic DNA was isolated with a Sherlock AX kit from A&A Biotechnology, according to a method developed by the manufacturer.

In the polymerase chain reaction (PCR), DNA of the β2ADR gene was amplified using a pair of primers terminal for both polymorphic regions, i.e., g.46A G and g.79C→G. Transition g.46A→G resulting in the substitution of arginine with glycine at position 16 of the β2ADR polypeptide chain leads to the formation of a restriction site for the NcoI enzyme (Holloway et al. 2000) (C.↓.CATG). The digestion of the PCR product with the SatI enzyme (GC.↓.NGC) allowed indentifying genotypes g.79C→G β2ADR (27Gln/27Glu).

The fragment of the β2ADR gene was amplified on a Mastercycler thermocycler. DNA fragments and the DNA size marker obtained from digestion were separated electrophoretically on 3% agarose gel stained with ethidium bromide using a kit from Bio-Rad (Fig. 22.1).

After the examination of the gene polymorphism of the β2-adrenergic receptor (β2-ADR) at nucleotide positions 46 and 79 (g.46 and g.79) we performed spirometry testing in all subjects. The pulmonary function was checked twice a day; before and 15 min after the administration of salbutamol. Spirometric testing was conducted with a Lungtest 1,000 apparatus (MES; Cracow, Poland). The spirometer was calibrated and current data were entered (temperature, humidity and ambient pressure conditions) before measurements. Testing was carried out according to the recommendations of the European Respiratory Society with volumes reported at BTPS parameters (body temperature, pressure saturated) (American Thoracic Society 1995; Bouhuys and van de Woestijne 1971; Green et al. 1994). The model adopted in this study concerned two spirometric measurements at one visit: baseline and 15 min after administration of 200 μg salbutamol (Drysdale et al. 2000; Santus et al. 2003; Taylor et al. 2000). Before the spirometric test, subjects were interviewed by a doctor, had their height and body mass measured. The highest measured values of spirometric indices were selected for further analysis.

Data were statistically analyzed with STATISTICA 6.0. computer software. The χ^2 test compared the frequency of genotypes and allele of the gene encoding the β2-adrenergic receptor. Spirometric indices were presented as means ±SD and distribution (minimum and maximum). Normality of

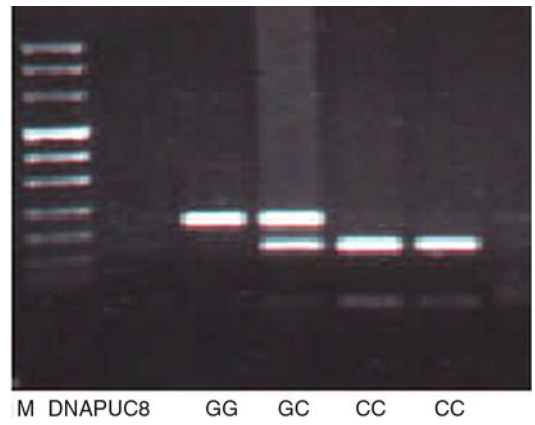

Fig. 22.1 β2-adrenergic receptor gene polymorphism at position g.79 (enzyme SatI-MBI Fermentas enzyme. M – molecular weight marker: GG-homozygote, GC-heterozygote, CC-homozygote)

distribution was analyzed with the Shapiro-Wilk test. A non-parametric Mann–Whitney U test was used for comparison of differences between the distributions other than normal, and a *t*-test was used for normal distributions. Significance of correlation between variables was evaluated with the Spearman rank coefficient of correlation. Relationships between the selected indices were evaluated based on a regression equation and ANOVA multi-factor analysis of variance. A $p<0.05$ was considered to be significant. A multiple regression model was used for the evaluation of the effect of body height, body mass, and genotype (with consideration of nucleotide positions 46 and 79) on changes in spirometric indices.

22.3 Results

The distribution of genotypes in the studied group conformed to the Hardy-Weinberg equilibrium. The study also demonstrated that both polymorphisms (SNP) g.46 and g.79 were closely correlated: D' 0.900655; $p<0.001$. The results for the identified polymorphism of the gene encoding β2ADR were confirmed through the sequencing of selected samples in order to test method reliability. Three genotypes were found in the subjects within nucleotide 46: g.46AA (16Arg/16Arg), g.46AG (16Arg/16Gly), and g.46GG (16Gly/16Gly) and another three within nucleotide 79: g.79CC (27Gln/27Gln), g.79GC (27Glu/27Gln); and g.79GG (27Glu/27Glu).

The basic values of spirometric indices in all subjects were within the normal range. The average value of FVC_{ex} was 108% of the average predicted value and FEV_1 was 102% of the average predicted value. Due to methodological reasons, in order to reduce the subjects' discomfort, VC was not measured after administration of salbutamol. A detailed analysis covered the correlation of the basic FVC_{ex} and VC in all studied subjects and in individual groups identified as based on their genotype. Basic values of FVC_{ex} were significantly correlated with VC ($r=0.91$), but were lower, as expected. The correlation between these parameters found in all subjects ($n=148$) is presented in Fig. 22.2.

The mean FEV_1 before salbutamol was 82% FVC_{ex}, and 85% FVC_{ex} of those after its administration. Te mean FVC_{ex} values did not differ before and after salbutamol. However, in some individual

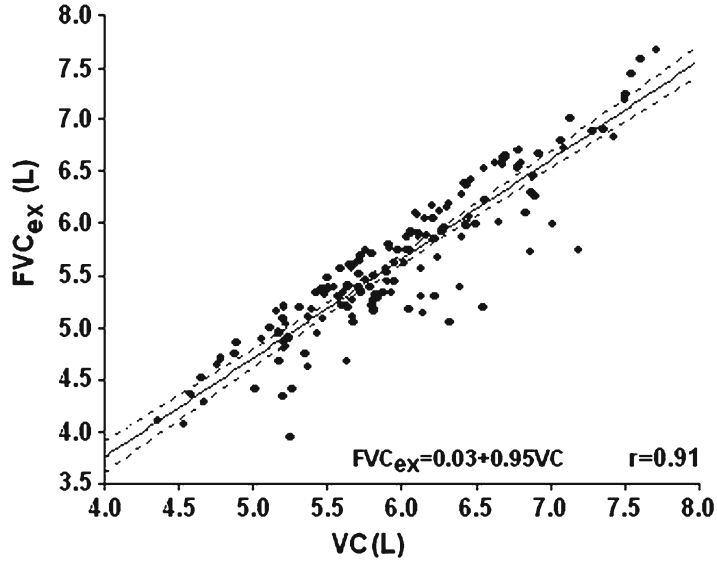

Fig. 22.2 Correlation between basic values of FVCex and VC in the study group ($n=148$)

Table 22.1 Spirometric indices before and after administration of salbutamol

	Before salbutamol	After salbutamol
FVC_{ex} (L)	5.65 ± 0.72	5.65 ± 0.68
$FEV_{0.5}$ (L)	3.24 ± 0.43	3.50 ± 0.42***
FEV_1 (L)	4.42 ± 0.56	4.69 ± 0.56***
FEV_2 (L)	5.19 ± 0.65	5.29 ± 0.65***
FEV_3 (L)	5.39 ± 0.69	5.43 ± 0.67*
PEF (L/s)	10.08 ± 1.32	10.36 ± 1.31***
MEF_{75} (L/s)	8.58 ± 1.42	9.12 ± 1.23***
MEF_{50} (L/s)	5.31 ± 1.34	6.37 ± 1.34***
MEF_{25} (L/s)	2.27 ± 0.64	2.80 ± 0.78***

Means ± SD, n = 79
*p < 0.02, ***p < 0.001

Table 22.2 Spirometric indices before and after administration of salbutamol, with consideration of the genotype g.46

	g.46AA (16Arg/16Arg) (n = 13)		g.46AG (16Arg/16Gly) (n = 29)		g.46GG (16Gly/16Gly) (n = 37)	
	Before salbutamol	After salbutamol	Before salbutamol	After salbutamol	Before salbutamol	After salbutamol
FVC_{ex} (L)	5.46 ± 0.72	5.47 ± 0.71	5.60 ± 0.72	5.59 ± 0.63	5.75 ± 0.72	5.75 ± 0.70
$FEV_{0.5}$(L)	3.13 ± 0.43	3.37 ± 0.35***	3.24 ± 0.46	3.52 ± 0.40***	3.29 ± 0.29	3.53 ± 0.41***
FEV_1 (L)	4.27 ± 0.62	4.51 ± 0.61***	4.42 ± 0.59	4.69 ± 0.54***	4.48 ± 0.53	4.74 ± 0.57***
FEV_2 (L)	4.90 ± 0.61	4.98 ± 0.57	5.18 ± 0.64	5.29 ± 0.61**	5.31 ± 0.66	5.41 ± 0.68***
FEV_3 (L)	5.14 ± 0.67	5.18 ± 0.63	5.35 ± 0.66	5.40 ± 0.63	5.50 ± 0.71	5.55 ± 0.70
PEF (L/s)	9.73 ± 1.15	10.31 ± 1.39**	10.13 ± 1.43	10.46 ± 1.35*	10.16 ± 1.30	10.31 ± 1.27
MEF_{75} (L/s)	8.08 ± 1.33	8.79 ± 1.33**	8.62 ± 1.63	9.29 ± 1.22***	8.72 ± 1.01	9.09 ± 1.20***
MEF_{50} (L/s)	5.24 ± 1.73	6.09 ± 1.54**	5.47 ± 1.39	6.49 ± 1.45***	5.20 ± 1.17	6.37 ± 1.20***
MEF_{25} (L/s)	2.19 ± 0.96	2.80 ± 1.10***	2.34 ± 0.62	2.89 ± 0.78***	2.24 ± 0.51	2.73 ± 0.65***

Means ± SD
*p < 0.02, **p < 0.01***p < 0.001

cases, FVC_{ex} values after salbutamol diverted appreciably from basic values. Because of that, we conducted a comparative analysis of the basic value and that after salbutamol based on the correlation of FEV_1 and FVC_{ex} changes ($\Delta FEV_1/\Delta FVC_{ex}$) (American Thoracic Society 1995). In 6 subjects, FEV_1 values increased after salbutamol, but the increase was unequal to changes in FVC_{ex}, which means that the $\Delta FEV_1/\Delta FVC_{ex}$ ratio decreased. These subjects were not considered in further analysis. Similarly, subjects in whom changes in FEV_1 by ±0.16 L were associated with concomitant changes in FVCex by ±0.2 L were excluded from further analysis. A decrease in $\Delta FEV_1/\Delta FVC_{ex}$ may be attributed to relaxation of bronchial walls after administration of a β2mimetic and their collapse during forced expiration or to a considerable pressure increase within the chest during forced expiration (Bouhuys and van de Woestijne 1971). Due to the exclusions outlined above, responses to salbutamol were evaluated in 79 subjects. Basic values and those after salbutamol were tabularized, and the significance of differences between them was analyzed in the entire group (Table 22.1) and in the individual g.46 (Table 22.2) and g.79 (Table 22.3) groups.

The response of bronchi to inhaled salbutamol was analyzed as the difference (Δ) from the baseline values in the individual groups according to g.46 and g.79 polymorphism. Only the ΔPEF values differed significantly between the g.46AA and g.46GG groups (p = 0.03) and between the g.79CC and g.79GC groups (p = 0.02). Greater increases of PEF were recorded in the g.46AA and g.79CC groups. ANOVA multi-factor analysis demonstrated a significant effect of genotype on PEF changes evoked

Table 22.3 Spirometric indices before and after administration of salbutamol, with consideration of the genotype g.79

	g.79GG (27Glu/27Glu) (n = 15)		g.79GC (27Glu/27Gln) (n = 42)		g.79CC (27Gln/27Gln) (n = 22)	
	Before salbutamol	After salbutamol	Before salbutamol	After salbutamol	Before salbutamol	After salbutamol
FVC_{ex} (L)	5.91 ± 0.72	5.94 ± 0.66	5.60 ± 0.70	5.57 ± 0.63	5.55 ± 0.75	5.59 ± 0.75
$FEV_{0.5}$ (L)	3.33 ± 0.34	3.59 ± 0.34***	3.26 ± 0.36	3.51 ± 0.34***	3.16 ± 0.56	3.43 ± 0.53***
FEV_1 (L)	4.57 ± 0.48	4.84 ± 0.50***	4.42 ± 0.49	4.67 ± 0.50***	4.33 ± 0.72	4.61 ± 0.71***
FEV_2 (L)	5.43 ± 0.66	5.56 ± 0.64*	5.18 ± 0.60	5.27 ± 0.61***	5.06 ± 0.72	5.15 ± 0.70
FEV_3 (L)	5.57 ± 0.70	5.71 ± 0.66	5.36 ± 0.64	5.39 ± 0.63	5.25 ± 0.73	5.32 ± 0.70
PEF (L/s)	10.30 ± 1.00	10.55 ± 1.08	10.14 ± 1.23	10.28 ± 1.22	9.82 ± 1.65	10.38 ± 1.62***
MEF_{75} (L/s)	8.75 ± 0.99	9.15 ± 1.05*	8.76 ± 1.27	9.23 ± 0.98***	8.13 ± 1.84	8.87 ± 1.70***
MEF_{50} (L/s)	5.10 ± 0.77	6.21 ± 1.01***	5.42 ± 1.24	6.47 ± 1.26***	5.23 ± 1.80	6.28 ± 1.69***
MEF_{25} (L/s)	2.26 ± 0.46	2.71 ± 0.58***	2.28 ± 0.57	2.84 ± 0.73***	2.26 ± 0.86	2.79 ± 0.99***

Means ± SD; n = 79
*p < 0.05, **p < 0.01***p < 0.001

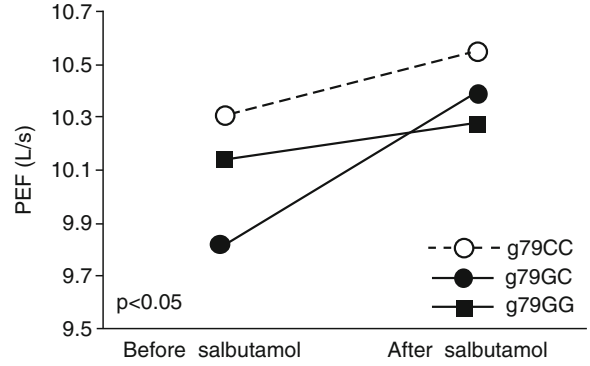

Fig. 22.3 Graphic interpretation of the ANOVA analysis of variance for PEF values in the g.79 groups

by salbutamol only in g.79CC (27Gln/27Gln) *vs.* g.79GC (27Glu/27Gln) group (p = 0.04). The crossing of lines in Fig. 22.3 demonstrates a correlation between the factors analyzed.

A multiple regression model was used for the evaluation of the effects of body height, body mass, and nucleotide positions 46 and 79 on PEF. A significant, although weak, correlation was found for the increases in ΔPEF only in the subjects with genotype g.79CC (27Gln/27Gln); ΔPEF = 0.17 + 0.403NT79CC ± 0.633 (r = 0.027; p = 0.01).

22.4 Discussion

Intensive research on β2ADR isoforms have been conducted for several years due to the physiological role of β2ADR and the frequent therapeutic use of its agonists. It has been claimed that polymorphic positions g.46A → G and g.79G → C may predispose people to the development of pulmonary, circulatory diseases, and mortality in septic shock (Barnes 1995; Nakada et al. 2010; Vacca et al. 2009). Current literature data demonstrate that the frequency of the genotypes in healthy subjects and patients is comparable (Green et al. 1994).

In the present paper, the relationship between polymorphism of β2ADR and the bronchi reaction to the inhaled salbutamol, which expresses changes in lung function, was evaluated. Subjects were divided into 6 groups: three based on the polymorphism of the β2ADR encoding gene at nucleotide position 46: g.46AA, g.46AG, g.46GG, and three based on the polymorphism of the β2ADR encoding gene at nucleotide position 79: g.79GG, g.79GC, g.79CC. Spirometric measurements performed before administration of salbutamol demonstrated the functional efficiency of the respiratory system in all subjects. The study objective was to answer the question of whether a 200 μg salbutamol dose administered to healthy subjects might cause a change in the tonus of smooth bronchial muscles reflected in lung function tests. The data obtained from 79 subjects, whose lung function tests were judged as error free and suitable for further analysis, demonstrated a significant increase in the values of spirometric indices following salbutamol. According to the study objectives, we further analyzed the response to salbutamol in the groups stratified according to the identified polymorphism of the β2ADR encoding gene. Administration of salbutamol caused in each group a significant increase in the values of spirometric indices. Watanabe et al. (1974) presented the results obtained in response to a bronchodilator test (isoetharine) carried out in healthy subjects. The authors demonstrated that a bronchodilator caused an insignificant increase in the mean FVC_{ex} and FEV_1 values, which is at variance with our present study. By contrast, Bouhuys and van de Woestijne (1971) found significant increases in FEV_1 and MEF_{50} in a bronchodilator test with isoproterenol and phenylephrine carried out in 22 healthy subjects, which conforms to the present results. Those authors, however, failed to show significant changes in PEF which in the present study was the only index significantly differentiating the groups of different polymorphism of the β2ADR. An increase in PEF in the g.46AA group was significantly greater that that recorded in the g.46GG group. Similarly, a change in PEF in the g.79CC group was significantly greater than that recorded in the g.79GC group. Other authors have reported results which are in conformity with the present study. Aziz et al. (1998) demonstrated that subjects with g.46GG achieve lower results in bronchodilator tests than those with g.46AA, which conforms to the present results. Similarly, Martinez et al. (1997) and Lima et al. (1999) after a single administration of salbutamol, obtained statistically better bronchial responses in subjects with g.46AA compared with those in the g.46GG group. Ramsay et al. (1999) found that patients with g.46AA demonstrated significantly better responses in bronchodilator tests with salbutamol than patients with g.46AG or g.46GG.

The present study had some limitations. We noted a substantial scatter of data associated with diversified responses in individual subjects. The research was conducted in men only, in a fairly homogeneous group to eliminate additional factors biasing the interpretation of results, which however also might have a bearing on the results.

22.5 Conclusions

- Salbutamol administered in a 200 μg dose to healthy subjects significantly increased the values of spirometric indices during forced expiration.
- The effects of salbutamol varied depending on the polymorphism of the β2ADR encoding gene. Subjects with the g.46AA genotype achieved a greater increase in PEF than those with the g.46GG genotype, and subjects with the g.79CC genotype achieved a greater increase than those with the g.79GC genotype.
- A difference in PEF increases in the g.46AA *vs.* g.46GG group may have resulted from lower basic spirometric values in the g.46AA group, and may not necessarily reflect the direct effect of the genotype.

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

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Chapter 23
Costs of Smoking-Attributable Productivity Losses in Poland

Joanna Lasocka, Michal Jakubczyk, and Rüdiger Siekmeier

Abstract In Poland smoking poses a severe socioeconomic problem. Not only does tobacco consumption cause an increase in direct medical costs due to the necessity for treatment of smoking-attributable diseases, but it also generates indirect costs due to productivity losses. The aim of this paper was to estimate the annual productivity loss due to smoking in Poland from the societal perspective and to compare the obtained results with the equivalent research in other selected countries (Germany, Sweden, and USA). The assessment was performed by the use of the human capital approach, considering loss of productivity until achieving the retirement age and gross income. Four distinct components of indirect costs of nicotine consumption were included: costs of premature mortality, costs of acquired disability, as well as costs of absenteeism and presenteeism caused by smokers. The costs of smoking-attributable productivity loss within a year amount to more than 15 billion PLN (1 Euro approx. 4 PLN) which is about 402 PLN per capita and 1418 PLN per smoker. This represents about 2.6% of Polish annual Gross Domestic Product (GDP), which is more than in Germany, Sweden, or the USA. This amount clearly shows the enormous socioeconomic burden and suggests the need for taking measures to reduce it.

Keywords Human capital method • Indirect costs • Productivity loss • Smoking-attributable fraction • Smoking

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23.1 Introduction

Cigarette smoking is a serious socio-economic problem in Poland and in other countries. It poses a health risk by causing cardiovascular and respiratory diseases as well as cancer, which can lead to death or permanent disability. The spreading epidemic of smoking entails increasing losses for entire societies and economies. Not only does it contribute to the increase in costs of medical treatment as a result of smoking-attributable diseases, but it also causes premature deaths, thus generating costs of lost productivity (Fagerström 2002). According to WHO, in the world about one billion people over 15 years old smoke, which represents one third of the population in this age. Annually, due to cigarettes, four million people die. Despite the awareness of the dangers of smoking and many anti-smoking campaigns, every day in the world 100,000 people begin to smoke (Krzyzanowska and Glogowski 2004). Analyzing the prevalence of smoking in the richest countries distinct diversity can be seen. Figure 23.1 shows the percentage of smokers in the G20 countries (including all EU countries) in the years 2000–2008 (by WHO most recent year of study). It clearly shows that despite the plentiful social campaigns aimed at increasing public awareness of the risk connected with smoking cigarettes, the percentage of smokers in Poland is still high compared with other countries.

The epidemic of smoking in Poland is one of the major social problems, whose costs are incurred not only by cigarette smokers, but by the whole society. This addiction is one of the major and most prevalent risk factors for many diseases and premature mortality (in the age of 35–69 years). No other factor has such a negative impact on the health status of the Poles as tobacco (Krzyzanowska and Glogowski 2004). According to the survey of the Oncology Center in Warsaw conducted in 2007, up to 34% of Polish men and 23% of Polish women smoke cigarettes every day.

The primary aims of the present study are (i) to determine the costs of smoking-attributable productivity loss in Poland within 1 year, i.e., indirect costs of smoking from a social perspective, and (ii) to compare and contrast the total costs of tobacco addiction with three other countries – Sweden (with one of the lowest smoking-prevalence), Germany (with one of the highest percentage of smokers) and the United States. The social perspective is adopted as a standard for the medical technology assessment in many European countries, including Finland, France, Netherlands, and Sweden (Report of the Panel on Cost-Effectiveness in Health and Medicine 1996). The literature points out arguments for (Jönsson 2009) and against (Brouwer et al. 2006) using such a perspective.

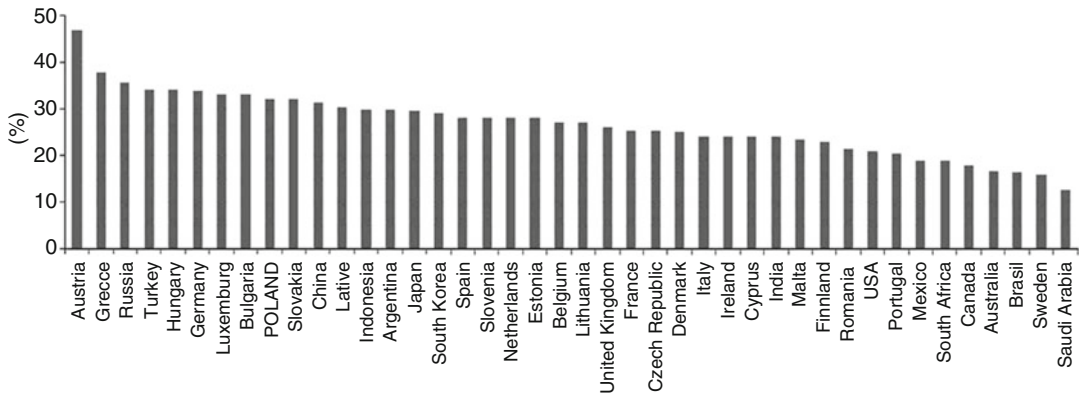

Fig. 23.1 Percentage of smokers in the G20 countries (WHO; http://data.euro.who.int/tobacco/?TabID=2404)

23.2 Methods

Four components of the indirect costs of nicotine addiction were taken into account: costs of smoking-attributable premature mortality, costs of acquired inability to work due to tobacco-related diseases, and costs of absenteeism and presenteeism of smokers. Human capital method was used with gross monthly salary as an approximation for the value of monthly productivity of person (Liljas 1998; Tranmer et al. 2005; Maciag 2008). Prevalence-based approach was chosen (Segel 2006), i.e., all the events that generate indirect costs among a cohort of all the smokers were analyzed in the 1-year period, regardless of the starting point of smoking. The costs of absenteeism and presenteeism are calculated for the period of analysis when they are actually incurred, whereas the costs of premature mortality happening in a given year and those of the inability to work acquired in that year are aggregated, encompassing the time also many years after the analysis period (according to the human capital approach – to the age of statutory retirement which in Poland is 65 years for men and 60 for women). If the population of smokers reached a steady state, then the aggregated value of the costs associated with events that happen in 1 year would equal the costs actually incurred in that year (and related, e.g., to earlier deaths).

In order to get the current value, the future costs were discounted at a rate of 5%, indicated in the guidelines of the Polish Agency for Health Technology Assessment. The discount rate of 5% is also used in other countries such as Sweden or Germany (Bolin and Lindgren 2007; Welte et al. 2000). The fact that future earnings must be increased in order to reflect their likely increase in productivity was also taken into consideration. The study assumed 1% annual rate of productivity growth, which is the standard assumption (Wendy et al. 2004). Due to the statistics conducted irregularly in Poland, the annual data from the years 2004–2010 were used for calculations, with the assumption that in this period trends in mortality, morbidity, salary structure, etc., did not change drastically.

To calculate the social costs incurred due to the premature mortality of smokers, the number of premature deaths due to this addiction in 1 year was estimated as the sum of the number of deaths for 15 most common smoking-attributable diseases reported among the Poles over 35 years old; below this age smoking rarely leads to death. For each disease, a smoking-attributable fraction (SAF) was evaluated, which determines the percentage of deaths attributable to smoking, based on relative risks (RR) (see Appendix). Relative risks associated with smoking come from the American Cancer Prevention Study II (Rockville 1989). These data are standardized and divided by age, gender, and smoking status (i.e., smokers, non-smokers, and former smokers). It should be stressed that they are probably not identical with the relative risks among the Poles, because of their different life style, type of cigarettes smoked, and other environmental or genetic factors. However, these are the best available data which are also used by European researchers (Brouwer et al. 2006; Welte et al. 2000).

To assess the productivity loss, the present value of future earnings (PVFE) was calculated for each age-group (the average age in the age-groups was adopted, i.e., 40 for the age-group 35–44, 50 for 45–54, 60 for 55–64 (men) or 55 for 55–59 (women)). The calculations (see Appendix) took into account the percentage of current and former smokers in Poland in the year 2006, employment rates and the percentage of housholds in the year 2007, the average annual salary in the year 2009, and the prediction of life length estimated in the year 2008; these data were retrived from the corresonding annual reports of the Polish Central Statiistical Office. The percentage of homemakers (i.e., housewives and househusbands) is included for a realistic estimation of the contribution of the production of men and women who are formally classified as economically inactive. The value of this work was determined by the method of the average rate of housewife.

In order to calculate the productivity loss due to smoking-attributable acquired inability to work, the number of people who acquired a permanent disability within 1 year by gender, age- and three major disease-groups (cancer, diseases of cardiovascular, and respiratory systems) was determined.

Then, for the above-mentioned diseases SAF[1] and PVFE were used. To estimate the costs of smoking-attributable sickness absenteeism, the data on the number of days of sickness absence of people insured in the Polish Social Insurance Institution by gender and disease-groups were multiplied by the proper SAF and the average daily wage.

While the term *sickness absenteeism* means absence due to illness, *presenteeism* is presence at work, despite being ill (Middaugh 2006; McCormack 2009). Presenteeism is defined as a loss of productivity, which follows when an employee comes to work, but as a result of a disease performs it below the potential. Nowadays, the term has gained a broader meaning. Too many personal phone calls, excessive internet use or additional cigarette breaks during work are regarded as examples of presenteeism (Levin-Epstein 2005). This means that smoking is not only connected with more frequent sickness absence, but also with the shortening of quality time at work, resulting from additional cigarette breaks. In Poland, no regulation entitles employees to leave the workplace to smoke; for that purpose an employee may only use official breaks. However, this is neither respected by the employees nor enforced by employers. In order to estimate the costs of additional cigarette breaks, due to the lack of reliable information, it was necessary to adopt a number of arbitrary assumptions. To calculate the number of smoked cigarettes at work it was assumed that smokers smoke about 25% of the average number of cigarettes smoked per day at work, while only one during the guaranteed break. Then, based on data from the literature (Parrott et al. 2000; Tsai et al. 2005) it was assumed that it takes a worker 6 min to smoke one cigarette. To calculate the number of smoking employees, the number of smokers belonging to labor force was used, under the assumption that in this group the unemployment rate is the same as in the whole of Poland. This deviates from reality, because smoking is highly prevalent among the unemployed, but detailed data on the subject are missing. In addition, it was optimistically presumed that 50% of smokers do not smoke during working hours (except for the guaranteed breaks), the second half however allow themselves to take some extra breaks.

23.3 Results

Cigarette smokers are exposed to a significantly increased risk of cancer, particularly of the respiratory system. Quitting smoking is associated with a reduction in relative risk (RR). The same applies to some extent to respiratory diseases (especially chronic lower respiratory tract diseases) and to cardiovascular diseases (especially caused by atherosclerotic disease). A similar situation also occurs for the values of SAFs, which are much higher for current than former smokers. Taking into account SAFs for different age-groups it can be observed that with increasing age these values among smokers are falling, whereas the inverse relationship occurs for former smokers. In total, over 24,000 people (of which 18,000 were men and 6,000 women) died prematurely due to smoking, representing over 6% of all deaths during the year and almost 60% of deaths of the above-mentioned main tobacco-related diseases. More than 2,500 men and nearly 400 women acquired permanent inability to work as a result of smoking cigarettes within 1 year. This was mainly due to cardiovascular diseases and cancer, which dominated in the older age-groups, especially among men. In all disease-groups, smoking led also to high absenteeism – on average, a smoking employee did not work almost 3 days/year due to tobacco-related diseases, mostly due to respiratory diseases. Moreover, in all three groups, men showed more absent days than women. Regarding the phenomenon of presenteeism, after taking into account all the assumptions, the results were achieved that four cigarettes for men and three for women are smoked at work beyond official breaks. This means that daily a male

[1] For such generalized disease groups SAF set by Peto and Lopez (2006) was used.

Table 23.1 Annual social smoking-attributable costs

Sex	Premature mortality (bln PLN)	Premature inability to work (bln PLN)	Sickness absenteeism (bln PLN)	Presenteeism (bln PLN)	Total costs of smoking (bln PLN)	Costs of smoking per capita (PLN)	Costs of smoking per smoker (PLN)
M	5.25	0.82	1.90	3.84	11.82	638.26	1877.24
F	0.86	0.09	0.83	1.76	3.54	179.69	781.27
Total	6.12	0.91	2.73	5.60	15.36	401.79	1418.37

smoker spends at work 24 min and a female smoker 18 min on addiction, which annually amounts to 13 and 9 days. The total smoking-attributable productivity loss from the societal perspective within a year amounts to over 15 billion PLN. Per capita, this corresponds to an amount equal to nearly 402 PLN and per smoker 1418 PLN (Table 23.1). To compare, the direct medical costs, i.e., costs of treatment of effects of smoking are estimated at 18 billion PLN, so only 20% higher than indirect costs (Krzyzanowska and Glogowski 2004). Summing up, the direct (perceived as an opportunity cost) and indirect costs, the total costs caused by smoking in 1 year from the societal perspective are amount to about 33 billion PLN.

23.4 International Comparison

Studies on costs of smoking have been conducted in many other countries (e.g., Welte et al. 2000; Centers for Disease Control and Prevention 2002; Bolin and Lindgren 2007). The value of total costs from the social perspective per capita and per smoker in Poland, Sweden, Germany, and the United States are presented (Table 23.2). All of them include both direct medical costs and indirect costs of lost productivity calculated using human capital method, prevalence-based approach, and SAFs. Although the studies were carried out in different years, the obtained results were converted to Euro at the average annual rate in 2010. However, it must be emphasized that these costs cannot be simply compared due to a number of reasons. Firstly, these studies differ slightly methodologically (especially when estimating the direct medical expenditures on the treatment of smokers) and include different components. For example, only in the Polish study productivity loss due to presenteeism was calculated, whereas the costs of perinatal diseases, burn deaths, or health consequences of secondhand smoking were not considered. In every country, slightly different smoking-attributable diseases were included. The most distinct study was carried out in the USA. It included costs of neither presenteeism and absenteeism, nor premature disability. However, it took into account all the components omitted in the Polish study (Table 23.3). Further, the human capital method is based in these studies mostly on gross salaries and obviously those are much higher in Germany, Sweden, and the USA than in Poland. That is why the total costs are also shown also as a percentage of GDP.

It is noticeable that the costs of smoking in Sweden are much lower than in other countries. That results from a smaller percentage of smokers in this country (Fig. 23.1). In Germany and in Poland, the percentage of smokers is much more similar and so are the estimated costs. What strikes are very high costs of smoking (total as well as per capita and per smoker) in the USA, as the smoking-prevalence there is lower than that in Poland or Germany. However, the total costs of smoking as a percentage of GDP are in Poland much higher compared with other countries, which reveals how serious this preventable problem is. Obviously, as stated above it is not possible to compare these costs exactly, but it seems that to some extent the differences between countries are reflected.

Table 23.2 International summary of costs of smoking

First author	Country	Total direct and indirect costs of smoking per capita (2010) (EUR)	Total direct and indirect costs of smoking per smoker (2010) (EUR)	Total direct and indirect costs of smoking in bln EUR (2010; %GDP)
Current study	Poland (2010)	219	772	8.35 (2.6)
Bolin and Lindgren (2007)	Sweden (2001)	76	558	0.75 (0.2)
Welte et al. (2000)	Germany (1993)	285	1,097	23.19 (1.0)
The Polish Social Insurance Institution (2002)	USA (1995–1999)[a]	582	3,351	155.86 (1.4)

[a]The results were depicted for 1 year

Table 23.3 Components of smoking-attributable costs included in different studies

Country	Sickness absenteeism	Presenteeism	Premature disability	Secondhand smoking	Perinatal diseases	Burn deaths
Poland	Y	Y	Y	N	N	N
Sweden	N	N	Y	N	N	N
Germany	Y	N	Y	N	Y	Y
USA	N	N	N	Y	Y	Y

Y yes, *N* no

23.5 Discussion

A large part of the total costs, almost 40%, constitute of the costs of smoking-attributable premature mortality (Fig. 23.2). However, it should be noted that also very high – almost comparable – are the costs of presenteeism. This can be explained by the fact that it was estimated for all smoking workers and not only for the age-groups above 35 years. In addition, there are a number of underlying assumptions influencing the final estimate. The lowest costs, less than 6%, the Polish society incurs due to smoking-attributable acquired inability to work. These costs might be underestimated, because of the use of SAF, designated for mortality and not for morbidity. This approximation is fully justified for diseases with short incubation periods which end in death within short periods of time. However, for diseases with long incubation periods or for chronic diseases, using SAF underestimates the number of patients.

Three-quarters of the costs of productivity loss is generated by male smokers. This is mainly due to their higher rate of employment, higher wages, longer working hours, a larger proportion of smokers (which is associated with higher SAFs in comparison with women), and greater number of cigarettes consumed. It should be noted that from the perspective of the state budget smoking may also generate savings. The state budget revenues from excise duties and VAT on tobacco products equal annually about 33.6 billion PLN, which significantly exceeds not only the medical expenses, but also the total costs estimated from the societal perspective. However, these costs should not be compared to the costs estimated in this paper due to the difference of perspectives. Tax revenues are transfers and therefore are neither a component of costs from the societal perspective, nor are they associated with the use of resources (Jakubczyk et al. 2010). On the other hand, the annual expenditure on cigarettes can be perceived as the opportunity cost of alternative use of resources. Since cigarettes are bought voluntarily, as opposed to health services, which are bought in response to the disease, this approach does not seem to be entirely legitimate and has not been raised in this paper. Yet

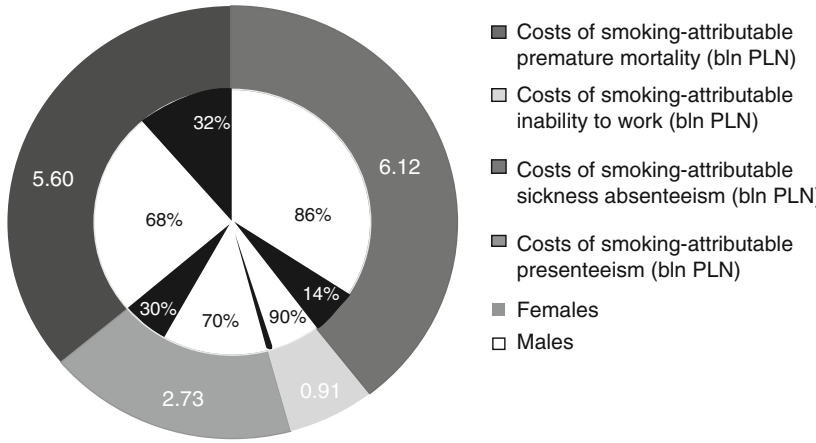

Fig. 23.2 Components of the indirect costs of smoking in Poland. Percentages of females and males are depicted in the inside circle

another issue is the fact that smokers who die prematurely generate lower costs associated with treatment of other diseases in the future. Taking into consideration future costs is an issue which is raised in the context of Health Technology Assessment (Johnston et al. 1999). Since the aim of this study is to estimate the costs of smoking and not to perform a cost-effectiveness analysis (the impact of smoking on the lost life years and on the reduced quality of life was not assessed), the above mentioned costs are not included. However, the fact that smokers could die or stop working for other reasons was taken into account. When estimating PVFE, the probability of death for each age-group and gender was included and it was assumed that the current structure of employment in Poland by sex and age will not change over the next years of their life. The annual social costs of smoking were estimated in this study using a human capital method. This approach has a strong foundation in the economic theory, but can give wrong estimates, e.g., if there are imperfections in the labor market and salaries do not reflect the true productivity (Glied 1996; Wendy et al. 2004). Nonetheless, the method of human capital is commonly used in estimating the costs of illnesses. The calculated social costs might be underestimated, because of not having included so-called passive smokers, i.e., non-smokers who are exposed to inhalation of cigarette smoke. Passive smokers (called also secondhand smokers) are much more vulnerable to smoking-attributable diseases, which results in their premature death or disability. Also, not included in the estimates is the lost productivity of families, friends, and visitors who are taking care of the patient, due to lack of relevant data.

Comparing the results of total costs of smoking from the societal perspective with other countries, it can easily be seen, that the epidemic of tobacco in Poland is one of the major social problems, whose costs are incurred not only by cigarette smokers, but also by the whole society. Despite the importance of this phenomenon, statistical data on smoking in Poland are relatively few, poorly detailed, and incomplete. The development of statistical databases on smoking, further research, and refinement of methods for estimating the costs of smoking seems thus crucial.

Acknowledgments In this article a number of epidemiological, social, and statistical data were retrieved from annual reports of the Polish Social Insurance Institution and from the Polish Central Statistics Office. These reports are judgement formative, but do not bear characteristics typical for indexed research papers contained in major citation and journal databases.

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

Appendix

The formula of smoking-attributable fraction (SAF) is as following (Bolin and Lindgren 2007; Schultz et al. 1991):

$$SAF_s = \frac{O_s \cdot (R_s - 1)}{(O_n + O_s \cdot R_s + O_f \cdot R_f)}$$

and

$$SAF_f = \frac{O_f \cdot (R_f - 1)}{(O_n + O_s \cdot R_s + O_f \cdot R_f)}$$

where:

O_s – percentage of smokers in the population,
O_f – percentage of former smokers in the population,
O_n – percentage of non-smokers in the population,
R_s – relative risk of death in the population of smokers,
R_f – relative risk of death in the population of former smokers,
1 – relative risk of death in the population of non-smokers,
SAF_s – SAF for smokers,
SAF_f – SAF for former smokers.

The formula of present value of future earnings (PVFE) is as following (Wendy et al. 2004):

$$PVFE_{y,g} = \sum_{n=y}^{59/64} P_{y,g}(n)\left[Y_g(n)E_g(n) + Y_g^h(n)E_g^h(n)\right](1+p)^{n-y} / (1+r)^{n-y}$$

where:

y – the current age of a person
g – gender
$PVFE_{y,g}$ – present discounted value of future earnings of a person of age y and gender g
$P_{y,g}(n)$ – probability that a person of age y and gender g will live to age n
$Y_g(n)$ – average annual salary of an employee of gender g and age n
$E_g(n)$ – percentage of the employed population of gender g and age n
$Y_g^h(n)$ – average annual value of homemaking of a person of gender g and age n
$E_g^h(n)$ – percentage of the homemaking population of gender g and age n
p – labor productivity growth (for both – the employed and the homemakers)
r – actual discount rate

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Chapter 24
Cigarette Smoking Among Students and the Influence of Legal Regulations on Passive Smoking

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Abstract Research suggests that reducing the degree of nicotine addiction in the population cannot be achieved only by prevention programs. Legislative measures are necessary to be taken by the state. The aim of this study was to assess the degree of tobacco abuse in three groups of students. It also assesses the influence of ban on smoking in public places on passive contact of students with tobacco. A customized survey made up of open and closed questions was conducted among 102 students of electrical faculty, 109 medical students, and 71 students of animal husbandry faculty. The results showed that significantly more women from the electrical faculty smoked. Among the students of animal husbandry, men smoke significantly more cigarettes than women. Women studying animal husbandry start smoking significantly earlier (by about 2 years) than women from other faculties. They are also significantly less likely to smoke cigarettes at school and at home. According to the study, the Polish law to ban smoking in public places, in force since the 15th of November 2010, did not make students quit smoking, although the rate of smoking students decreased. Students did not observe restrictions on smoking in their environment. The study indicates a positive influence of the anti-nicotine legislation on passive smoking, just after 3 months from its introduction.

Keywords Health promotion • Low regulations • Tobacco smoking • Respiratory diseases

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24.1 Introduction

In the twentieth century, the tobacco epidemic killed 100 million people worldwide. During the twenty first century, it can kill one billion (WHO 2008). The majority of tobacco smokers start smoking in adolescence; 50% of these young people become heavy smokers within 16–20 years (Gawlikowska-Sroka et al. 2009; Kowalewska et al. 2004). Transition from high school to college is a critical period to adopt healthy habits and life style. In the last decade, the prevalence of smoking has generally increased in the examined colleges and universities (Morrell et al. 2008; Clarkin et al. 2008). Therefore, it is important to understand the factors that might influence students' smoking habit. Researches suggest that reducing the degree of nicotine and alcohol addiction in the population cannot be achieved only by prevention programs. Members of the European Parliament in 2007 voted that only a full smoking ban in all closed workplaces, including catering and drinking establishments, and all public buildings and transport can protect the health of employees and non-smokers (WHO 2008). In Poland new anti-tobacco bill which includes a list of places with a total ban on smoking was introduced in the autumn of 2010.

The aim of this study was to assess the degree of tobacco abuse and awareness of the dangers of smoking in three groups of students from various colleges and departments. It also assesses the influence of the smoking ban in public places on passive contact with tobacco of the students.

24.2 Methods

The study was performed in conformity with the Declaration of Helsinki for Human Experimentation and the protocol was approved by a local Ethics Committee.

The study was conducted in 2011. It included three groups of students from two universities in the city of Szczecin in Poland. Questionnaires were completed by students of medical faculty, Pomeranian Medical University (47 males, 62 females), students of animal husbandry faculty from West Pomeranian University of Technology (15 males, 56 females) and students of the faculty of electrical engineering of West Pomeranian University of Technology (68 males, 34 females).

A survey questionnaire of the authors' own design, composed of open and multi-choice questions, was used in the study. Our questionnaire was prepared on the basis of an international standard questionnaire from the HBSC study (Health Behaviour in School-Aged Children: A WHO Collaborative cross-national study) (Currie et al. 2001), GHQ-12 scale (General Heath Questionnaire) (Goldberg 1978) and Student's Life Satisfaction Scale (Hubner 1991). To assess the statistical significance, the level of significance of $p < 0.05$ was adopted.

24.3 Results

We found the highest number of smoking students, both males and females, in the faculty of animal husbandry (Fig. 24.1a, b). Additionally, we found that female students from the electrical engineering faculty smoke or had episodes of smoking significantly more often than male students from the same faculty – Chi^2 11.37, $df = 2$, $p = 0.003$.

Smoking habits and their beginning and length in time in the students of the various universities investigated are shown in Tables 24.1, 24.2 and 24.3. The first experiments with cigarette smoking in the group of the animal husbandry faculty took place earlier than in the others groups, especially in female students of this faculty, who began smoking significantly earlier (by about 2 years) than women

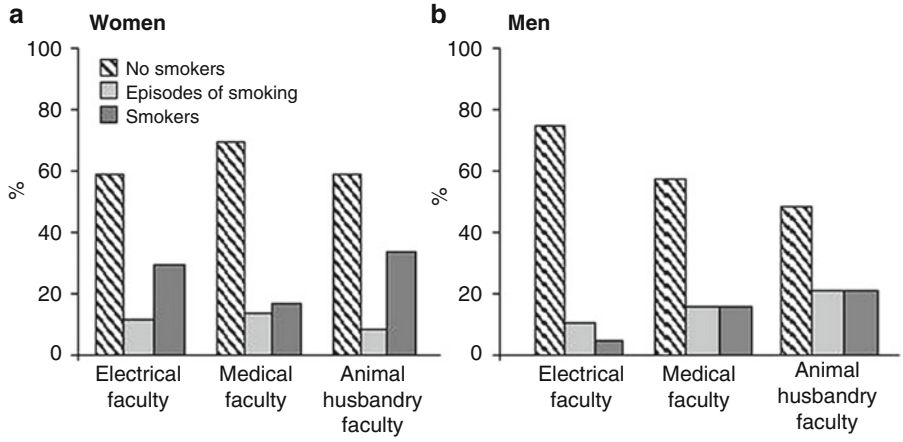

Fig. 24.1 **Tobacco addiction** in females (**a**) and males (**b**)

Table 24.1 Students from the electrical engineering faculty

	Women		Men	
	Mean ± SD	Min-Max	Mean ± SD	Min-Max
Smokers for (year)	4.9 ± 2.8	2–10	6.2 ± 2.9	1–11
First experiment in cigarette smoking at age	17.6 ± 2.5	14–23	16.1 ± 2.8	10–19
Average number of cigarettes smoked/day	10.4 ± 5.7	4–20	12.3 ± 6.5	2–20

Table 24.2 Students from the medical faculty

	Women		Men	
	Mean ± SD	Min-Max	Mean ± SD	Min-Max
Smokers for (year)	3.3 ± 1.5	1–5	4.8 ± 4.5	1–17
First experiment in cigarette smoking at age	17.2 ± 2.1	14–21	16.7 ± 1.6	15–19
Average number of cigarettes smoked/day	6.7 ± 3.6	3–15	6.2 ± 6.2	0.5–20

Table 24.3 Students from the faculty of animal husbandry

	Women		Men	
	Mean ± SD	Min-Max	Mean ± SD	Min-Max
Smokers for (year)	5.0 ± 1.9	3–10	4.8 ± 4.5	1–17
First experiment in cigarette smoking at age	15.7 ± 1.3	13–18	16.7 ± 1.1	15–19
Average number of cigarettes smoked/day	8.3 ± 5.9	1–20	6.2 ± 6.2	0.5–20

from other universities. The male students from the electrical faculty smoked significantly more cigarettes per day than females. The male students from the medical faculty smoked significantly less than male student from other faculties. All groups smoked in similar situations, but students from the animal husbandry faculty significantly more often smoked on the university premises (Chi^2 5.98, df = 2, p = 0.050), while significantly less medical students smoked on the university premises (Chi^2 7.55, df = 2, p = 0.022).

The parents of smoking students smoked cigarettes in less than 50% of cases (Fig. 24.2). Interestingly, the parents of smoking male students smoked by about 6–8 percentage points less frequently than those of female students. Also, the parents of medical smoking students, regardless of the latter's gender, smoked less frequently, compared with the other faculties but the differences were not significantly.

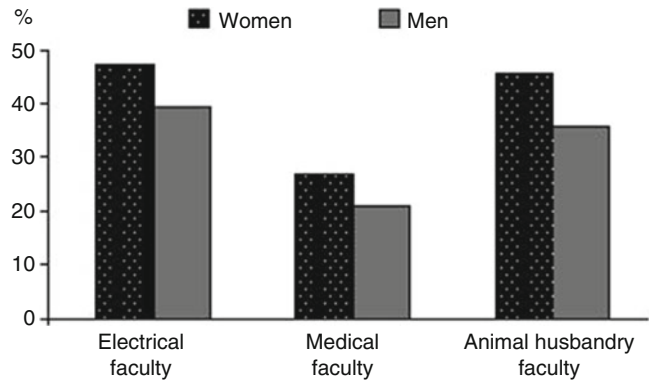

Fig. 24.2 The percentage of cigarette smoking in smoking students' parents; distribution between genders of smoking students

The partners of both smoking women and men were usually, in about 80–96%, smokers. The smoking female students had significantly more often, in a range of 10 percentage points, smoking partners than the smoking male students (Chi^2 6.800, df = 1, p = 0.01). About 98% of the students said that tobacco smoking was unhealthy. The following was most frequently mentioned as negative effects of tobacco smoking: laryngeal cancer, lung diseases, lung cancer, heart diseases, bad skin, coughing, yellow teeth, bad condition and bad smell. According to the study, the Polish law to ban smoking in public places did not make students of the study groups quit smoking. It resulted, however, in a reduction of smoking, especially among women of the electrical faculty (Chi^2 7.080, df = 1, p = 0.008). About 45% students from the medical university and the electrical faculty observed a reduction of smoking in public places. Both females (Chi^2 10.390, df = 2, p = 0.006) and males (Chi^2: 6.124, df = 2, p = 0.047) from the animal husbandry faculty were significantly more likely to believe that the new law did not affect the restriction on smoking in their environment.

24.4 Discussion

Among the populations of college and university students, the prevalence of smoking (cigarette and hookah) has increased (Sutfin et al. 2011; Akl et al. 2011). Transition from high school to college is a critical period to adopt healthy habits and life style. Therefore, it is important to understand the factors that might influence students' smoking habits (O'Cathail et al. 2011). Studies found that among college students, 50% of occasional smokers continued to smoke, and about 14% converted to daily smoking. Smoking varies by gender, with males more likely to smoke than females (Thompson et al. 2007, 2010). A second element with high influence of smoking is the type of school and accommodation during study. Public college students are more likely to smoke than those from private schools. Smoking prevalence is higher among those who live in fraternities or sororities and among those who live off campus. Smoking rates are lowest among those who live in residence halls or at home with their parents (Thompson et al. 2007; Clarkin et al. 2008). In the present study, our observations were similar concerning medical students. Smoking rates were lower for female students. A rather surprising finding was a significantly higher number of smoking women than men from the electrical faculty. Peer influence and social factors for smoking are prominent in this age group, but parents also continue to play an important role (Al-Mohamed and Amin 2010). We observed that smoking students came from smoking families and they significantly more often had smoking partners. Additionally, we found

that students from the animal husbandry faculty started smoking earlier and they smoked more cigarettes per day than other students. This shows that teenagers from rural areas may start smoking earlier that those from urban areas.

Htay et al. (2010) compared smoking habits of medical students and community youths and noted a lower rate of smoking in the group of medical students. Clarkin et al. (2008) observed that health care students reported lower rates of smoking than undergraduate students, even though both groups demonstrated similar knowledge of tobacco-related health risks. Smoking rates are generally lower among health care professionals (Morrell et al. 2008; Mumtaz et al. 2009). In the present study, we observed a similar situation. Students from the medical university presented the lowest nicotine addiction level and they smoked the lowest number of cigarettes per day. Medical students smoked significantly less in university premises. It can be associated with the fact that very often they are in hospitals where there is less opportunity to smoke than in other university buildings. These observations are encouraging because the awareness of dangers connected with tobacco smoking has a crucial role in medical profession (Arnett and Baba 2011; Miller et al. 2011; Patelarou et al. 2011). Colleges and universities provide an important setting for interventions aimed at assisting young adults in developing and maintaining health promoting behaviors which lower the risk of chronic diseases. Introducing prophylactic programs on negative health effects of tobacco is significantly associated with reductions in students' intentions to use tobacco (Stigler et al. 2011). The data indicate that college smokers wish to quit and plan to quit before graduation, suggesting that efforts to assist smokers in quitting during the college years may be fruitful (Thompson et al. 2007). Price barriers it is next element which may reduce tobacco use in college students and young adults (Clarkin et al. 2008).

In Poland, since the 15th of November 2010 a new law to ban smoking in public places was introduced. Three months later, about 45% of students observed restrictions on smoking in their environment. It did not make the students investigated in the present study quit smoking, but it led to a reduction in smoking by them. That confirms the necessity of legal regulations to reverse the tobacco epidemic.

24.5 Conclusions

1. The study indicates that the problem of smoking among young people is still an extremely important issue and requires the introduction of better prevention programs.
2. Our findings are in line with VanKim et al. (2010) and suggest that health behavior interventions and activities should be different in different student environments and faculties.
3. Preliminary observations show a reduction in passive smoking just 3 months after the introduction of an anti-nicotine legislation.

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

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Chapter 25
Medical Students' Aptitude Toward Smoking in Warsaw, Strasbourg and Teheran

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Abstract Cigarette smoking is a leading cause of preventable death in the world. Medical students play a role in smoking prevention especially as future physicians, but also as role models in society. Their approach, although influenced by medical education, is based on cultural and socio-economic background. The aim of this study was to analyze smoking habits, prevalence and attitudes towards smoking cessation in medical students from three different countries: Poland, France and Iran. A questionnaire on tobacco smoking was distributed among medical students from three Medical Universities: in Warsaw, Strasbourg and Teheran. The study population consisted of 1,036 students: 499 from Poland, 367 from France and 170 from Iran. The percentage of smokers among medical students was 14% in Warsaw, 14.4% in Strasbourg and 3.5% in Teheran. The prevalence of ex-smokers was 13.6%, 18%, and 1.2% respectively. The use of nicotine replacement therapy or pharmacological aid in smoking cessation was 9% in Warsaw, 7% in Strasbourg, and none in Teheran. In Strasbourg students willing to choose surgical specialization were more likely to be smoking with OR 2.6 (95% CI 1.4–5.0). Never-smokers were more likely than actual smokers to discourage their friends and family from smoking. In Warsaw OR was 3.8 (95% CI 2.0–7.2), in Strasbourg 6.2 (2.6–14.4) and 7.2 (1.0–82.6) in Teheran. In conclusion, similarities in smoking prevalence and attitudes between medical students in Warsaw and Strasbourg were observed, while in Teheran the percentage of smokers reported was much lower. Pharmacological aid or nicotine replacement therapy in smoking cessation was rarely used among medical students.

Keywords Smoking habits • Education • Medical students • Tobacco • Smoking cessation

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25.1 Introduction

Tobacco is frequently described as the most important single preventable cause of death (CDC 2011; WHO 2009). The WHO reports that up to half of its users will die of tobacco-related disease, which currently means nearly six million people annually (WHO 2011). This includes more than 600,000 passive smokers (WHO 2011). As there is no safe level of second-hand smoke (WHO 2009), the strong need for limiting the tobacco epidemic arises not only to save smokers' lives but also non-smokers from gradually being killed by secondhand smoke from their co-workers or family members.

Smoking prevalence is strongly influenced by cultural and socio-economic background differences between countries. The WHO Report on the Global Tobacco Epidemic in 2009 (WHO 2009) gives adult daily tobacco smokers percentages based on local data with 25% in France (2005, aged 12–75), 29% in Poland (2007, older than the age of 14) and 12% in the Islamic Republic of Iran (2005, aged 15–64).

Physicians are very important in smoking prevention, not only in their professional life but also as role models in society. It is well established that short (up to 3 min) medical doctor interventions have a significant influence on smoking abstinence, with longer advice having even greater impact (Stead et al. 2008a). On the other hand, smoking physicians are widely believed to be less active in smoking cessation advising and adopt a passive attitude towards smoking (Kawakami et al. 1997; Polyzos et al. 1995). Thus, smoking habits among medical doctors is a negative phenomenon in many aspects (including putting at risk the health of invaluable specialists, reducing the efficiency of the health care system due to their deaths from smoking, absenteeism, and presenteeism). This can also to some extent jeopardize smoking prevention. It is worth mentioning that some countries have experienced a reduction in physician smoking which preceded a decrease in the overall population (Josseran et al. 2005).

Medical students play a strategic role in smoking prevention; they will soon become physicians and they already act as an example for their families and friends. They are more open to suggestions while still in their training period so they seem to be a better target of anti-smoking actions than senior doctors. Their smoking patterns vary between countries, which can be attributed to cultural and socio-economic reasons. Although smoking among medical students was examined in many aspects, it was mostly done in a single country or region (Smith and Leggat 2007). Comparison between different countries in one study is scarce.

The aim of this study was an analysis of smoking habits, prevalence, and attitudes towards smoking cessation in medical students representing major cities in three different countries: Poland, France and Iran.

25.2 Methods

The study was in conformity with the Declaration of Helsinki for Human Research and was approved by a local Ethics Committee. Students from three different universities: Warsaw Medical University and the Faculty of Medicine of Strasbourg University (formerly Louis Pasteur University) in 2008/2009 and Teheran University of Medical Sciences in the 2009/2010 academic year were examined in ivSMS (Influenza Vaccination and Smoking in Medical Students) Study. The students were asked about demographical data, smoking and influenza vaccination status, and their attitudes concerning these subjects. The results of this study concerning influenza vaccination have been published elsewhere (Machowicz et al. 2010).

Anonymous, self-administered questionnaires were given to students taking part in obligatory courses. Completed questionnaires were collected into anonymous batches. After discarding five questionnaires without a smoker status provided and four others from students aged over 30, 1,036 questionnaires were analyzed: 499 from Warsaw, 367 from Strasbourg, and 170 from Teheran. The students who were asked to fill out the questionnaire were from the 2 to 5th in Strasbourg, 6th

in Warsaw, and 7th year of study in Teheran. The respective mean (±SD) study years were 3.6 ± 0.9, 3.4 ± 0.9, and 4.3 ± 1.5; and the students' age was 21.4 ± 1.3, 22.1 ± 1.6, and 22.3 ± 1.9 years. In Teheran, 52% respondents were female, while in Warsaw and Strasbourg this proportion was slightly higher (67% and 66%, respectively). The percentage of students starting to smoke during medical studies was calculated by subtracting the time of smoking (in years) from the year of study.

Statistical analyses were performed using SAS System 9.22. Fisher's exact test was used to compare groups in regards to quantitative variables. Univariate logistic regression was performed for every factor to test association with smoking status.

25.3 Results

Smoking prevalence among medical students was significantly higher in Warsaw 14% (95% CI 11.1–17.4) and Strasbourg 14% (95% CI 11–18.4) compared with Teheran 3.5% (95% CI 1.3–7.5) (Fig. 25.1). The percentage of ex-smokers presented a similar pattern, with the lowest value for Teheran 1.2% (95% CI 0.1–4.2) and higher results for Warsaw 14% (95% CI 10.7–17) and Strasbourg 18% (95% CI 14.2–22.3).

25.3.1 Smoking Initiation

Over a third (37% (95% CI 25.4-49.3)) of the smokers started this habit during their medical study in Warsaw and in Strasbourg 37% (95% CI 24.1–51.9), while in Teheran this proportion was 50% (95% CI 11.8–88.2). Smoking friends were frequently cited as a factor in smoking initiation. Smoking by celebrities was the most often reported reason in Teheran, which made a significant difference from the two other cities analyzed ($p \leq 0.002$ for each comparison). Among other causes frequently mentioned were curiosity, stress, and socializing (Table 25.1).

25.3.2 Discouraging Others from Smoking

The majority of medical students stated that they warned members of their families and friends that smoking is harmful to their health and advised them to quit smoking. The highest level of 88% was observed in Strasbourg (95% CI 84–91.1) which was significantly different from 77% in Teheran

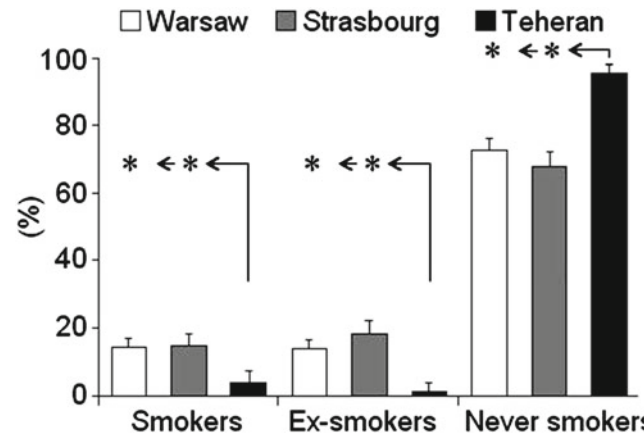

Fig. 25.1 Smoking prevalence among medical students. Error bars: 95% confidence intervals. *P < 0.0001 for the differences among student groups representing each city in each category

Table 25.1 Reasons for smoking initiation (smokers and ex-smokers); % (95% CI)

	Warsaw (n = 138)	Strasbourg (n = 119)	Teheran (n = 8)
Example of friends	35 (28–44)	29 (21–38)	25 (3–65)
To show maturity	9 (5–15)	9 (4–15)	0 (0–27)
Example of parents	6 (3–11)	6 (2–12)	0 (0–27)
Example of older siblings	1 (0–5)	4 (1–10)	0 (0–27)
Example of celebrities	2 (0–6)	1 (0–5)	38 (9–76)*
Others	52 (44–61)	35 (27–45)	25 (3–65)

*Different from the two other results; P ≤ 0.002

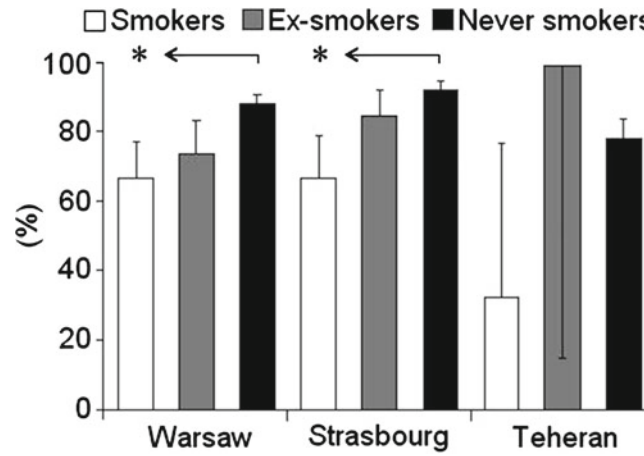

Fig. 25.2 Percentage of students declaring they discourage their families and friends from smoking. Error bars: 95% confidence intervals. *P < 0.0001 for the differences among students between the categories

(95% CI 69.5–83.4). Warsaw was placed in-between with 84% (95% CI 80–86.8). Positive answers were the least frequent among smokers (Fig. 25.2). Never smokers were more eager than actual smokers to discourage others from smoking, with OR of 6.2 in Strasbourg (95% CI 2.6–14.4; p < 0.0001), 3.8 in Warsaw (95% CI 2.0–7.2; p < 0.0001), and 7.2 in Teheran (95% CI 1.0–82.6; p < 0.03). Ex-smokers presented intermediate values. In Strasbourg, their declared activity in smoking prevention was higher than among actual smokers with OR of 2.5 (95% CI 1.1–7.1; p < 0.03).

25.3.3 Smoking Cessation Methods

Students could describe which smoking cessation method they used. The majority wrote that they used strong will or did not use any method at all. No one reported gradually lowering the number of cigarettes smoked. Nicotine replacement therapy was declared only in Warsaw by 6.9% (4/58; 1.9–16.7) of the students who answered this question. One student used cytisinum 1.7% (0–9.2%). In Strasbourg some students (7.1% (3/42; 1.5–19.5)) were trying to quit using varenicline.

25.3.4 Smoking Patterns

The answers to the question at what occasions the students smoke concerned mostly social occasions, also linked to alcohol consumption. Smokers from Warsaw were more likely to smoke while socializing with OR of 3.74 (95% CI 1.95–7.06) (Table 25.2). Smoking before eating was the least frequently

Table 25.2 Situations in which students smoke; % (95% CI)

	Warsaw (n = 70)	Strasbourg (n = 53)	Teheran (n = 6)
Stress	67 (55–78)	62 (48–75)	67 (22–96)
Socializing	93 (84–98)*	64 (50–77)*	83 (36–100)
With alcohol	86 (75–93)	83 (70–92)	50 (12–88)
On empty stomach	29 (18–41)	17 (8–30)	0 (–)
After a meal	59 (46–70)	60 (46–74)	67 (22–96)
In the street	50 (37–62)	32 (20–46)	0 (–)
During a break	59 (46–70)	77 (64–88)	50 (12–88)
Others	7 (2–16)	11 (4–23)	0 (–)

*Results different from each other; $P < 0.0001$

chosen answer. In Strasbourg, male students were more likely to be smokers (than never smokers) with OR 1.89 (95% CI 1.03–3.46). There were more potential smokers among the students willing to choose a surgical specialty in the future: OR 2.63 (95% CI 1.38–5.01). These tendencies were also found for smokers compared with ex-smokers with OR of 2.47 (95% CI 1.15–5.32) and 2.29 (95% CI 1.03–5.07), respectively. In Warsaw and Teheran these trends were not significant.

25.3.5 Smoking and Influenza Vaccination

Some observations connecting two parts of the questionnaire concerning smoking and influenza vaccination were made. In Warsaw, smokers declared more frequently than never smokers that they had influenza or influenza-like infections during the last season, with OR 2.14 (95% CI 1.28–3.60). In Teheran, the smokers were less likely to be vaccinated against influenza than never smokers, with OR 0.16 (95% CI 0.03–0.83). Concerning the knowledge of indications for influenza vaccination, the smokers from Warsaw were less likely to give a completely correct answer than never smokers, with OR 0.38 (95% CI 0.2–0.73). In Strasbourg, this relation was the opposite, with OR 1.99 (95% CI 1.06–3.72).

25.4 Discussion

Smoking prevalence among medical students was found to be generally lower than in the general populations of the examined countries. Data presented in an extensive international review of 66 manuscripts on smoking in medical students (Smith and Leggat 2007) placed the results of this study among medium (Warsaw and Strasbourg) and low (Teheran) levels. 14% of smokers in Warsaw was closer to 13% smokers in their sixth year of medical study in Gdansk than to 21% observed in the same cohort in the first year of medical school (Sieminska et al. 2009) and similar to 14.8% among the 6th year medical students in Wroclaw (Kurpas et al. 2009). It is difficult to compare the present results with those of a French study regarding the smoking habit among medical students (Riou França et al. 2009) which reports 4.4% of daily smokers, 17.7% occasional smokers, and 2.2% of ex-smoker. Particularly, the last figure is way off from the 14% and 18% of ex-smokers found in Warsaw and Strasbourg in the present study. The present figure of 3.5% of smokers in Teheran is lower than the 14.4% reported in Semnan in Iran (Nazary et al. 2010), but that study was restricted to male students. A lower prevalence of smokers among Iranian female students (Ahmadi et al. 2001; Roohafza et al. 2011) was not confirmed in the present study.

Comparisons regarding physicians are more complex because the medical specialty needs to be taken into account. Specialists connected with internal medicine were generally found to have a lower prevalence of smokers, like Polish pulmonologists – 11.3% (Czajkowska-Malinowska et al. 2008) or French cardiologists – 8.1% (Aboyans et al. 2009). These values are lower than 14% found in our study among medical students in Warsaw and Strasbourg. The result for students in Teheran (3.5%) is much lower than the observations for Iranian general practitioners: 15% (Peykari et al. 2010) and 16.6% (Heydari et al. 2005). In contrast, a proportion of smokers among French general practitioners (32.1%) (Josseran et al. 2005) was higher than our data show for students. The most recent data for Poland also reveal a higher proportion of smoking medical doctors than in the present findings for students: 24% among male and 15% among female doctors (both regular and occasional smokers). A connection between the male gender and smoking is consistent with the results for French general practitioners (33.9% smokers among males *vs.* 25.4% among females) in Strasbourg; interestingly, the situation was the reverse among French adolescents (42% girls *vs.* 22% boys) (Hastier et al. 2006). The highest proportion of smokers in Poland is reported among anesthesiologists (25%), gynecologists (18%), and surgeons (16%), with the lowest values for internists (10%) and dermatologists (9%). A connection between choosing a surgical specialty and smoking observed in Strasbourg may shed a new light on a higher prevalence of smokers in such specializations. It can be attributed to stress (Tselebis et al. 2003) or to the example of smoking colleagues at work; but in our study this predisposition was observed before starting work. This suggests an important role for psychological factors, associating vulnerability to smoking with the same traits of character which are responsible for choosing a surgical specialty.

Connections between smoking and influenza vaccination are interesting but sometimes contradictory: smokers in Strasbourg were presenting a higher level of knowledge concerning the indications for influenza vaccination, while in Teheran it was lower. It is possible that this is also associated with psychological factors and with the fact that smokers pay less attention to prophylactic disease prevention. Smoking cigarettes, despite knowing the dangers of smoking, may be typical for people who do not vaccinate themselves against influenza despite obviously evident indications for being vaccinated. A higher declared influenza morbidity in smokers in Warsaw is an example of the observation that smokers are more prone to this infection and additionally its course is more severe in this group (Arcavi and Benowitz 2004).

Taking example of friends was found of more importance as a reason of smoking initiation than taking example of family members. In Teheran, students declared the influence of seeing smoking celebrities in their decision to start smoking. This finding might be used in tobacco prevention, e.g., by introducing anti-tobacco campaigns with celebrities or anti-tobacco advertising before or after movies or TV programs in which celebrities smoke.

Over a third of smokers started this addiction during medical study in Warsaw and Strasbourg, while in Teheran this proportion was even higher, a truly alarming finding. It shows that smoking prevention during studies could be far more efficient. Similar data was shown in Poland with 20% of smokers picking up this habit during medical study (Sieminska et al. 2009), one-third in Slovak Republic (Kavcová et al. 2004), and 32% in Turkey (Senol et al. 2006). Although the students try to explain this phenomenon by citing stress of medical studies, they actually do not support this explanation, as in the present report the students most often report that the reason for starting smoking was peer pressure and the desire to fit into the group activities. Preventive actions should be started as early as possible in medical education. Emphasis should be put not only on health aspects but also on the unprofessionalism of such behavior. Creating a brochure or leaflet in the welcome address for new students may be a cost-effective solution.

The answers on discouraging others from smoking show how important it is to aim smoking prevention at medical students. Never smokers are at least two times more eager to discourage others from smoking, so it is clear that picking up the habit of smoking by medical students should be actively prevented. Also it seems important to not only decrease the smoking initiation rate, but also

to increase the number of students who successfully quit smoking. Medical students rarely (<10%) used pharmacological aids or nicotine replacement therapy in Warsaw and Strasbourg, whereas in Teheran they did not use it at all. In a large meta-analysis (Fiore et al. 2008), varenicline was found to give better results in a 6-month abstinence period than nicotine replacement treatment (NRT). In another extensive review (Stead et al. 2008b), NRT was shown to increase the rate of quitting by 50–70%. Nevertheless, medical students neglect this efficient help. This attitude may influence the advice they give as doctors in the future to their smoking patients. Polish medical students emphasize that during their medical study they are not appropriately prepared for the interactions with patients during the time spent at the diagnosis and treatment of nicotine addiction (Sieminska et al. 2009).

25.5 Conclusions

Numerous similarities in smoking patterns were observed between medical students in Warsaw and Strasbourg, while in Teheran smoking prevalence was significantly lower. The vulnerability to smoking may be, to some extent, connected with the traits of character responsible also for the choice of future career. Although the percentage of smoking students was found to be lower than that among physicians, there is still a lot of room for improvement, especially in terms of smoking initiation during studies and of providing help for smoking cessation.

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Chapter 26
Epidemiology of Pertussis in an Urban Region of Poland: Time for a Booster for Adolescents and Adults

Aneta Nitsch-Osuch, Ernest Kuchar, Grazyna Modrzejewska, Iwona Pirogowicz, Katarzyna Zycinska, and Kazimierz Wardyn

Abstract Since the last decades, an increase of reported incidence of pertussis has been observed in many countries, including Poland, despite high vaccination coverage among infants and children. Before the vaccinations era, pertussis was a major cause of morbidity and mortality among infants and young children. Currently, pertussis is increasingly reported in adolescents and adults. The objective of this paper was to present the epidemiology of pertussis in Mazovian region in Poland in years 2005–2009. In this report we analyzed retrospectively the epidemiological data collected by the Sanitary Station in Warsaw, Poland. A total of 1,455 cases of pertussis were reported in the Mazovian region of Poland in the years 2005–2009. The incidence of pertussis ranged from 2.4/100,000 (2006) to 7.9/100,000 (2008). The incidence was the highest in two groups: infants (>1 year of age; from 13.3/100,000 in 2005 to 32.7/100,000 in 2007) and teenagers (age of 10–14 years; from 11.8/100,000 in 2006 to 68.5/100,000 in 2008). The highest proportion of cases was also reported in the 10–14 years age-group (from 26.4% in 2009 to 46.0% in 2008). The number of hospitalizations due to pertussis ranged from 137 (2005) to 46 (2006), while the percentage of cases requiring hospitalization ranged from 37% (2005) to 25% (2007 and 2008). Three hundred ninety two (27%) cases of pertussis were reported among patients with negative or not confirmed history of pertussis vaccination. We conclude that there is an urgent need for booster vaccination against pertussis in adolescents and adults in Poland.

Keywords Booster • Epidemiology • Infection incidence • Pertussis • Vaccination

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26.1 Introduction

Pertussis, commonly known as whooping cough, is an important cause of death in infants worldwide, and continues to be a public health concern even in developed countries (WHO position paper 2010). Before vaccines against pertussis became widely available, pertussis was one of the most common childhood diseases, but following universal vaccination, a dramatic reduction (>90%) in incidence and mortality was observed in the industrialized world. However, in the last decades, an increase of reported incidence of pertussis has been observed in many countries, despite high vaccination coverage among infants and children (Gurtis et al. 1999; Tan et al. 2005). Currently pertussis is increasingly reported in older children, adolescents, and adults (de Melker et al. 2000; Hewlett and Edwards 2005; Cherry 2006; Lasserre et al. 2011). Various explanations have been given to account for the pertussis re-emergence, including increased awareness of the disease, improved diagnosis (general availability of better diagnostic tests), adaptation of causative agent (genetic changes in *Bordetella pertussis* resulting in increased toxin production) (Cherry 2006; He and Mertsola 2008; Mooi et al. 2009; Mooi 2010). The most significant factor seems to be waning of vaccine-induced immunity that lasts 4–14 years (Hellenbrand et al. 2009).

Since new vaccines against pertussis containing a reduced dose of the pertussis antigens (Tdap; tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine) designed for adolescents and adults have become available, the question of recommendations for boosters for teenagers and adults has been raised. Some countries have already offered adolescents and adults a booster of Tdap (tetanus toxoid, diphtheria toxoid, and acellular pertussis vaccine) (Table 26.1) (Wiese-Posselt and Hellenbrand 2010; EUVAC NET data).

In Poland, despite consistently high (94–96%) pertussis vaccination coverage for several decades, TDPw (tetanus toxoid, diphtheria toxoid, and whole-cell pertussis vaccine) was introduced into the

Table 26.1 Immunization schedules against pertussis in selected European countries

Country	Primary vaccination	Booster vaccination for adolescents	Booster vaccination for adults
Austria	2–4–6 months	12–24 months 13–16 years	Every 10 years
Belgium	2–3–4 months	15 months 5–7 years 14–16 years	Cocoon
Finland	3–5–12 months	4 years 14–15 years	–
France	2–3–4 months	16–18 months 11–13 years	27–28 years, cocoon, health care workers
Germany	2–3–4 months	11–14 months 5–6 years 11–15 years	Cocoon, health care workers
Italy	3–5–11 months	5–6 years 11–15 years	–
The Netherlands	2–3–4 months	11 months 14 years	–
Switzerland	2–4–6 months	15–24 months 4–7 years (11–15 catch up)	–
Luxemburg	2–4–6 months	12 months 5–6 years 15–16 years	Every 10 years

Table 26.2 Epidemiology of pertussis in Poland

Year	Number of reported cases	Incidence rate (No. of cases/100,000)
1998	2,871	7.43
1999	876	2.27
2000	2,269	5.87
2001	2,411	4.68
2002	1,788	6.24
2003	2,034	5.33
2004	2,954	7.74
2005	1,925	5.04
2006	1,520	3.99
2007	1,987	5.21
2008	2,164	5.68
2009	2,391	6.26

national immunization schedule in 1960, an increased number of pertussis cases has been observed since 1998, with epidemic peaks every 4–5 years (Table 26.2) (Annual Reports of National Institute of Public Health 2005, 2006, 2007, 2008, 2009).

Currently, according to the Polish national immunization programme, pertussis vaccine is administered to infants at 2, 4, 6, and 16–18 month of life (the whole cell pertussis vaccine – TDPw, is used universally and acellular pertussis vaccine – TDPa may be used alternatively, but only DTPw is reimbursed) and a booster with acellular vaccine has been started in 2005 for children aged 6 (TDPa vaccine) (Paradowska-Stankiewicz and Rudowska 2010). Regarding Poland, more epidemiological observations are needed to recommend additional doses of acellular pertussis vaccine with a reduced concentration of antigens (Tdap) for adolescents and adults.

The objective of this report was to present the epidemiology of pertussis in the Mazovian region of Poland. This is an urban region including Warsaw, the capital city of Poland, with a population of approximately five million.

26.2 Methods

The study was in conformity with the Declaration of Helsinki (1989) for Human Research and was approved by a local Ethics Committee. The retrospective analysis of epidemiological data collected by the Sanitary Station in Warsaw, Poland was conducted. According to the Polish regulations, all physicians are obliged to report any confirmed or suspected cases of pertussis to the Sanitary Inspection Stations. Data are collected and analyzed at national and regional levels. Data collected for the epidemiological statistics include: age, sex, place of living, course of the disease (including requirement of hospitalization), results of laboratory tests and history of vaccinations. The analyzed period covered the years 2005–2009.

Cases of pertussis reported to the Sanitary Inspection were classified according to national recommendations published by the National Institute of Health as:

- confirmed – clinical symptoms present – a cough illness lasting at least 2 weeks with one of the following: paroxysms of coughing, inspiratory ‘whoop’ or post-tussive vomiting, without other apparent cause, as reported by a health professional, and laboratory confirmation of the disease (isolation of *Bordetella pertussis* from clinical specimen or positive polymerase chain reaction (PCR) for *Bordetella pertussis* or a significant increase of specific antibodies class IgG or IgA);

- probable – meets the clinical case definition – not laboratory confirmed, but was epidemiologically linked to a laboratory-confirmed case;
- suspected – only clinical symptoms typical for pertussis, with no epidemiological link or laboratory confirmation.

The incidence rate for 100,000 population was calculated. Official demographical data (population of the Mazovian region with age stratification) were supported by the Central Statistical Office available on: www.stat.gov.pl. Incidence data for Poland were taken from the National Institute of Hygiene bulletin 'Infectious diseases and poisonings in Poland' available on: www.pzh.gov.pl, which is annually published by the National Institute of Public Health.

26.3 Results

The total of 1,455 pertussis cases was reported in 2005–2009 in the Mazovian region of Poland. The number of reported cases ranged from 124 in 2006 to 433 in 2005 (Fig. 26.1). The incidence rate of pertussis ranged from 2.4/100,000 in 2006 to 7.9/100,000 in 2008 (Fig. 26.2). Every next year, more cases were diagnosed among females (Fig. 26.1) and the incidence rates were also higher for females than males; from 3.0/100,000 in 2006 to 9.2/100,000 in 2005 (Fig. 26.3).

The incidence was highest in two groups: patients younger than 1 year, from 13.3/100,000 in 2006 to 32.7/100,000 in 2007, and at the age of 10–14 years, from 68.5/100,000 in 2008 to 11.8/100,000 in 2006. The proportion of pertussis cases was highest (60%) among adolescents aged 10–19, 20% of pertussis cases were diagnosed in patients aged 20–64, and 4% of cases were among infants younger than 1 year of life.

The majority of reported pertussis cases (89%) were classified as confirmed, 8% as suspected, and 3% as possible. One thousand sixty three cases (73%) were diagnosed among people previously vaccinated against pertussis. Three hundred ninety two cases (27%) were among patients with negative or not confirmed history of pertussis vaccination. Vaccinations against pertussis were not performed because: (i) people were born before 1960 (161 patients), (ii) unknown reason – lack

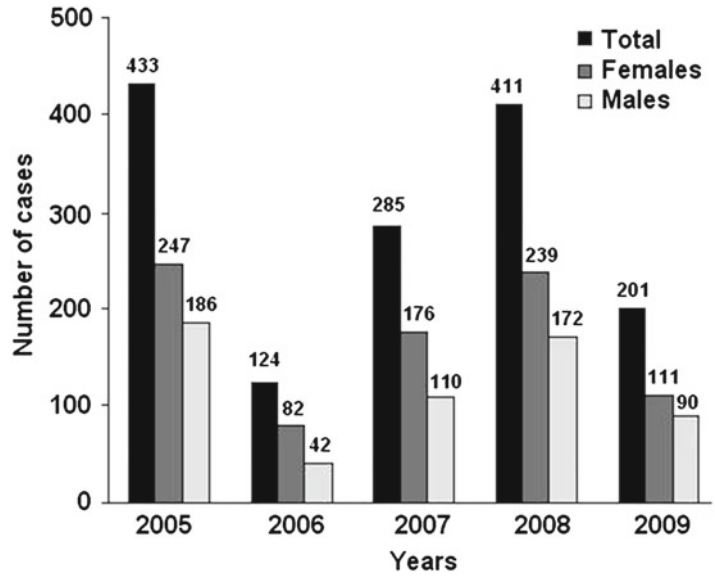

Fig. 26.1 Total number of pertussis cases and its distribution by sex, Mazovian region 2005–2009

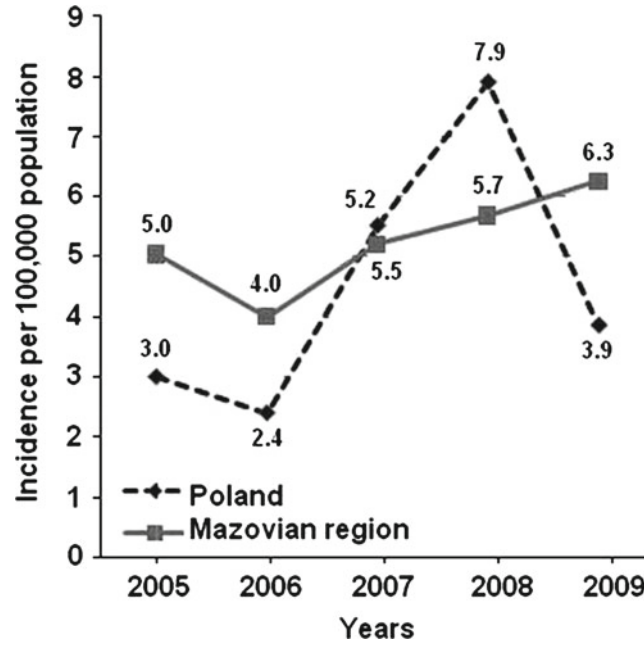

Fig. 26.2 Incidence rates of pertussis in Mazovian region and Poland, 2005–2009

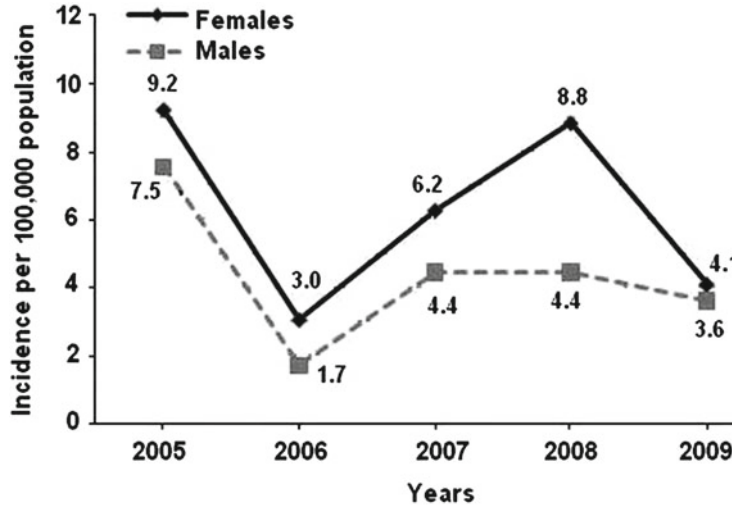

Fig. 26.3 Incidence of pertussis by sex, Mazovian region 2005–2009

of written documentation of vaccination (126 patients), (iii) medical contraindications (41 patients), and (iv) young age – too young for vaccination (18 patients) or the vaccination schedule was not yet completed (46 patients). The most common reason for lack of pertussis vaccination (41% cases) was being born before the introduction of the universal and mandatory vaccination in 1960.

Among 60 children younger than 1 year with laboratory confirmed pertussis, 50 (83%) did not complete the full three-dose vaccination scheme and 73% received either none or only one dose of vaccine. The number of hospitalizations due to pertussis ranged from 137 in 2005 to 46 in 2006, while the percentage of cases requiring hospitalization ranged from 37% in 2005 to 25% in 2007 and 2008 (Fig. 26.4). The highest proportion of patients requiring hospitalization was observed among infants younger than 1 year (72–100%) (Table 26.3).

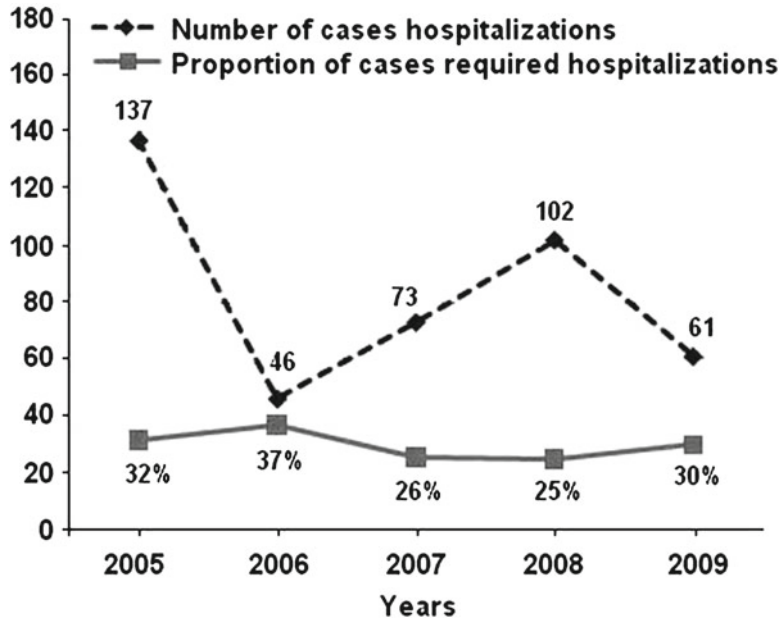

Fig. 26.4 Total number and proportions of hospitalizations due to pertussis in Mazovian region, 2005–2009

26.4 Discussion

According to reports from other countries, the epidemiology of pertussis has changed. In the pre-vaccine era, pertussis was a common disease and was observed almost exclusively in children; more than 90% of cases were noted in children aged less than 10 years. Recently, about 65–70% of reported cases have been observed in people aged >10 years (WHO position paper 2010). We observed the same pattern of age distribution of pertussis cases in the studied population; the disease was diagnosed mainly among adolescents aged 10–19 (60% of cases)) and adults younger than 65 years (20% of cases). Pertussis in adolescents and adults is important for two reasons. Firstly, it is not always a benign disease in those groups of patients. Adults and adolescents with pertussis often fail to present the full-blown clinical picture of the disease. Although the complications are less common than in newborns and infants, they still occur and include: pneumonia (4%), sinusitis (13%), otitis media (4%), urinary incontinence (4%), rib fractures (2%), weight loss (3%), fainting (2%) (Serres et al. 2000; Cherry 2005; Galanis et al. 2006) and intracranial hemorrhage in the elderly (5%) (Mertens et al. 1999).

Secondly, unrecognized pertussis in adults is a major source of pertussis in young infants for whom the disease is severe and may be fatal. In recent years, several studies have looked for contact cases of pertussis in infants hospitalized with pertussis. In 30–80% cases the most common source of the infection were close family members of an ill child: parents, grandparents, and siblings (Bisgard et al. 2004; Crowcroft et al. 2003; Tanaka et al. 2003; Kowalzik et al. 2007; Wendelboe et al. 2007). In fact, increasing incidence among infants is reported; cases per 100,000 infant population in the US were 34.2 in the 1980s and 51.1 in the 1990s (CDC 2005). We also observed a similar situation: 60 (4%) of patients were younger than 1 year of life and the incidence in this group of patients was similar to that calculated for adolescents. For these young infants, pertussis may be a serious disease with the highest reported rates of hospitalizations (>90%) and complications including pneumonia (15–25%), seizures (2–4%), encephalopathy (0.5–1%), and death (0.5–1%) (Crowcroft et al. 2003; Halasa et al. 2003;

Table 26.3 Hospitalizations due to perstussis in the Mazovian region in 2005–2009

Age (year)	2005			2006			2007			2008			2009		
	No. of pertussis cases	No. of hospitalizations due to pertussis	Proportion of hospitalized cases	No. of pertussis cases	No. of hospitalizations due to pertussis	Proportion of hospitalized cases	No. of pertussis cases	No. of hospitalizations due to pertussis	Proportion of hospitalized cases	No. of pertussis cases	No. of hospitalizations due to pertussis	Proportion of hospitalized cases	No. of pertussis cases	No. of hospitalizations due to pertussis	Proportion of hospitalized cases
			%			%			%			%			%
<1	16	15	94	7	6	86	18	13	72	9	9	100	10	9	90
1	5	3	60	7	4	57	9	5	56	15	9	60	4	4	100
2	8	3	38	6	4	67	4	3	75	11	2	18	3	1	33
3	2	1	50	3	2	67	5	1	20	3	1	33	10	4	40
4	10	6	60	4	1	25	9	2	22	7	3	43	4	1	25
5–9	82	29	35	18	9	50	24	7	29	24	11	46	19	10	53
10–14	184	50	28	35	10	29	104	23	22	18	45	24	53	16	30
15–19	52	22	42	19	4	21	43	10	23	57	11	19	25	4	16
20–24	8	1	13	3	0	0	9	1	11	7	1	14	4	0	0
25–29	6	0	0	3	1	33	8	0	0	8	1	13	4	0	0
30–34	12	0	0	2	0	0	8	0	0	8	1	13	9	1	11
35–39	11	0	0	2	0	0	4	1	25	12	1	8	7	1	14
40–44	9	0	0	4	2	50	6	2	33	13	1	8	2	0	0
45–49	7	2	29	1	0	0	8	2	25	9	1	11	10	2	20
50–54	6	0	0	4	1	25	12	1	8	7	1	14	8	2	25
55–59	3	0	0	1	0	0	3	0	0	6	1	17	9	0	0
60	5	0	0	1	0	0	4	0	0	9	1	11	11	4	36
>65	7	5	71	4	2	50	8	2	25	15	2	13	9	2	22

Cherry 2005; Blandiardi and Ferrera 2009). 25–37% of patients with pertussis in our group were hospitalized and majority of them were infants younger than 1 year and young children, which is not a surprising result in view of the factors above mentioned. The same problem exists in other countries. The rate of hospitalization for pertussis among infants ≤6 months old in the US per 100,000 live births increased from 64.7 in 1994–1998 to 77.9 in 1999–2003 (CDC 2005). In our group of patients with pertussis younger than 1 year, the hospitalization rate was also the highest one.

The strength of our study lies in an insight into our local epidemic situation. The limitation, on the other hand, is the lack of enough information concerning the duration of hospitalization due to pertussis and possible sources of infection in households. In our group, 50 out of the 60 children younger than 1 year who acquired pertussis did not complete the full scheme of three dose vaccination against it. We may expect that some of these cases could have been avoided by (i) limitation of medically unjustified contraindications for vaccination, (ii) reduction of medically groundless delays in realization of vaccination program, and (iii) reduction of spreading the disease among close contacts of infants (by realization of the 'cocooning strategy'). Maternal and family or household vaccination (cocooning) is very important in the control of the pertussis. This strategy has been recommended in several developed countries, it may help protect unvaccinated newborns and partially vaccinated infants (ACIP 2006; Committee on Infectious Diseases 2006; Parkins et al. 2009; Quinn and McIntyre 2007; Rohani et al. 2010).

In our study, the incidence of the disease was higher among females than males, although the reasons for this difference are unclear and might have to do with social factors, care of children, or professional factors (women more frequently work in contact with children as nurses or teachers). However, there may be another factor influencing the spread of the disease to infants, namely as a result of mothers spending a lot of time with an infant (in Poland mainly mothers receive pregnancy leave), while themselves having a cough illness that had not been recognized as pertussis and may, in fact, be a source of the disease.

Most cases of pertussis in our group were noted among previously vaccinated people, both adolescents and adults. The same problem exists in other countries (Cherry 2010; de Greeff et al. 2008). As previously mentioned, vaccination against pertussis in infancy and early childhood does not provide lifelong protection, which is why booster doses should be recommended (Ntezayabo et al. 2003; Parkins et al. 2009). Our results strongly confirm the implementation of booster of pertussis vaccine with reduced antigen concentrations (Tdap) for teenagers and adults.

The strategy of immunization against pertussis should include, not only universal infant vaccination and routine booster for pre-teenagers, but also a booster for teenagers and routine booster dose for adults aged <65 years, the use of Tdap rather than Td for wound management and the immunization of health care workers and 'cocooning strategy' for persons who expect close contact with infants younger than 12 months (ACIP 2006; Committee on Infectious Diseases 2006; Parkins et al. 2009).

Currently, the Polish national immunization schedule includes routine vaccination of children up to the age of 6 only. There have been published recommendations of Polish experts concerning the pertussis vaccination with Tdap, but they should be more widely implemented into everyday practice. For example, current vaccination schedules include a booster vaccination against tetanus and diphtheria (Td) at the age of 14 and 19; these doses of Td could be replaced by Tdap. Carrying out the intensive campaigns promoting the 'cocooning strategy', along with the need to immunize adults against pertussis (including health care workers, teachers, caregivers of children, and seniors) is strongly recommended. Our data provide support for the wider usage of new Tdap vaccine in Poland. Analysis of pertussis epidemiology will remain important from the perspective of both public health and vaccinology; which is why epidemiological studies on a national and regional level are essential.

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Chapter 27
Rhinitis as a Cause of Respiratory Disorders During Pregnancy

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Abstract Rhinitis is a common disease of women during pregnancy. It can start in almost any gestational week and disappears after delivery. The main symptoms are sneezing, nasal congestion or running nose. The diagnosis is usually based on history, physical examination, blood tests, and exclusion of the other more common types of rhinitis. The etiology remains to be clarified. The rhinitis may be caused by numerous substances and hormones secreted during pregnancy (PGH, VIP, estrogen, progesterone). They lead to changes in the nasal mucosa in the form of increased activity of serous-mucous glands and increase of their vasculature. The best treatment is using saline irrigations, exercise, and mechanical alar dilators. The nasal decongestants provide only temporary relief. The aim of this study was to evaluate the prevalence of pregnancy rhinitis. The study was conducted on 117 pregnant women in the province of the West Pomerania in 2009–2010. The information was obtained from interviews, questionnaires, and data contained in pregnancy records. About 39% of pregnant women suffered from pregnancy rhinitis. Most such ailments were found during 13th and 21st week of gestation. Doctors should pay more attention to symptoms which result from pregnancy rhinitis, which are reported by their patients. The quality of prenatal care understood as an education of pregnant women as far as pregnancy rhinitis is concerned, is much insufficient. Pregnancy rhinitis significantly affects quality of life of pregnant women and, as a result, it may affect fetal development.

Keywords Rhinitis • Pregnancy • Prevalence • Respiratory disorders

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27.1 Introduction

27.1.1 Definition

Pregnancy rhinitis is an inflammation of nasal mucosa appearing during the pregnancy in a woman who previously had no breathing problems. One or more of following symptoms can be observed in its course: obstruction of nasal ducts, sneezing, itching, presence of nasal discharge ('running nose'). Symptomatology is therefore very similar to allergic rhinitis; however no association to any allergen can be traced. It is similar to infectious rhinitis as well, but there is no connection to viral, bacterial or fungal infection. Pregnancy rhinitis lasts for at least 6 weeks in any period of pregnancy. However, it is most frequently observed during the first trimester. Symptoms of pregnancy rhinitis usually disappear within 2 weeks after delivery.

27.1.2 Etiology

The etiology of pregnancy rhinitis lacks explanation. Its placement within hormonal rhinitis group suggests the influence of hormones and specific substances released during the pregnancy, but it still remains uncertain. Progesterone acts as vasodilator and retains water in the tissues which promotes congestion and edema. However, according to some studies (Ellegård et al. 1998) the progesterone level in women with and without rhinitis is similar. Vasoactive intestinal peptide (VIP) and prolactin levels increase during the pregnancy and can influence blood vessels, but it has been shown long ago (Ottessen et al. 1982) that those increased levels are mainly observed in fetal circulation and not in the mother's peripheral circulation. Estrogen seems to have an influence on nasal permeability. Its decrease may cause atrophic rhinitis in women after menopause. Hormonal replacement therapy brings good effects as far as nasal, pharyngeal and oral mucosa are concerned. Increased estrogen levels during oral contraception cause congestion and nasal obstruction (Toppozada et al. 1984). Hyperactivity of nasal mucosa to histamine has been observed during the peak phase of ovulation's estrogen, which could explain the feeling of 'full' nose during pregnancy (Haeggström et al. 2000). There were reports about significantly increased placental growth hormone among women suffering from pregnancy rhinitis (Ellegård et al. 1998).

27.1.3 Differential Diagnosis

Pregnancy rhinitis should always be distinguished from rhinosinusitis, in which nasal congestion may be the only symptom, especially during the initial phase of the disease (Lindbaek 2004). Serous, mucous or purulent discharge from the middle nasal meatus, foul smell, unilateral purulent discharge, unilateral pain of the nose or cheek, clearly indicate sinusitis as the cause. Things do not, however, always seem to be so clear, since nasal congestion may completely exclude any nasal examination and X-rays are counter indicated in pregnancy. What remains available is taking history and a further observation of the patient. Since pregnancy rhinitis closely resembles allergic rhinitis, it is essential to conduct precise interview with the patient, concerning her pre-pregnancy ailments. If the patient suffered from allergy before the pregnancy, that can augment the symptoms of pregnancy rhinitis. Also, a prolonged use of decongestants may cause rhinitis medicamentosa, a rebound swelling of nasal mucosa (Graf and Juto 1994).

Nasal granuloma gravidarum (pregnancy tumor, pregnancy granuloma or teleangiectatic polyp) is a benign fast growing tumor causing nasal obstruction. In histological picture, it is practically undistinguishable with pyogenic granuloma. Contrary to pregnancy rhinitis, it is practically always

unilateral and tends to bleed. Precise examination reveals an easily bleeding spot, which can be treated, but it frequently disappears on its own after pregnancy (Park 2002).

27.1.4 Possible Influence on the Child

Symptoms of pregnancy rhinitis manifest especially during night. Women have problems with falling asleep, snore, wake up frequently, and may be tired and sleepy during the day. Abnormal breathing course – through the open mouth, promotes airways infections. All that probably may influence the fetal development. Studies point to the frequent co-existence with pregnancy rhinitis of hypertension, preeclampsia, intrauterine growth retardation and lower Apgar scores (Hu et al. 1999; Eccles 2000; Franklin et al. 2000).

27.1.5 Treatment

Causative treatment cannot be used in pregnancy rhinitis. Congestive symptoms are relieved with decongestants (topical or oral) but their side effects have to be considered. Physical methods are completely safe. Sleeping with the head in the raised position is a well known and proven method to relieve upper airways obstruction, various angles of the location of the head on the pillow were reported (Eccles 2000; Lee 2006). External nasal dilators applied to the nasal antrum also proved effective (Turnbull et al. 1996). Nasal cavities can be rinsed with saline solution which gives temporary but significant relief, decreases the amount of discharge and removes crusts, as well as moisturises the mucosa. It can be repeated many times.

The aim of our present study is to evaluate the prevalence of hormonal rhinitis and to clarify its risk factors during pregnancy.

27.2 Methods

The survey used in the study was conducted between March 2009 and May 2010 among 117 pregnant women aged 19–40 in the outpatient clinics of the 1st and 2nd University Hospitals and of an Independent Public Specialty Health Care Unit, as well as in the private ob-gyn practices in the city of Szczecin (West Pomerania province, Poland). The questionnaire contained questions concerning socio-economical status, physical activity during pregnancy, number of pregnancies and diet. Blood pressure data, weight gain and information concerning pregnancy complications were collected from the history records. All examined subjects were asked about nasal congestion at all visits during pregnancy as well as after the delivery. They were also asked about risk factors such as: smoking, asthma, dust or animal allergy, hay fever as well as month of conception. The patients were asked to use one of the pharmacological agents: nasal decongestant, oral decongestant or nasal corticosteroid. Acquired data were categorized and statistically analysed.

27.3 Results

The mean age of the women examined was 30 years, 50% had secondary education, 46% had higher education, and 4% had primary education. Seventy two percent of the women defined their socio-economical status as average, 7% as good, 2% as very good, and 19% as bad.

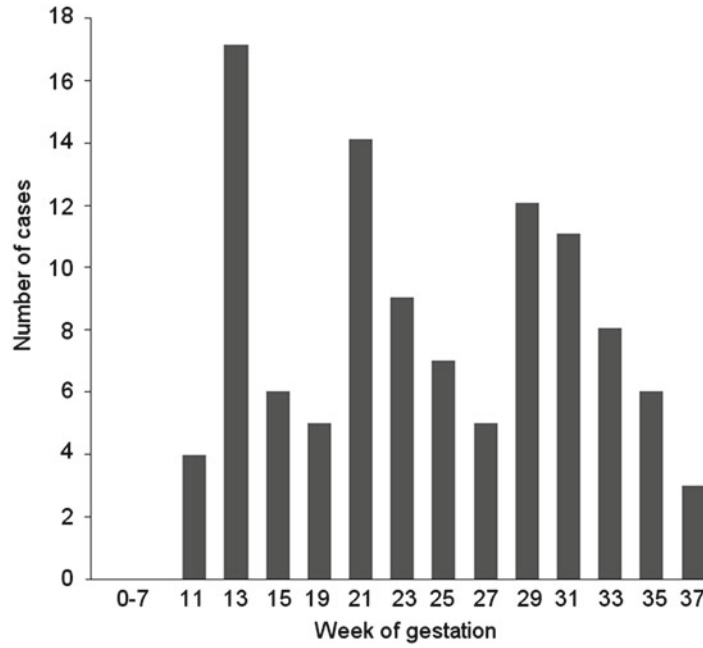

Fig. 27.1 Subjective nasal congestion registered upon all visits during pregnancy in 117 women

Pregnancy rhinitis was present in 45 patients (39%). The patients often complained of common cold during pregnancy. Most of them noted such complaints during 13th and 21st week of pregnancy. However, the data show that the complaints were frequent through the gestational weeks 7 through 35 (Fig. 27.1). Similar results were obtained by Ellegård (2005) and Vlastarakos et al. (2008). Nine percent of the patients reported nasal stuffiness at all times and time 65% at some time, and it was more common in multiparous than in nulliparous women. Age, BMI and smoking habits were associated with nasal stuffiness.

The incidence of pregnancy rhinitis in our study was significantly higher in smokers than in non-smokers (odds ratio 1.7; confidence interval 1.1–2.3). The irritating effect of smoking was found to induce nasal congestion, and 33% of patients who had rhinitis were smokers. Ellegård et al. (1998) and Schatz (1999) found similar results in their studies. Data collected from the history records indicated that among pregnant women known to have allergy (house dust mainly), 12% showed increasing allergic symptoms during pregnancy and returned to their normal pre-pregnancy state after delivery (Fig. 27.2). In 23 of the 117 women who experienced pregnancy rhinitis, *in vitro* tests for ten airborne allergens were performed. The overall sensitization was not raised in the group of women with pregnancy rhinitis compared with those without it.

Not all women had all symptoms, but overall the effects were usually similar to allergic rhinitis or sinusitis, or bad 'cold'. Many subjects complained about having nasal obstruction, episodic sinusitis, dyspnea, headache involving forehead, temples, cheeks and orbital region, tiredness, sensation of pressure and dripping nose as well as problems with breathing during sleep. Other indicated symptoms included eyes itching, lacrimation, throat pain and earache.

Nearly half of the women reported the sensation of chilliness appearing few days after the onset of common cold, they had fever, shivers, headache, throat pain, enlargement of lymph nodes. As a result, in 32 examined pregnant women upper airways infection developed while in 8 of them ear infection began. Among pregnant women suffering from pregnancy rhinitis, 19 indicated that they suffered from sinusitis – one of them underwent 12 biopsies (Fig. 27.2). In all smoking women intensity of rhinitis symptoms was dependent on pregnancy. They formed the largest group indicating symptoms (Fig. 27.3).

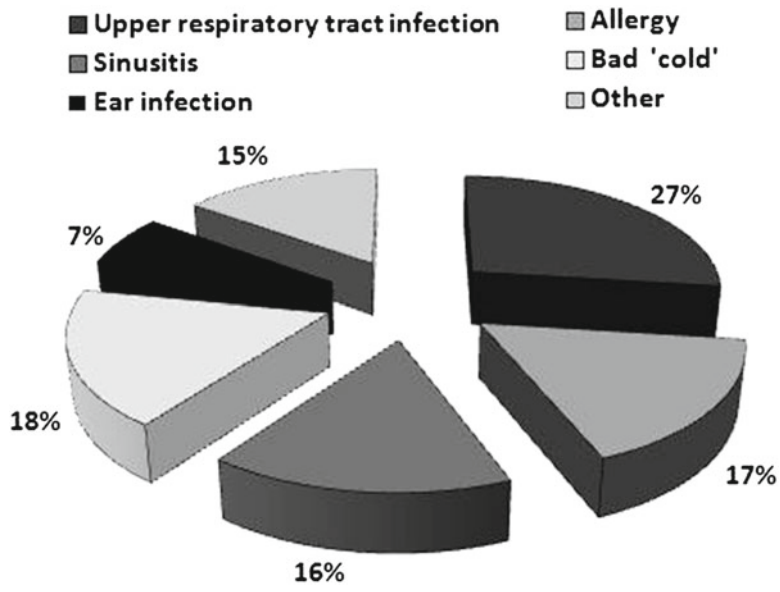

Fig. 27.2 Diseases accompanying pregnancy rhinitis in 117 women

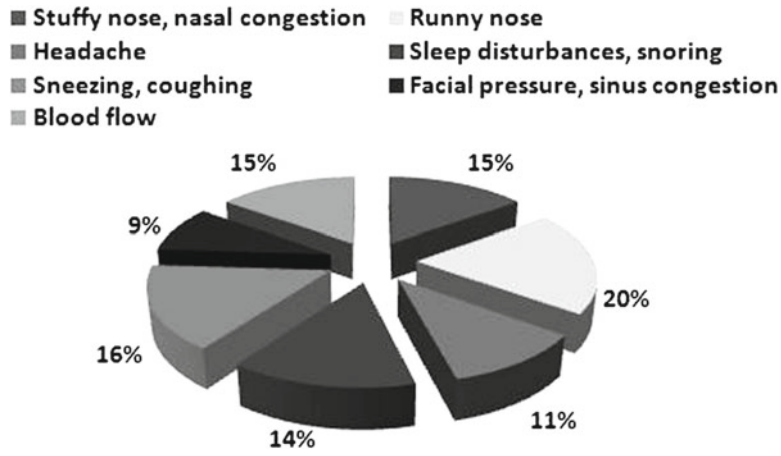

Fig. 27.3 Most common complaints among pregnant women

Almost all women acknowledged they consulted their symptoms with their doctor fearing they might affect the child as the infection could spread *via* the placenta.

Only 5% of women were informed about the rhinitis during their first antenatal care visit, and they were found to be significantly less worried about their nasal congestion. As Rambur (2002) suggests, pregnant women should all be informed about pregnancy rhinitis during their first antenatal care visit. The lack of information often made the pregnant women indicate in their questionnaires insufficient help from the doctor when they reported their symptoms. Nevertheless, 38% of surveyed women reported that they received at least one medication, 26% got it during a high risk period of the first trimester of pregnancy. However, the majority of the women tried to treat their rhinitis by themselves.

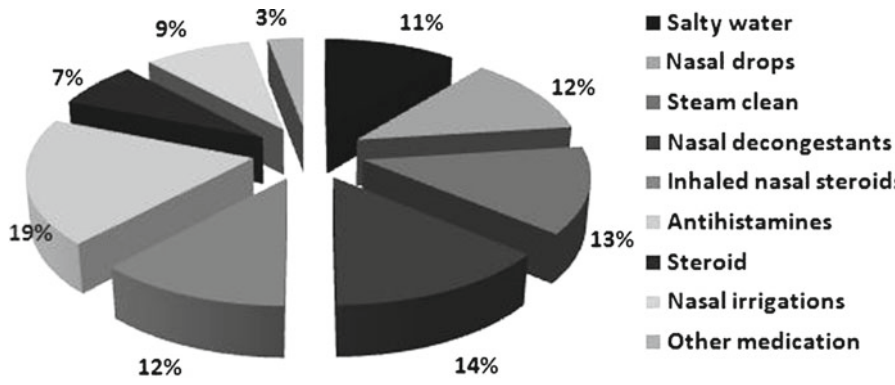

Fig. 27.4 Methods used by pregnant women to relieve nasal obstruction

The information on self-treatment was received from the doctors (38%), other pregnant women (21%), books (12%), internet (35%), and other sources (11%). The measures self-applied most often included: higher liquid intake (especially water), avoiding caffeinated drinks, increasing the humidity at home, avoiding irritants (cigarette smoke), and raising the head position during sleep. Other measures applied are summarized in Fig. 27.4. Antibiotics were used by 50% of the pregnant women.

The last investigated issue was the influence of pregnancy rhinitis on the quality of life of women and on the fetus. All women with pregnancy rhinitis had problems with breathing through the nose, tiredness (reduction of physical activity), sleeping, snoring (fetal oxygen deficiency), and upper airways infections. Women in their first pregnancy, those with higher education and those describing their socio-economic status as bad, seemed to have the biggest problems in dealing with these symptoms.

27.4 Discussion

Rhinitis is one of the most common diseases encountered by physicians of various specialties. Its appropriate qualification facilitates diagnostic procedures and allows for proper treatment. Classification of non-allergic rhinitis is heterogeneous and often causes doubts (Grzanka et al. 2010). Pregnancy rhinitis is placed in this group as an example of hormonal rhinitis. Nomenclature inconsistency and the lack of strict diagnostic criteria have an adverse impact on diagnosis and treatment. This problem may be caused by insufficient knowledge and too little interest in pregnancy rhinitis among doctors directly dealing with pregnant women, such as family doctors and obstetricians. They are also responsible for the diagnosis and treatment, or for directing the patient to an ENT surgeon. Unfortunately, the problem of pregnancy rhinitis is frequently ignored by those specialists.

Pregnancy rhinitis is still not fully understood ailment. Thanks to recent studies it is well known that it may affect from 9% to 42% of pregnant women (Bende and Gredmark 1999; Ellegård 2005; Shushan et al. 2006). It should interest the medical professionals not only because of its prevalence, but also because it affects the women's well being and fetal development. Also, vulnerability of pregnant women with rhinitis toward upper airway infections is widely stressed. Allergies present before pregnancy are likely to become more severe due to the problems with proper air flow through the nose (inefficient filtration, cleaning, humidification and warming of the air directed to the lungs). It is absolutely certain that the quality of life of women with pregnancy rhinitis dramatically decreases, while pregnancy is a period during which it should be especially high.

The ideal is that the pregnant women with rhinitis find their way to an ENT surgeon as fast as possible. She stands then a better chance for the proper diagnosis and appropriate treatment. Professional

examination and proper information about her symptoms form a large part of therapeutic success. The knowledge about rhinitis can improve women's disposition and her acceptance of the ill condition.

Treatment of pregnancy rhinitis is difficult and rarely fully satisfactory both for the patient and for the doctor. The proper diagnosis can protect pregnant patients against ineffective and potentially harmful for the fetus pharmacological treatment. Due to the predominance of nasal mucosa congestion, the use of topical decongestants brings relief. They have, however, a short-term effect and patients tend to abuse them. This may lead to the development of rhinitis medicamentosa. The impact of topical decongestants on the fetus cannot be excluded (Baxi et al. 1985). Therefore, they should not be used longer than for a period of 5 days (Lekas 1992). Oral decongestants such as pseudoephedrine and phenylopropanolamine are effective in various types of rhinitis. The routine of prescribing them differs from country to country. In Sweden, phenylopropanolamine is considered relatively safe, while in the U.S. pseudoephedrine is preferred (Dykiewicz et al. 1998). Earlier reports about the risk of gastroschisis in the fetus have not been confirmed (Werler et al. 2002). Such drugs, however, may cause various systemic responses such as an increase in blood pressure, tachycardia, lower appetite, tremors, or insomnia.

The use of antihistamine drugs and nasal steroids is only justified in cases of allergic rhinitis, nasal polyps, and rhinitis medicamentosa coinciding with pregnancy. Benefits from their use should exceed possible side-effects (Piette et al. 2006). However, if the allergic etiology is excluded those drugs will have no effect. It is worth noting that the best results in relieving the symptoms of pregnancy rhinitis can be obtained by simple measures such as rinsing of the nasal cavity with saline solution or optimal head rest during sleep. Physical activity, adjusted to the pregnancy period plays a crucial role. It improves breathing – by decreasing congestion, allows for easy falling asleep and keeps the body mass in optimal range. Body mass is a crucial factor in such phenomena as snoring and night dyspnea (Dzieciolowska-Baran et al. 2010). Our studies confirm that women maintaining high physical activity have a better tolerance for pregnancy rhinitis symptoms.

27.5 Conclusions

1. About 39% of pregnant women suffer from pregnancy rhinitis.
2. Symptoms of rhinitis are most often found during 13th and 21st week of gestation.
3. Pregnancy rhinitis develops almost always among smoking women and among those with dust allergy.
4. Medical professionals should pay more attention to pregnancy rhinitis symptoms reported by their patients.
5. The quality of prenatal care understood as an education of pregnant women as far as pregnancy rhinitis is concerned, is much too low.
6. Pregnancy rhinitis significantly affects quality of life of pregnant women and, as a result, it may affect fetal development.

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

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Chapter 28
Subglottic and Tracheal Stenosis due to Wegener's Granulomatosis

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Abstract Wegener's granulomatosis (WG) is characterized histologically by necrotizing granulomatous angitis that most commonly involves the upper, lower respiratory tract and kidneys, but may affect any organ system. Otolaryngological manifestations are frequent and diverse but subglottic stenosis and tracheal stenosis are less common. The aim of the study was to assess the clinical features and the response to treatment in WG patients with subglottic or tracheal stenosis. The disease activity at the time of examination was scored in 55 patients with WG (29 females, 26 males) according to clinical, serological, radiological and bronchoscopic findings: subglottic and tracheal stenosis were observed in 9% and 5% of WG patients, respectively. CT scans of the larynx and trachea showed mucosal thickening extended 3–4 cm below the vocal cords in three and the thyroid cartilage in one patient. The degree of narrowing of the axial luminal diameter ranged 50–90%. Mechanical dilation of the stenosis and long-acting local corticosteroids may be of therapeutic benefit, along with conventional immunosuppressive treatment.

Keywords Wegener's granulomatosis • Subglottic stenosis • Tracheal stenosis • Local corticosteroids • Necrotizing granulomatous angiitis

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28.1 Introduction

Wegener's granulomatosis (WG) is a multi-system PR3-ANCA vasculitis characterized by a necrotizing disease of different organs. Upper respiratory tract involvement such as sinusitis, rhinosinusitis, epistaxis, ulceration of nasal mucosa, and a saddle nose deformity are leading manifestations of WG. Subglottic stenosis and tracheal stenosis are particularly life threatening presentations of WG and have been found to occur in 15–25% and 3–7%, respectively.

Subglottic stenosis might occur in the absence of systemic disease or in generalized disease (Belloso et al. 2008). Patients present symptoms of dyspnea, hoarseness, cough, and stridor. The exact pathogenesis of subglottic stenosis in WG patients remains unclear but it is thought to be autoimmune in character (Churg et al. 2010). It has been suggested that the underlying inflammatory process is a trigger for chronic irritation, scarring, and progressive airway narrowing. Narrowing of the upper respiratory tract at the cricoid cartilage area along with that of the upper tracheal rings becomes a major diagnostic and therapeutic challenge in WG patients (Blaivas et al. 2008).

28.2 Methods

The study was approved by a local Ethics Committee. Fifty five patients, 29 females and 26 males, of the mean age of 46.6 ± 12.5(SD) years, with biopsy-proven pulmonary WG treated at the Primary Systemic Vasculitis Outpatients Clinic of the Czerniakowski Hospital in Warsaw, Poland, from January 2000 till December 2010 were entered into the study. All patients fulfilled the American College of Rheumatology criteria for classification of WG and the Chapel Hill Consensus Conference definition, and also EUVAS ANCA-associated vasculitis definition for WG. Disease activity was confirmed by clinical scoring, laboratory variables and imaging procedures (CT of the nasal cavity, sinuses, larynx and trachea). DEI and BVAS indexes were determined to measure the organ involvement and disease activity. The data collected also included the age at onset of subglottic stenosis symptoms, actual symptoms, history of intubation, endoscopic procedures, open surgery data, laser therapy, and local and systemic immunosuppressive treatment.

Data were shown as means ± SD or as medians. A Wilcoxon test was used for statistic analysis. $P < 0.05$ was considered statistically significant.

28.3 Results

Subglottic stenosis and tracheal stenosis were observed in 9.0% and 5.5% of generalized WG cases, respectively. Sinonasal involvement in WG was noted in 78.0% of the patients. Laboratory data at the time of the study are presented in Table 28.1. Seven patients underwent primary functional endoscopic sinus surgery or dacryocystorhinostomy prior to the study. The sinus surgery included refractory chronic rhinosinusitis or mucocele decompression in five patients, dacryocystorhinostomy was made for epiphora or chronic dacrocystitis in two patients, and orbital decompression was made for pseudotumor of orbit in one patient. One other patient had a history of intubation. No patient had a history of gastroesophageal reflux disease. Out of the 55 CT scans of the larynx and trachea, three showed the mucosal thickening extending 3–4 cm below the vocal cords and one below the thyroid cartilage. The narrowing of the axial luminal diameter was in a range of 50–90%. Spiral CT scans with multiplanar images and 3-dimensional reconstruction of the laryngotracheal lumen were performed in all cases prior to endoscopy. Endoscopic examination revealed a radish, friable mass, obstructing the airway and extending 1–3 cm down from vocal cords in four patients. In two patients, the vocal cords and

Table 28.1 Laboratory data in Wegener's granulomatosis (WG) with and without subglottic or tracheal stenosis

	WG with subglottic or tracheal stenosis (n = 8)	WG without subglottic or tracheal stenosis (n = 47)	p
CRP (mg/dL)	11.7 ± 7.8	7.5 ± 0.98	0.001
Fibrinogen (mg/dL)	426.5 ± 164.2	212.6 ± 21.6	0.006
Leukocytes/μL	8,900 ± 3,500	7,400 ± 2,500	NS
GFR (mL/min)	54.21 ± 16.8	66.8 ± 12.4	0.05
PR3/ANCA	68 ± 8.0	48.2 ± 4.6	0.01
DEI	12 (8–14)	6 (3–9)	0.004
BVAS-WG	12 (18–21)	8 (6–16)	0.001

Table 28.2 Treatment of subglottic or tracheal stenoses accompanying Wegener's granulomatosis (WG)

Therapeutic management	WG with subglottic or tracheal stenosis (n = 8)
ILCD – long-acting local corticosteroid injections	5
ILCD >3 procedures	3
Urgent tracheostomy	2
Endoscopic dilation	8
Resection of stenotic segment	2
Placement of silicone stent	2
Carbon-dioxide laser ablation	1
Open laryngotracheal surgery	2

thyroid cartilage were involved. Two other patients required an urgent tracheostomy due to severe airway stenosis. Therapeutical management is presented in Table 28.2. Local relapses were usually treated with endoscopic dilation and mechanical removal of granulomatous formation along with typical immunosuppressive treatment. In addition, carbon-dioxide laser therapy, similar to that used by Strange et al. (1990), was used in one patient. Open laryngotracheal surgery with reconstruction and resection of stenotic segment and placement of a silicone stent was performed in two patients who had a severe, refractory scarring.

28.4 Discussion

Subglottic and tracheal stenosis, with scaring and occlusion of the respiratory tract, are a dangerous, life-threatening complication of Wegener's granulomatosis. The etiology of the stenosis is unclear and difficult to determine. Differential diagnosis should include congenital, traumatic, neoplastic, inflammatory, and infectious factors. A history of trauma, tracheal intubation and gastroesophageal reflux disease before the onset of subglottic stenosis were not observed in our study in contrast to other authors (Solns-Laque et al. 2008). An isolated appearance of subglottic stenosis due to WG is rare (Schokkenbroek et al. 2008), but may also be the only presenting manifestation of the disease. Subglottic and tracheal stenoses are often observed in females in generalized disease. Symptoms develop gradually, from non-specific cough, shortness of breath, or vocal changes, finally to stridor when a critical point of stenosis is reached, (Wierzbicka et al. 2010). In the present study, all patients had an involvement of additional organs. Endoscopy was performed to assess the airway narrowing, but high disease activity made it impossible to perform endoscopic examinations in two patients. Spiral CT scans and 3D-CT of the larynx and trachea provided complementary information for adequate

treatment and prognosis. The therapeutic options in subglottic and tracheal stenoses due to WG included conventional immunosuppressive therapy, endoscopic dilation, mechanical or laser excision or surgical resection with silicon stent implementation, but also tracheotomy. Tracheotomy, although life saving, has adverse effects on the patient's quality of life and is connected with potentially serious complications. Mechanical dilation of the stenosis (ILCD) and long-acting local corticosteroid injections along with conventional immunosuppressive treatment may be helpful (Wolter et al. 2010; Targonska-Stepniak and Majdan 2010). It is thought that corticosteroid injections reduce inflammation and alleviate circumferential injury, thus reducing the risk of fibrosis and new scar formations. Furthermore, ILCD is a safe and repeatable procedure with minimal complication in the management of subglottic stenosis due to WG. Recently, topical mitomycin C is increasingly used as adjuvant treatment in the management of selected stenoses in fresh circular sutured wounds (Smith and Elstad 2009; Roediger et al. 2008). This alkylating agent inhibits cell division, fibroblast proliferation and protein synthesis. However, in the present study we did not apply mitomycin C – one patient who developed a circumferential subglottic stenosis responded well to carbon dioxide laser therapy. On the other hand, vasculitis and chronic inflammation may produce extensive scar formation after laser airway manipulation. Surgical management should be reserved for patients with fixed lesions and it is recommended that airway manipulation be limited to special cases and not during high disease activity (Hernandez-Rodrigez et al. 2010). Open laryngotracheal surgery with resection of a stenotic segment, reconstruction, and placement of silicone stent was performed in two patients with severe, refractory scarring. Our study showed that mechanical dilation of a stenotic area and long-acting local corticosteroids along with conventional immunosuppressive treatment of Wegener's granulomatosis may be the most helpful therapy.

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

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Chapter 29
Pulmonary Aspergillosis: Therapeutic Management and Prognostic Factors from 16 Years of Monocenter Experience

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Abstract Twenty three patients of the University Hospital Bonn were reviewed following surgical procedures for pulmonary aspergilloma, including the choice of antifungal therapy, diagnostic findings, decision-making in treatment, and treatment outcomes of the past 16 years. We used pathological records to identify aspergilloma patients. A review of patients' records and follow-up phone calls to patients, families, or general practitioners were done. Data collected from 1995 to 2011 included patients with aspergilloma (n = 15), multiple aspergillomas (n = 2) and chronic necrotizing pulmonary aspergillosis (n = 6). Classification and diagnosis were based on pathological records. The decision to use systemic antimycotic therapy was based on perioperative findings suspecting parenchymal involvement of the fungal infection. Seventeen patients received systemic antimycotic chemotherapy. Compared with the use of Amphotericin B, newer drugs such as voriconazol, caspofungin, or posaconazol showed no better result in the morbidity and mortality of the patients. Postoperative complications requiring extended therapy and/or prolonged ICU stay (>48 h) were seen in 12 (52.2%) patients. During follow-up there were ten deaths; one death (4.4%) from aspergillus-associated sepsis, nine deaths from patients' underlying diseases (n = 4 within <3 months, n = 6 within >3 months of follow-up). In conclusion, in our cohort, immunocompromised patients with no documented preexisting lung-cavities were most likely to develop pulmonary aspergilloma. Postoperative morbidity (52.2%) was high, but related mainly to patient co-morbidity; postoperative mortality was reasonably low. Patients showing classical symptoms or immunocompromised patients should be considered for surgery. Encapsulated Aspergilloma without invasion of surrounding parenchyma requires no antifungal chemotherapy.

Keywords Necrotizing pulmonary aspergillosis • Multiple aspergillomas • Pulmonary aspergillosis • Surgery for aspergilloma • Voriconazol

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29.1 Introduction

Aspergillus fumigatus is the most prevalent airborne fungal pathogen causing severe and often fatal invasive infections in immunocompromised hosts in developed countries (Latgé 1999). Recently, an increasing number of patients suffering from fungal infections have been reported in immunocompromised patients, especially in hemato-oncological patients (Dixon et al. 1996; Lass-Flörl and Dierich 2004). A variety of symptoms is wide; coughing, dyspnea, chest pain, reduced general condition, fever, blood-tinged sputum or hemoptysis are some of the typical symptoms observed in patients suffering from pulmonary aspergillosis. However, these symptoms are nonspecific for fungal infection. Chest x-ray (CRX), computed tomography (CT) scanning, bronchoalveolar lavage (BAL) sample with hemagglutination test (HAT), galactomannan immunoassay, polymerase chain reaction (PCR), or blood cultures are common diagnostic tools, but the results often can be misleading (Kappe and Rimek 2004; Lopes da Silva et al. 2010; Franquet et al. 2001; McCarthy and Pepys 1973). There are different pulmonary presentations of aspergillosis, namely: pulmonary aspergilloma, chronic necrotizing pulmonary aspergillosis (CNPA), allergic broncho-pulmonary aspergillosis (ABPA) and invasive pulmonary aspergillosis (IPA) (Fig. 29.1).

Each entity requires different therapy. Any form of pulmonary aspergillosis can change into the invasive form of pulmonary aspergillosis (IPA), which is characterized by infiltrative growth and hematologic spread in association with a high mortality rate (Saraceno et al. 1997; Safirstein 1973; Soubani and Chandrasekar 2002). Early diagnosis and specific treatment improve survival and may prevent IPA (von Eiff et al. 1995). An increase in immunocompetence may even change a beginning IPA to an encapsulated condition like a ‘pseudo-aspergilloma’. A delay in antifungal therapy in IPA is still a main reason for high morbidity and mortality rates; more than 50% in neutropenic patients and up to 90% in hematopoietic stem-cell transplantation recipients with IPA (von Eiff et al. 1995; Yeghen et al. 2000; Fukuda et al. 2003) (Fig. 29.2).

The present study was designed to review and analyze our procedures and outcome in patients treated surgically for pulmonary aspergillosis. The emphasis was on initial clinical presentation, applied diagnostics, choice of systemic antifungal therapy, the short and long term outcome after surgical procedure, and possible differences in therapy outcomes over the past 16 years.

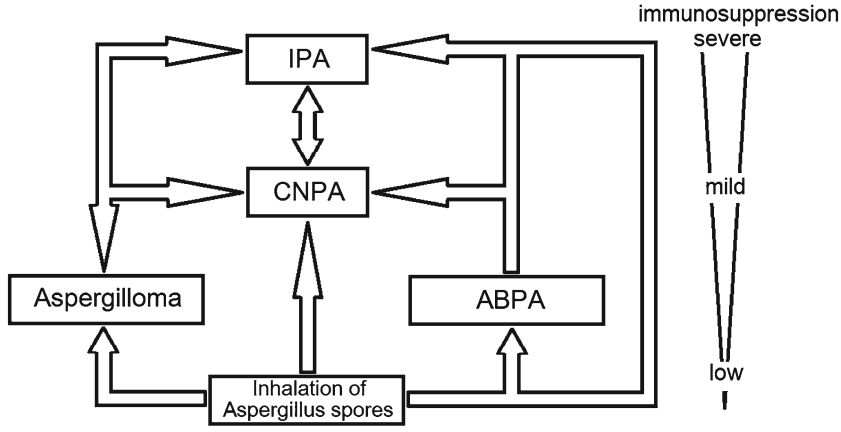

Fig. 29.1 Clinical spectrum of conditions depending on the grade of immunosuppression. *ABPA* allergic broncho-pulmonary aspergillosis, *CNPA* chronic necrotizing pulmonary aspergillosis, *IPA* invasive pulmonary aspergillosis

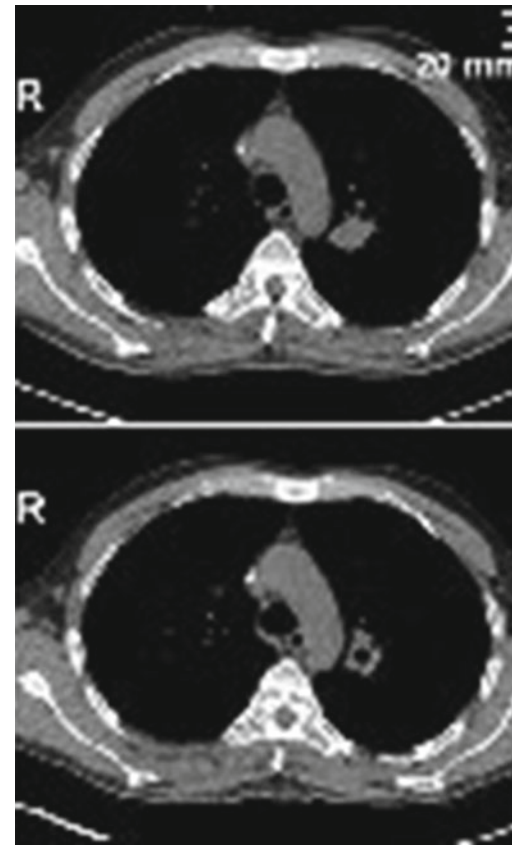

Fig. 29.2 CT scan showing the transformation from a beginning IPA to a 'pseudo-aspergilloma'. The upper scan – a ground-glass attenuation surrounding a pulmonary nodule: 'Halo-sign' indicates the beginning of an invasive pulmonary aspergillosis. The bottom scan - two weeks later this process transformed into an encapsulated 'pseudo-aspergilloma' with the air-crescent sign, which was surgically resected. Scale bar, shown in the upper right corner of the upper panel, is the same for both panels.

29.2 Methods

The study, performed at the University Hospital of Bonn, Germany, was in conformity with the Declaration of Helsinki of the World Medical Association and was approved by the Ethics Committee of Bonn University School of Medicine. Pathological records from January 1995 until February 2011 were used to identify patients suffering from pulmonary aspergillosis. Out of the 551,830 entries in the search engine of the Institute for Pathology, the University Hospital Bonn, Germany, 23 patients with surgical treated pulmonary aspergillosis were identified by different filter algorithms (e.g., aspergilloma, multiple aspergillomas and chronic necrotizing pulmonary aspergillosis). Patients' records were reviewed focusing on age, gender and symptoms before diagnosis, radiological techniques and findings, localization and expansion and parenchymal participation of the aspergillus colonization. Another focus was on the choice of systemic antifungal therapy, decision making for surgical performance, surgical techniques, postoperative complications, short term outcome (3 months) and long term outcome (3 months after surgery until February 2011). Follow-up phone calls to patients, families or general practitioners were done to gather information about possible reoccurrence of fungal infections and therapy-associated disabilities, e.g., chronic dyspnea or recurrent hemoptysis.

29.3 Results

From 1995 to 2011, 23 patients of the University Hospital Bonn underwent surgical procedures for singular pulmonary aspergilloma (n = 15), multiple pulmonary aspergillomas (n = 2), and chronic necrotizing pulmonary aspergillosis (n = 6). The patients included 19 men and 4 women with a median age of 39 years (13–76 years; mean 41 ± 16 years), two patients were children, 13 and 14 years old. The detailed patients' characteristics are displayed in Table 29.1.

There were no significant differences regarding morbidity and outcome between the patients with singular aspergilloma compared with those suffering from other forms of pulmonary aspergillosis as shown in Table 29.2. Furthermore, we compared the characteristics of the patients suffering from hematological diseases with those of the patients without hematological neoplasia as shown in Table 29.3. We observed significant differences in the initial symptoms and the diagnostics in the two cohorts. The patients suffering from hematologic neoplasia never reported pulmonary symptoms such as coughing or hemoptysis, whereas this was the leading clinical finding in non-hematological neoplasia patients.

The most common indication for surgery in the immunocompromised patients (n = 20) were radiological findings pointing to the suspicion pulmonary aspergillosis or tumor lesions. The surgical procedures performed were 18 thoracotomies, 4 thoracoscopies, and 1 sternotomy including 12 wedge resections, 7 lobectomies, 2 bi-lobectomies, 1 segment resection and 1 lingual resection with wedge resection. Decision of the use of systemic antimycotic therapy was made by preoperative, intraoperative, or post-operative findings suspecting parenchymal participation of fungal infection. Seventeen patients received systemic antimycotic chemotherapy at any time during the disease: ten patients postoperative, six patients pre- and postoperative, one patient only preoperative; six patients received no antimycotic chemotherapy at all. All patients with hematologic neoplasias were treated with antifungals, whereas only 8/14 (57.1%) of the patients without hematological neoplasias received antifungal medication.

Compared with the use of Amphotericin B (n = 6), we did not seen any better results in the morbidity and outcome of the investigated patients treated with newer drugs such as itraconazol (n = 7), voriconazol (n = 9), caspofungin (n = 2), or posaconazol (n = 2). Comparison of the different systemic antifungal agents is questionable due to varying indications and varying points of time of the beginning of therapy as well as the duration of therapy. Severe postoperative complications requiring additional or extended therapy included atelectasis, hemothoraces, pleural effusions, wound infections, requirement of blood transfusions, respiratory insufficiency, or prolonged ICU stay were observed in 12 (52.2%) patients, with no differences between hematological underlying diseases compared with others; nor were there differences between the singular aspergilloma group and multiple aspergilloma or CNPA patients. Comparing the findings in the patients undergoing surgery for pulmonary aspergillosis before and after 2003, the only significant finding was that the patients suffering from singular aspergilloma were more frequently in the hospital in the recent past, rather than M.A. and CNPA patients who were more often seen before 2003 (Table 29.4). During the follow-up, there were ten deaths: one death (4.4%) occurred due to aspergillus-associated sepsis 13 days after lobectomy in a liver-transplant rejection patient, nine deaths resulted from patients' underlying diseases with no putative aspergillus association. Of these nine patients, three died within the short-term of 3 months, two died 6 months, one patient 10 months, one patient 5 years, one patient 8.5 years, and one patient 9 years after surgery (Table 29.1).

29.4 Discussion

Over 16 years, we could identify only 23 surgically treated cases of pulmonary aspergillosis in tertiary care at a German University hospital. Decline in the incidence and prevalence of tuberculosis over the past 20 years (http://www.who.int/tb/publications/global_report/2010/gtbr10_a2.pdf) might be a reason

Table 29.1 Patients' characteristics

	Type	Year of surgery	Sex	Age of on-set	Underlying disease	Symptoms (before surgery)	Therapy	Complications	Antifungal drugs	Cortisone	Death due to: Or if alive: Pulmonary impairment
P1	A.	6/95	M	39	none	Coughing	TS + WR	None	None	No	NPI
P2	A.	5/02	M	38	HIV	Recur. fever + DGC	TS + WR	Minor pneumothorax, 4 years post-OP: bronchopneumonia with positive aspergillus-Ag in serum	Pre-/post-OP: Itra.	No	† 8.5 years post-OP; (HIV)
P3	A.	11/02	M	34	CML	Routinely	TT + WR	Re-thoracotomy (hemothorax)	Pre-OP: Itra., AMB, switch to Vori., post-OP: Vori.	No	† 2 months post-OP (hemorrhagic complications)
P4	A.	3/04	M	50	Alcohol abusus	Coughing, blood-tinged sputum	TT + WR	Pneumonia	None	No	† 5 years post-OP (uncertain)
P5	A.	10/06	M	27	AML	DGC	TT + lobectomie	Wound infection, total atelektasis, prolonged ICU stay	Post-OP: AMB, Cancidas	No	NPI
P6	A.	2/07	F	14	ALL	DGC	Start: TS, switch to TT + lobectomy	2d ICU stay	Pre-OP: AMB + Vori.; in 2008: Posa.	Yes	NPI
P7	A.	4/08	M	49	ALL	Recur. Infections, DGC	TT + WR	Ventilation difficulties	Pre-OP: Caspo., Vori.; post OP: Vori.	Yes	NPI
P8	A.	6/00	M	59	AML	Fever during chemotherapy DGC	TT + lobectomie	Minor pneumothorax (no treatment)	Pre-OP: Itra.; post-OP: none	Yes	† 6 months post-OP (stem-cell therapy)
P9	A.	6/08	F	55	Lung cancer	Recur dyspnoea	TT + atyp. WR	Ventilatory decompensation + pneumonia for 6 weeks	Post-OP: Vori.	No	NPI
P 10	A.	4/07	M	38	Teratoma, stem-cell transpl., NIDDM II	DGC	TT + atyp. WR	Pneumothorax, thorax drainage	Post-OP: Vori.	No	NPI
P 11	A.	12/09	M	29	TB	Hemoptysis	TS + lobectomy	Mediastinal emphysema, high pleural drainage output	None	No	NPI

(continued)

Table 29.1 (continued)

	Type	Year of surgery	Sex	Age of on-set	Underlying disease	Symptoms (before surgery)	Therapy	Complications	Antifungal drugs	Cortisone	Death due to: / Or if alive: Pulmonary impairment
P 12	A.	11/09	M	53	COPD °I-II	Coughing with blood-tinged sputum	TT + atyp. WR	Post-OP: rec dyspnoea	None	No	Persistant dyspnea
P 13	A.	7/08	M	76	Exacerbation of COPD, CHD, AAA	CT after attempted suicide; DGC, zoster infection: septical progress	TS + WR	Prolonged ICU stay, long-term ventilation, catecholamines, dialysis, tracheostomy, pleural effusions, MRSA super-infected	Post-OP: Vori. for 10d, no improvement > Posa. (with improvement)	No	† 2 months post-OP (Sepsis)
P 14	A.	12/10	M	49	AML	Routinely	TT + bisegment resection	Epistaxis, 2 units of RBC, Pneumothorax; 4 months post-OP: Rethoracotomy after lung infarction	Post-OP: Vori.	No	NPI
P 15	A.	2/08	M	67	Lung cancer	dyspnea	TT + lobectomy	Wound infection, persisting coughing, end-stage tumor disease	Post-OP: Vori.	Yes	† 6 months post-OP (lung cancer)
P 16	M.A.	8/01	M	29	COPD	Coughing, hemoptysis, fever, DGC, dyspnea	TT + atyp. WR	Pleural effusion; under post-OP AMB therapy increase in creatinine level, switch to Itra	7 days pre-OP AMB, 6 months post-OP: Itra.	Yes	NPI
P 17	M.A.	12/95	M	35	HIV, hemophilia A	Fever, coughing, DGC	TT + atyp. WR	Pleural effusion, modest pneumothorax (no treatment needed)	None	No	† 10 months post-OP (HIV)
P 18	CNPA	7/97	F	41	Alcohol abusus	DGC	TT + upper bilobectomy	None	Post-OP: Itra.	No	NPI
P 19	CNPA	8/95	M	23	Testicular tumor, pneumonia with abscesses	Fever, fatigue, DGC	TT + lobectomy	Pleural effusion, spontaneously regressive	None	No	NPI

P 20	CNPA	1/02	M	13	ALL	Recur. infections	TT + atyp. WR	Dystelectasis, resp. insufficiency. Pleural callous, pneumonia, pleural effusion	Pre-OP: AMB, post-OP: Itra.	Yes	† 3 months post-OP (ALL)
P 21	CNPA	3/01	M	56	ALL	Routinely	Lingula resection + WR	Atelectasis, bleeding, chambered pleural effusions	Post-OP: Itra.	Yes	† 9 years post-OP (ALL)
P 22	CNPA	7/08	M	18	ALL, HMSN	DGC	TT + upper bilobectomy	Dystelectasis	Post-OP: AMB	Yes	Loss of follow-up
P 23	CNPA	3/09	F	47	Liver-transplant (rejection), (s.a. TB)	Coughing	TT + lobectomy	Pleural effusion, (>10 units of RBC) MOF	Pre-OP: Vori., Caspo.	Yes	† 13 days post-OP (sepsis)

A aspergilloma, *AAA* aortic abdominal aneurysm, *Ag* antigen, *All* acute lymphoblastic leukemia, *AMB* amphotericin B, *AML* acute myelogenous leukemia, *Caspo* caspofungin, *CML* chronic myelogenous leukemia, *CNPA* chronic necrotizing pulmonary aspergillosis, *COPD* chronic obstructive pulmonary disease, *CRX* chest radiograph, *d* days, † death, *HMSN* hereditary motor and sensory neuropathy, *f* female, *FEV1* forced expiratory volume in 1 s, *ICU* intensive care unit, *m* male, *Itra.* itraconazol, *DGC* deterioration of general condition, *M.A.* multiple aspergillomas, *NIDDM* non-insulin-dependent diabetes mellitus, *NPI* no pulmonary impairment, *OP* surgery, *P* patient, *PEG* percutaneous endoscopic gastrostomy, *Posa* posaconazol, *RBC* red blood cells, *recur.* recurring, *s.a.* state after, *s.o.* suspicious of, *TB* tuberculosis, *TS* thoracoscopy, *TT* thoracotomy, *Vori.* voriconazol, *WR* wedge resection

Table 29.2 Differences in underlying disease and outcome in simple aspergilloma patients *vs.* patients with multiple aspergilloma and CNPA

Predisposing conditions and diseases	Singular aspergilloma (n = 15)	Multiple aspergillomas & CNPA (n = 8)	p*
Leukemia (including ALL, AML, CML)	6	3	0.633
COPD	2	1	0.731
Solid neoplasia	3	1	0.565
HIV	1	1	0.585
Alcohol abuse	1	1	0.585
TB	1	0	0.652
Liver-transplant rejection (+TB in the past)	0	1	0.348
No underlying disease	1	0	0.652
Deterioration of general condition (incl. fever)	7	5	0.389
Dyspnoea, coughing	5	4	0.367
Hemoptysis, blood-tinged sputum	3	1	0.565
Routinely done radiography during therapy	2	1	0.731
Findings in sectional imaging (CT/MRT)	3	0	0.257
Perioperative antimycotics	11	6	0.666
Severe postoperative complications[a]	8	4	0.611
Death in short-term follow-up	2	2	0.435
Death in long-term follow-up	4	2	0.666

ALL acute lymphocytic leukemia, *AML* acute myeloid leukemia, *CML* chronic myeloid leukemia, *CNPA* chronic necrotizing pulmonary aspergillosis, *COPD* chronic obstructive pulmonary disease, *M.A.* multiple aspergillomas, *TB* tuberculosis

*Fisher's *t*-test

[a]including: atelectasis, hemothorax, major pleural effusion, wound infection, requirement of blood transfusions, respiratory insufficiency, additional therapy and/or prolonged ICU stay

Table 29.3 Patients suffering from hematological diseases *vs.* patients suffering from no hematological diseases

Characteristics	Patients with hematological disease (n = 9)	Patients with *no* hematological disease (n = 14)	p*
Leukemia (including ALL, AML, CML)	9	–	–
COPD	–	3	–
Solid neoplasia	–	4	–
HIV	–	2	–
Alcohol abuse	–	2	–
TB	–	1	–
Liver-transplant rejection (+TB in the past)	–	1	–
No underlying disease	–	1	–
Deterioration of general condition (incl. fever)	5	7	0.567
Dyspnoea, coughing	0	8	**0.006**
Hemoptysis, blood-tinged sputum	0	4	0.113
Routinely done radiography during therapy	3	0	**0.047**
Findings in sectional imaging (CT/MRT)	2	1	0.332
Perioperative antimycotics	9	8	**0.030**
Severe postoperative complications[a]	6	6	0.246
M.A. or CNPA	3	5	0.633
Death in short-term follow-up	2	2	0.517
Death in long-term follow-up	2	4	0.888
Loss to follow-up	1	0	0.391

ALL acute lymphocytic leukemia, *AML* acute myeloid leukemia, *CML* chronic myeloid leukemia, *CNPA* chronic necrotizing pulmonary aspergillosis, *COPD* chronic obstructive pulmonary disease, *M.A.* multiple aspergillomas, TB tuberculosis

*Fisher's *t*-test

[a]including: atelectasis, hemothorax, major pleural effusion, wound infection, requirement of blood transfusions, respiratory insufficiency, additional therapy and/or prolonged ICU stay

Table 29.4 Differences between the patient group before 2003 and the one treated until 2011

Predisposing conditions and diseases	Patients 1995–2002 (n = 10)	Patients 2003–2011 (n = 13)	p*
Leukemia (including ALL, AML, CML)	4	5	0.636
COPD	1	2	0.602
Solid neoplasia	1	3	0.404
HIV	2	–	0.178
Alcohol abuse	1	1	0.692
TB	–	1	0.565
Liver-transplant rejection (+TB in the past)	–	1	0.565
No underlying disease	1	–	0.435
Singular aspergilloma	4	11	**0.037**
M.A. + CNPA	6	2	**0.037**
Deterioration of general condition (incl. fever)	7	5	0.140
Dyspnea, coughing	4	5	0.637
Hemoptysis, blood-tinged sputum	1	3	0.404
Routinely done radiography during therapy	2	1	0.398
Findings in sectional imaging (CT/MRT)	–	3	0.162
Perioperative antimycotics	7	10	0.537
Severe postoperative complications[a]	4	8	0.274
Death in short-term follow-up	2	2	0.596
Death in long-term follow-up	4	2	0.197

ALL acute lymphocytic leukemia, *AML* acute myeloid leukemia, *CML* chronic myeloid leukemia, *CNPA* chronic necrotizing pulmonary aspergillosis, *COPD* chronic obstructive pulmonary disease, *M.A.* multiple aspergillomas, *TB* tuberculosis

*Fisher's *t*-test

[a]including: atelectasis, hemothorax, major pleural effusion, wound infection, requirement of blood transfusions, respiratory insufficiency, additional therapy and/or prolonged ICU stay

why a typical aspergilloma patient with a lung cavity secondary to tuberculosis was rarely seen at our hospital (n = 2). The number of all detected patients was slightly less our study compared with that in other surgical studies (Table 29.5). A Moroccan study included 278 surgically treated patients in 22 years of observation time. Remarkably, 73% of the patients had a condition after tuberculosis (Caidi et al. 2006). In our study mostly immunocompromised patients (20/23), with no history of tuberculosis, were found (21/23). Notably, the two patients suffering from pulmonary aspergillosis after tuberculosis were both born abroad. Six of the 23 patients did not receive systemic antifungal treatment. According to the current guidelines from the Infectious Disease Society of America (IDSA) there is only moderate evidence to support a recommendation for the use of voriconazol or itraconazol in aspergilloma patients. Surgery (or no therapy) is recommended in these patients. There is good evidence to support a recommendation for the use of systemic antifungals in CNPA patients; there is no recommendation for surgery (Saraceno et al. 1997; Zmeili and Soubani 2007; Walsh et al. 2008). Since the decision for surgery in these patients in our cohort was made by radiological findings suspecting a space-occupying lesion rather than CNPA, definite diagnose was made after pathological findings of intraoperative samples. Surgery did not seem to have a negative influence in the long-term outcome of these patients.

Five of the six patients in our cohort, not treated with systemic antifungals, suffered from aspergilloma or multiple aspergillomas. The efficiency of systemic antifungal agents in patients suffering from aspergilloma has been controversial; itraconazol has been reported to show high tissue penetration (Tsubura 1997). Instillation of antifungal agents have only been reported in small numbers of patients and shown inconsistent success (Itoh et al. 1995; Yamada et al. 1993; Munk et al. 1993; Jewkes et al. 1983). Due to poor evidence, our hospital did not favor this treatment option. No major

Table 29.5 Patient numbers and mortality rates of different publications of the last 30 years

Authors, country of survey, and year of publication	No. of patients surgically treated	Operation- and/or aspergillus associated mortality rate (%)
Caidi et al. (Morocco, 2006)	278	5.7
Kim et al. (South Korea, 2005)	88	1.1
Schulte et al. (Germany, 2005)	28	7.1
Ueda et al. (Japan, 2001)	8	0
Regnard et al. (France, 2000)	89	5.7
Babatasi et al. (France, 2000)	84	4.8
Csekeo et al. (Hungary, 1997)	84	9.5
Chen et al. (Taiwan, 1997)	67	1.5
el Oakley et al. (UK, 1997)	24	8.3
Massard et al. (France, 1992)	63	9.5
Stamatis and Greschuchna (Germany, 1988)	29	6.9
Daly et al. (USA, 1986)	53	22.6
Battaglini et al. (USA, 1985)	15	13.3
Soltanzadeh et al. (USA, 1977)	14	7.1
Garvey et al. (USA, 1977)	11	9.1
Aslam et al. (USA, 1971)	9	0

complications occurred during short or long-term follow-up in our patients who did not receive systemic antifungals. Therefore, we submit that the omission of systemic antifungals might be justified in those distinct cases. A decision for that approach is only to be made after exclusion of parenchymal infiltration in radiological findings and/or after surgery.

The overall mortality rate in our study was high as ten patients died during the follow-up (43.5%): six with aspergilloma, three with CNPA, and one with multiple aspergillomas. However, only one death (4.3%) was caused by directly-linked postoperative complications (aspergillus associated sepsis with massive bleeding). Four patients died during the short-term (≤3 months) and six patients during the long-term follow-up period. One child in our study died 3 month after the surgery for aspergilloma due to therapy resistant acute lymphoblastic leukemia (ALL) complications. The other child suffering from accompanying ALL is still alive and has no pulmonary impairments. Compared with other studies (Table 29.3) our directly-linked postoperative mortality seems to be reasonably low. An indication that surgery for pulmonary aspergillosis led to the deaths of the other nine patients could not be substantiated.

We conclude that surgery for treatment of aspergilloma is feasible and safe for patients who are fit enough for surgery. Patients with hematologic neoplasias show reduced pulmonary symptoms at the initial presentation and are often diagnosed incidentally at routine diagnostics. CNPA patients did not seem to have disadvantages when treated surgically if diagnosis is uncertain before surgery.

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Chapter 30
Influence of Rapid Influenza Test on Clinical Management of Children Younger than Five with Febrile Respiratory Tract Infections

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Abstract Children are an important vector for spreading influenza and they are at increased risk for complications. The appropriate diagnosis of influenza may help start early antiviral treatment and may optimize the use of antibiotics and additional laboratory tests. The objective of this study was to describe the influence of rapid influenza detection test (RIDT) on clinical management of children with acute febrile respiratory tract infections. The method consisted of a prospective, open, cohort study conducted in three primary care clinics in Warsaw, Poland, during the epidemic influenza seasons of 2009/2010 and 2010/2011. A total number of 256 children of the age 0–5 years with symptoms of febrile respiratory tract infection were enrolled into the study. A 115 of them were tested with RIDT (BD Directigen EZ FluA + B) and another 141 children, who were not tested, constituted a control group. We found that RIDT gave positive results in 35 (30%) out of the 115 tested children. Antibiotics, additional blood tests and urinalysis were administered more often in the control group compared with the rapid test group (16% *vs.* 7%; 14% *vs*. 5%, and 47% *vs.* 32%, respectively). Chest radiograms were made only in six cases of children from the control group. We conclude that in children with symptoms of acute febrile respiratory tract infection, the rapid influenza detection test

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provides a rational use of antivirals, reduces an inappropriate use of antibiotics, and decreases a number of additional tests conducted.

Keywords Children • Clinical management • Diagnosis • Influenza • Rapid test

30.1 Introduction

Influenza is an acute infection of the respiratory tract which is transmitted *via* respiratory droplets and direct contact. Influenza type A (with a pandemic and epidemic potential) and B (with an epidemic potential) infections are common in the pediatric population. Nevertheless, the burden of the disease in children is underestimated. Depending on the age, the incidence rate may be 1.5–3 times higher than that for adults and is estimated to be between 10% and 40% each year (Long et al. 1997). Influenza in children leads to a significant increase in primary care and emergency department visits and in hospitalizations due to complications (Monto and Sullivan 1993).

The diagnosis of influenza is based on clinical symptoms and on the results of additional laboratory tests confirming presumptive diagnosis, including rapid influenza detection tests (RIDT), real time polymerase chain reaction, direct immunofluorescence, or viral culture. There are no typical symptoms for influenza, but the disease may be suspected in the presence of acute onset, cough, and fever >38.5°C. A presumptive diagnosis requires confirmation and the viral culture has been considered the gold standard for influenza diagnosis, but the delay in obtaining results makes it impractical for clinical-decision making (Call et al. 2005). The polymerase chain reaction is more sensitive than standard viral culture, but is not widely available and expensive (Weinberg et al. 2004). As an alternative, RIDT is relatively inexpensive and can provide timely diagnostic information (Poehling et al. 2002).

The accuracy of the interpretation of rapid-test results depends on many factors including: clinical presentation of disease, duration of symptoms, age of a patient, prevalence of influenza in the community, and test characteristics (Grijalva et al. 2007). A timely diagnosis of influenza allows providing antiviral therapy and implementing measures to limit the spread of the disease. Unnecessary antibiotic therapy and ambulatory and hospital testing may thus be avoided (Uyeki 2003). The use of RIDT is helpful in diagnosis of influenza and decreases the average cost per suspected and infected patient (González-Canudas et al. 2011).

The objective of the present study was to assess the influence of RIDT on clinical management of children with acute febrile respiratory tract infections. We addressed the issue by comparing the management of infected children in whom the RIDT was performed with those in whom it was not.

30.2 Methods

The study protocol was approved by a local Ethics Committee and informed consent was obtained from the children's parents. The study was prospective and was conducted in three primary care clinics in the Warsaw area in Poland during the pandemic influenza A (H1N1) of 2009/2010 and the post-pandemic season of 2010/2011. A total number of 256 children of the age 0–5 years who fulfilled the inclusion criteria (acute onset of the disease, fever >38°C, cough, and/or sneezing) were enrolled into the study: 115 of them were tested with RIDT and another 141 children were not (control group). Gender and age characteristics of the rapid test and control groups are illustrated in Table 30.1.

In the patients from the rapid test group, the nasopharyngeal swabs were taken by trained personnel using sterile artificial viscose sticks. Each patient had a nasopharyngeal specimen taken, which was then tested according to the manufacturer's recommendations. This swab method was chosen because

Table 30.1 Gender and age of children from the rapid test and control groups of patients

	Rapid test group (n = 115)	Control group (n = 141)
Girls/boys	75/40	87/54
Patients aged <1	12	18
Patients aged 2–5	103	123

Table 30.2 Additional tests and prescription of antibacterial or antiviral therapy in the rapid test and control groups of patients

	Rapid test group (Positive/ negative test result)* (n = 115)	Control group (n = 141)	p
Blood tests	6 (1/5)	20	0.018
Urinalysis	23 (3/20)	45	0.032
Chest X-ray	0	6	0.025
Antibacterial therapy	8 (0/8)	22	0.032
Antiviral therapy	4 (0/4)	0	0.026

of its superior combination of sensitivity and specificity for the chosen RIDT (BD Directigen™ EZ Flu A + B). The RIDTs were performed immediately on-site at the general practitioner's office. Positive and negative test results were determined by the use of a visual key provided within the test kits.

The analysis of medical management of children from the rapid test and control groups included the use of antiviral drugs, antibiotics, and the need to perform additional tests (X-ray examination, blood tests, and urinalysis). Data were first analyzed using descriptive methods. The categorical variables were tested using the chi-square and Fisher exact tests. $P < 0.05$ was accepted as indicative of statistically significant differences.

30.3 Results

Among the 115 children included into the rapid test group, the positive results were found in 35 (30%) of them; in 18 out of the 58 (31%) in the 2009/2010 season and 17 out of the 57 (30%) in the 2010/2011 season. The antiviral treatment (oseltamivir) was prescribed only for four children with positive results of RIDT. Antibiotics were administered more often in the control group compared with the rapid test group (respectively for 16% *vs.* 7%). No child with a positive result of RIDT was prescribed an antibiotic.

Additional blood tests (WBC and/or CRP) were ordered more often for children from the control compared with the rapid test group (14% *vs.* 5%, respectively). Urinalysis was conducted in 47% of patients from the control group and in 32% patients from the rapid test group; the difference was statistically significant. Chest radiograms were made only in six cases of children from the control group. Comparison of the frequency of the additional tests is summarized in Table 30.2.

30.4 Discussion

The present study seems the first describing the use of RIDT in the pediatric population of the age 0–5 years in Poland. We found the incidence rate of influenza among these children of about 30%. This figure is considered high, but should not be surprising in view of the timing of the study which

was performed during the pandemic period and post-pandemic seasons. Nevertheless, the high incidence rate demonstrates that influenza is indeed a common infectious disease in young children.

This study evaluated the influence of RIDT results on physicians' management and treatment of pediatric patients with acute febrile respiratory tract infection. The results demonstrate that performing RIDTs resulted in a significant reduction of additional tests, including complete blood cell count, CRP, urinalysis, or chest radiographs. We showed therefore that physicians' awareness of a rapid diagnosis of influenza in pediatric emergency departments streamlines the management of children suspected of having influenza. Our results are comparable with those described in other studies (Sharma et al. 2002).

In our study, only patients with positive results of RIDT were ordered antiviral oseltamivir therapy and we find this observation of essential importance. The use of antiviral agents has been shown to hasten resolution of illness, but the effective utilization requires that the child is started on appropriate therapy within 48 h of symptoms onset (Poehling et al. 2002; Uyeki 2003). Positive results of RIDT may help make the decision of implementation of antivirals which should not be overused because of the risk of resistance and the possibility of adverse effects such as increased nervousness, jitteriness, or confusion (Bonner et al. 2003).

On the other hand, antibiotic therapy in patients with positive results of RIDT was administered less often, which is another positive aspect. With substantial literature on antibiotic resistance and because of increasing pressure to utilize antibiotics only for proven bacterial diseases, the diagnosis of viral illness becomes more paramount to decrease inappropriate antibiotic usage (Bonner et al. 2003). Performing the RIDT seems to have a positive influence on physicians' confidence concerning not using antibiotics and also reassures the children's parents.

We would like to stress is that the results of RIDT should be interpreted cautiously and the tests performed in ambulatory care settings. Data from the literature indicate that during the 2009 A(H1N1) pandemic season, sensitivity and specificity of RIDT, the same as the ones used in our study (DB Directigen EZ Flu A + B), although relatively low, was similar to that present in any seasonal influenza and high enough to diagnose the disease in children (Chan et al. 2002; Blázquez et al. 2010). However, we support the idea that, particularly for children with high risk conditions for a severe course of influenza during high-prevalence periods of influenza, empiric initiation of antiviral treatment and confirmation of negative results of RIDS tests ought to be conducted (Cruz et al. 2010).

The major limitation of the study was a relatively small number of patients enrolled and the lack of randomization of patients for the RIDT and control groups. Nevertheless, we believe we have shown that rapid influenza tests serve well to assist clinical decision-making concerning the management of influenza. These tests seem helpful in the situation when clinical findings may identify patients with influenza–like illness, but are not particularly useful for confirming or excluding the diagnosis of influenza.

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Chapter 31
Influenza Immunization Rates in Children and Teenagers in Polish Cities: Conclusions from the 2009/2010 Season

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Abstract The aim of this study was to determine influenza vaccine coverage among children aged 0–18 years in inner city practices in Poland in the 2009/2010 season and factors that might have influenced low vaccination coverage. A retrospective review of 11,735 vaccination charts of children aged 0–18 from seven randomly selected general practices in the capital city of Warsaw and one large practice in the city of Wroclaw was performed. We calculated the numbers of children who were vaccinated in the 2009/2010 season and analyzed the age distribution of vaccinated children. We also reviewed the vaccination history in patients who were vaccinated against influenza including: previous influenza vaccinations, modification (widening) of standard immunization scheme, and a proportion of children who completed the recommended two-dose schedule of vaccination. In the calculations, 95% confidence intervals were used. Out of the total of 11,735 children surveyed, 362 (3.1%, CI: 2.8–3.4%) were vaccinated against influenza in the 2009/2010 season. For 115 of these 362 (31.8%, CI: 27.0–36.6%) children it was their first vaccination against influenza. The mean age of a vaccinated child was 6.0 ± 4.3 years. Children aged 2–5 were most commonly vaccinated (153/362, 42.3%, CI: 37.2–47.4%), while infants (aged 6–12 months) were vaccinated rarely (15/362, 4.4%, CI: 2.2–6.2%). In the group of children younger than 8 years (86/362 children) who were vaccinated for the first time in their life only 29/86 (33.7%, CI: 23.7–43.7%) completed the recommended two-dose schedule. In conclusion, the importance of vaccinating children against influenza is hugely understated in Poland. General physicians should actively recommend annual influenza immunization of children. Recommendations of National Immunization Program concerning influenza vaccine should be clearer, simpler, and easier to implement.

Keywords Influenza • Immunization • Prevention • Public health • Vaccination

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31.1 Introduction

Influenza is a serious vaccine-preventable infectious disease that continues to contribute to significant morbidity and mortality worldwide. Rates of serious complications are the highest among persons over 65 years of age (Thompson et al. 2003, 2004), children younger than 2 years and persons of any age who have medical conditions that place them at an increased risk for complications from influenza (Izurieta et al. 2000; Heikkinen et al. 2004).

The burden of the disease among infants and young children is underestimated (Heikkinen et al. 2004, 2006; Poehling et al. 2006). The incidence of influenza in children under 5 years of age is greater than in the elderly, with estimates showing an attack rate of 30% of respiratory illnesses peaking in the age group of 1–2 years (Poehling et al. 2006). Outpatient visits associated with influenza in young children are 10–250-fold more common than hospital cases (Poehling et al. 2006), but healthy children under 1 year of age are hospitalized for influenza-associated illnesses at similar rates to those of adults in high-risk groups (Neuzil et al. 2000). Children under 2 years of age are at highest risk of influenza and are the most likely to develop serious complications such as pneumonia, secondary bacterial infection, and sepsis (Neuzil et al. 2002). Although overall influenza-associated mortality rates in children are not high, a US study shows that 63% of the influenza-associated pediatric deaths are reported in children less than 5 years of age (Bhat et al. 2005).

Annual influenza vaccination benefits have been clearly demonstrated and vaccination for high-risk groups is well recognized in Europe and the rest of the world as a means of preventing infection and the complications that develop from influenza. High risk groups include infants and children with existing health complications as well as the elderly (>65 years of age) and vaccination of these groups is current practice in many countries (Nichol et al. 2007; Mangtani et al. 2004).

Annual influenza vaccination was first recommended for children aged 6–23 months and 2–4 years by the Advisory Committee on Immunization Practices (ACIP) in 2004 and 2006 respectively (Harper et al. 2004; Smith et al. 2006). In August 2008, ACIP expanded its seasonal influenza vaccination recommendations to include all children aged 5–18 years as well (Fiore et al. 2008). Universal vaccination of healthy children is not widespread in Europe despite clear demonstration of the benefits of vaccination in reducing the large health and economic burden of influenza (Cohen et al. 2011). Data from the National Seasonal Influenza Survey in Europe indicated that the universal vaccination against influenza of children older than 6 months is recommended in two countries: Austria and Estonia, while in Latvia, Romania, and Slovenia vaccination is recommended for children of the age 6 months–2 years, in Finland 6 months–3 years, in Slovakia 6 months–5 years (Usonis et al. 2010).

In Poland, influenza vaccination has been recommended on the yearly basis since 1994, but for adults older than 55 years and patients with underlying medical conditions only (Brydak 2011). Vaccination against influenza is not included into national immunization schedule and parents who decide to vaccinate their children must pay for the vaccine. At present, the Polish National Immunization Program recommends vaccination for children from certain risk groups (immunodeficiency, asthma, diabetes, chronic cardiac, pulmonary and renal insufficiency) and in cases of those children in whom the concern arises from ‘epidemiological indications’.

The influenza vaccination schedule in children older than 9 years consists of a single dose of vaccine, while in younger children vaccinated for the first time in their life – two doses of vaccine are recommended with the minimum interval between them of 4 weeks. Children younger than 36 months should be given a half dose of vaccine (0.25 mL) twice (Fiore et al. 2008). In Poland, there are only trivalent inactivated vaccines available.

The influenza vaccine coverage in Poland remains at a very low level (6–9%) in the general population (Kroneman and van Essen 2007). Official data indicate that the influenza vaccine coverage among children younger than 5 years is also very low – less than 2% (Nitsch-Osuch et al. 2010). The official data available at the national level are obtained from obligatory reports created by

practitioners who vaccinate patients. Official reports give only the number of vaccinated people and distribution of vaccines according to the age and geographical area, but they do not include other relevant details, for example, full or partial vaccination, history of previous influenza vaccinations and co-administration of influenza vaccines with other pediatric vaccines. Influenza vaccination is not included in the National Programme of Immunization for children, which means that parents (patients) have to cover the cost of vaccine.

The objective of our study was to determine influenza vaccine coverage among children aged 0–18 years in inner-city practices in the capital city of Warsaw and in the city of Wroclaw in the 2009/2010 season and to analyze previous influenza vaccination history in children vaccinated during this season to determine the factors that may have influenced low vaccination coverage.

31.2 Methods

We conducted a retrospective review of 11,735 vaccination charts of children aged 0–18 years from 7 randomly selected general practices in the capital city of Warsaw and in the city of Wroclaw, Poland, in the 2009/2010 season (up to March 31. 2010). The proportion of children who were vaccinated was compared with the official reports concerning influenza vaccine coverage among children in Poland taken from National Institute of Public Health. The age distribution of vaccinated children was analyzed. We also reviewed the vaccination history among children who were vaccinated in the 2009/2010 season including: previous influenza vaccinations, modification (widening) of standard immunization scheme, co-administration of influenza vaccine with other pediatric vaccines and the proportion of children who completed the recommended two dose schedule of vaccination. In the calculations, 95% confidence intervals were used.

31.3 Results

We found that 362/11,735 (3.1%, CI: 2.8–3.4%) children were vaccinated against influenza (received one or two doses of a vaccine). For 115/362 (31.8%, CI: 27.0–36.6%) children, the season 2009/2010 was the first one when they were vaccinated against influenza (Fig. 31.1). The mean age of a vaccinated child was 6.0 ± 4.3 years. Most of the vaccinated children (153/362, 42.3%, CI: 37.2–47.4%) aged 2–5 years, while infants (aged 6 months–1 year) were vaccinated very rarely (15/362, 4.1%, CI: 2.2–6.2%). Distribution of vaccinated children by age illustrates Fig. 31.2. In the group of children younger than 8 years (86/362), who were vaccinated for the first time in their life, only 29/86 (33.7%, CI 23.7–43.7%) completed the recommended two-dose schedule of vaccination. The mean

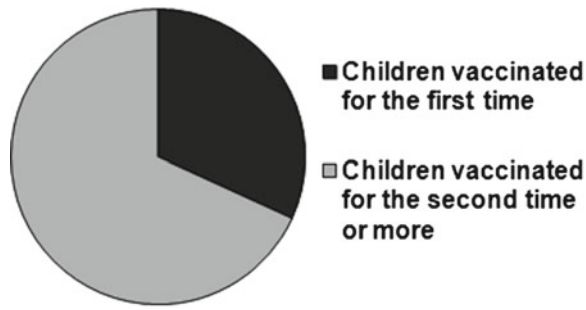

Fig. 31.1 Influenza season of 2009/2010

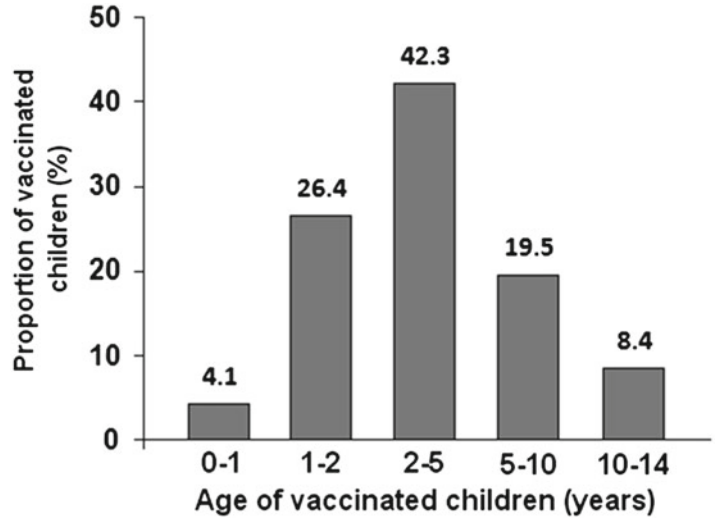

Fig. 31.2 Distribution of influenza vaccination between children's ages

Table 31.1 Vaccines recommended in Polish Program on Immunization

Name of vaccine	Trade name
Monovalent vaccines	
Meningococcal type C, conjugated	NeisVac C, Meningitec, Menjugate
Live Varicella	Varilrix
Tick Born Encephalitis (TBE)	FSME Immun
Hepatitis A	Havrix Junior
Combined and polyvalent vaccines	
Diphtheria, Tetanus and acellular Pertussis (DTaP)	Infanrix
Diphtheria, Tetanus, acellular Pertussis, inactivated Polio and Haemophilus influenzae B (DTaP-IPV-Hib)	Infanrix IPV Hib, Pentaxim
Diphtheria, Tetanus, acellular Pertussis, hepatitis B, inactivated Polio and Haemophilus influenzae B and (DTaP-HB-IPV-Hib)	Infanrix Hexa
Pneumococcal conjugated	Prevenar, Prevenar 13, Synflorix
Live Rotavirus	Rotarix, Rotateq
Human Papilloma Virus (HPV)	Silgard, Cervarix

age of children who received partial and full vaccination did not differ significantly (3.6 ± 2.3 *vs.* 3.4 ± 1.6 years). Co-administration of influenza vaccine with other pediatric vaccines was marginal; there were 6/362 such children only (1.7%, CI: 1.3–3.3%).

In the majority of the vaccinated children (198/362, 54.7%, CI: 49.6–59.8%) the universal schedule of immunization was modified (widened) by the use of combined or monovalent recommended vaccines (listed in Table 31.1, paid by parents not by the government).

31.4 Discussion

Influenza vaccine coverage among children and teenagers in our group was low (3.1%), despite the fact that Warsaw and Wroclaw are large cities in Poland where access to medical services is very good. We might have expected that the general knowledge, conscience, and perception of vaccinations – both among patients (or parents of patients) and medical professionals in large Polish

cities should have been better. Although the percentage of vaccinated children in the study group was slightly higher than that among all children in Poland (2.6%), the result is unacceptably low, especially when we compare our figures with data from other countries. In the U.S., the full vaccination coverage in the 2009/2010 season ranged from 15.3% among children aged 13–18 years to 34.7% in those aged 6–23 months (Pabst et al. 2010). In Spain, influenza vaccine coverage rate among children older than 6 months was 6.8% (Jiménez-García et al. 2008). Our results provide one more proof that Polish society does not accept influenza vaccination among children and teenagers and that Polish physicians hugely understate the importance of vaccinating children. There is an open question: why is it so? In the literature, the most common reason given by parents of non-vaccinated children is 'lack of awareness' (85.6%), which is why more educational activities describing the benefits of influenza vaccination directed to patients (parents) and medical professionals are strongly recommended (Esposito et al. 2006). Studies have demonstrated the effectiveness of interventions that aim to increase influenza vaccine coverage among children; a multifaceted strategy that comprises education, reminders, standing orders, and express immunization service had a strong positive influence at 10 city practices (Zimmerman et al. 2004). Many studies have shown that a physician's recommendation is the most important factor influencing the patients' attitude to influenza and vaccination rate (Sievert et al. 1988).

In the present study, there was a great discrepancy between the high rate of modification of the vaccination scheme (54.7%, CI: 49.6–59.8%) and the low influenza vaccination rate (3.1%, CI: 2.8–3.4%), which we can only be explained by physicians being not active enough in recommending influenza vaccinations. One possible explanation of this phenomenon is that Polish national immunization program recommends vaccination of high risk children (immunodeficiency, asthma, diabetes, chronic cardiac, pulmonary and renal insufficiency) and in those children in whom the concerns arise from 'epidemiological indications'. In countries where simple 'universal vaccination' of children is recommended, vaccination rate is high (e.g., the U.S.). It is possible that Polish physicians are not confident enough in their knowledge concerning immunizations and actual official recommendations, and if there are any doubts they choose not to recommend vaccinations, as they perceive not vaccinating as a 'safer' option.

One third of the patients in our group received influenza vaccine for the first time in their life and the question is how many of them will repeat vaccination in the future years. The 2009/2010 season was exceptional because of pandemic AH1N1v. The pandemic vaccine was not available in Poland and the patients were recommended to use the seasonal flu vaccine, which they did and which resulted in a shortage of vaccine in pharmacies and warehouses. Most of the children who were vaccinated against influenza were preschool children, which was a positive situation specifically because these children are the main sources of influenza viruses. What is also worth highlighting, influenza vaccination in children may reduce influenza-associated hospitalizations in older adults and household contacts (Horwitz et al. 2000). Besides receiving influenza vaccine for their own protection, children should be vaccinated to prevent them from contributing to the spread of influenza within the household and community (Chi et al. 2010). On the other hand, the proportion of children less than 2 years among the vaccinated against influenza was extremely low (<2%) which should be considered as a negative observation, since children of this age group are at high risk for influenza complications, hospitalizations, and an increased number of visits to outpatient clinics (Heikkinen et al. 2004, 2006). Some authors from other countries reported that influenza vaccination rates were highest among toddlers (40.5%) (Chi et al. 2010).

Only 33.7% of children younger than 8 years who were vaccinated against influenza for the first time in their life fulfilled a two-dose schedule of vaccination. Our data are here comparable with those already published, e.g., in the U.S. each year, nearly half of children who receive the first dose of vaccine, fail to receive a recommended second dose (Verani et al. 2007). It has been described that complete influenza vaccination might have been associated with: suburban location of practice (as a result of closer contact with medical staff in the community), lower patient volume in practice and implementation of specific vaccination strategies (including working hours in evenings and weekends),

factors associated with the child: existing high-risk conditions, frequent (more than six) visits in practice, and visits from October to January (Poehling et al. 2010; Chi et al. 2010). According to the available data, parents of school children expect free immunization of their children conducted at schools which should be paid for by insurance (Allison et al. 2010).

According to the international recommendations, influenza vaccine may be co-administrated with other pediatric vaccines. However, in our patients less than 2% received an influenza shot with another vaccine at the same day. We may conclude that visits conducted from September to March, during which other pediatric vaccines are administered, could be treated as missed opportunities for influenza vaccination. Missed opportunities could be major contributors to low influenza vaccine coverage; even more than 80% of all possible occasions to vaccinate might have been missed (Verani et al. 2007).

Our study has several limitations. We were not able to establish the risk status of children (coexisting diseases like bronchial asthma and other chronic disorders). Another bias may be connected with vaccinations which had been conducted but they had not been reported in medical documentation; but the risk of the latter bias seemed rather low. On the other hand, a significant advantage relating to our study is that contrary to the official reports, which provide only vaccination coverage rates, we were able to estimate the history of vaccinations. This information included previous vaccinations, co-administration of influenza vaccine with other vaccines and, what is most interesting, the proportion of children who received the full course of influenza vaccination.

Our results demonstrate that the importance of vaccinating children against influenza is hugely understated in Poland, and the rate of delivery of influenza vaccine to children and teenagers aged 0–18 is inadequate. We conclude that general physicians probably trivialize influenza morbidity and do not actively recommend influenza vaccinations, which causes as a consequence that vaccine coverage among children in Poland is extremely low. General physicians should actively recommend annual influenza immunization in children and the recommendations of the National Immunization Program concerning influenza vaccine should be clearer, simpler, and easier to implement.

Conflicts of interest: Authors do not declare any conflict of interests in relation to this article.

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Chapter 32
Pharmacotherapy for Sarcoidosis: An Example of an Off-Label Procedure

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Abstract Sarcoidosis is a granulomatous multiorgan diseases with an unknown etiology, with the predominant lung involvement. Immunosuppressive agents such as corticosteroids, methotrexate, azathioprinum, ciclosporinum A, chlorambucil, cyclophosphamide, hydroxychlorochinum, indomethacin, pentoxyfillinum, thalidomide, leflunomidum, and adalimumab, or infliximab have been used in its treatment. It should be emphasized that the Summary of Products Characteristics (SPC) of these drugs does not specifically recommend their use in the therapy for sarcoidosis. That makes the application of the drugs in sarcoidosis an off-label use, which is not formally accepted by the authorities but is supported by medical bibliography or recommendations given by scientific bodies. Thus the off-label drugs raise legal, but also ethical and medical problems. The dosing regimen and the required duration of therapy for sarcoidosis are missing. In effect the therapy usually follows the recommendations from the American and European Respiratory Societies (ATS/ERS), based on the long-term medical research. The American Food and Drug Administration recognizes the existence of the off-label use. European legislations do not precisely specify the rules for the admissibility of the off-label use. The doctrine of law assumes that the off-label use constitutes a medical experiment. Therefore, the commencement of therapy with such drugs requires patients' informed consent, which must be kept along with other medical records. Insufficient knowledge of the legal regulations may result in civil and professional liability of a physician supervising the therapy of a sarcoidosis patient, especially in case of adverse effects.

Keywords Legislation • Medicinal product • Off-label use • Sarcoidosis • Professional liability

32.1 Introduction

Sarcoidosis is a multisystem disease of unknown etiology characterized by granuloma formation. It usually affects the lungs, mediastinal and/or peripheral lymph nodes and the liver. It can be asymptomatic or take acute forms with joint involvement, enlargement of hilar lymphadenopathy and erythema

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nodosum (Löfgren syndrome) and/or chronic forms with spontaneous remission of the disease in its early stage (in approx. 70%), resulting in disability, most frequently due to respiratory insufficiency (in approximately 10%), or in death (in 1–5%) (ATS 1999).

The disease is diagnosed on the basis of clinical symptoms and the presence of non-caseating granulation tissue in the organs affected by the pathological process, following the exclusion of other causes. Infectious, organic, chemical, autoimmunological and genetic factors are mentioned (ATS 1999). It is highly likely that genetically predisposed individuals, when exposed to the above-listed environmental factors, will manifest an intense granulomatous inflammation in the affected organ (predominance of $CD4^+/CD8^+$ lymphocytes) and a relative deficiency in the number and activity of $CD4^+$T cells in the peripheral blood, which leads to peripheral anergy (ATS 1999).

The current treatment for sarcoidosis includes immunosuppressant and biological drugs. The most commonly used drug is oral prednisone 20–40 mg a day for the first 1–3 months, and subsequently the dose is gradually reduced over 6–12 months depending on the stage and remission of the systemic lesions, or for up to 2 years in cardiac sarcoidosis (Baughman et al. 2008; Schutt et al. 2010; Coker 2009). If there is no improvement after 3 months of treatment (too small a dose of the drug, drug-resistance, presence of fibrotic lesions) and/or there are concomitant adverse reactions, immunosuppressant drugs are used, such as: azathioprine, methotrexate or hydroxychloroquine (Baughman et al. 2008; Schutt et al. 2010; Coker 2009) and biological drugs, anti-TNF-α antibody (Infliximab, Adalimumab) or a TNF-α inhibitor – soluble receptor for TNF-α (Etanercept), due to its major role in the formation of sarcoid granulation tissue. Other drugs which proved to be effective in patients with sarcoidosis are thalidomide and pentoxifylline, which also block the activity of TNF-α. (Baughman et al. 2008; Schutt et al. 2010; Coker 2009). Lately there have also been isolated reports on the efficacy of tetracyclines and macrolides in the treatment of sarcoidosis (Baughman et al. 2008; Schutt et al. 2010; Coker 2009).

The above-listed drugs used in sarcoidosis treatment do not have formally approved therapeutic indications for this disorder and are therefore used as off-label drugs. Off-label use of a drug means that it is prescribed empirically; a dose or form of administration of a drug has not been submitted for evaluation, and hence has not been accepted by the regulatory authorities. All medicinal products need to be given a marketing authorization by a relevant regulatory body. In European Member States drugs are approved by national registration bodies and at the European Community level the body responsible for marketing authorization of drugs is the European Medicines Agency (EMA), while in the USA a similar function is played by the Food and Drug Administration (FDA). The marketing authorization is granted if the drug is judged to be safe and effective for a given indication following a given administration regimen. FDA recognizes the existence of off-label use, whereas European legislation does not explicitly regulate the procedure. The term ‘off-label use’ was first mentioned by Higgins (1988). Physicians, based on their knowledge and on currently available information, may use a drug for an indication not stated in the approved labeling if it seems reasonable or appropriate. There are 4 basic cases of off-label drug use:

- use of a medicinal product using a route of administration not listed in the approval documents (e.g., oral administration of a drug available in the injection form or administration of a drug available in the tablet form as a suspension or suppository) or a dose regimen different from the approved one,
- use of a drug according to the indication but in a population of patients for whom dosage is not established (e.g., in children),
- use of a drug for an indication not listed in the approval documentation but supported by reliable data confirming its safety and efficacy (controlled randomized clinical trials have been conducted; scientific societies’ recommendation),
- use of a drug for a new indication that has not been proven yet but for which there is scientific evidence giving grounds for expecting it to be effective and safe (Gazarian et al. 2006).

The use of drugs in off-label clinical situations not covered by the approved indications is a common issue in contemporary medicine, especially in rare disease symptoms (Poole and Dooley 2004). Off-label prescribing may lead to innovative new uses of old medications (Chen et al. 2010) but also, in the case of newly approved medications, offers the possibility of enhancing health because innovations advance the standard of care much more rapidly than the regulatory bodies approve new uses. In literature, there are reports of very frequent off-label use of drugs in pediatrics and neonatology (Jacqz-Aigrain 2011), oncology (Gillick 2009; Devita 2009) and dermatology (Brockmeyer et al. 2009), hematology (Bernardi and Pegoraro 2008) and palliative medicine (Pavis and Wilcock 2001).

Since there is no therapeutic alternative to off-label treatment in different conditions, including sarcoidosis, the physician and patient must take the decision to undertake a therapy not formally approved by the regulatory body.

Off-label use of drugs is a problem on the borderline of medicine and law. The persistent need to use drugs off-label constitutes a serious concern. In fact, upon prescribing a drug off-label, the physician is required to take special responsibility. Formally, he is prescribing something that the regulatory body has not acknowledged as safe and effective (Henry 1999). That is often the case in sarcoidosis treatment and stems from the fact that an indication for 'sarcoidosis treatment' may not be registered by the marketing authorization holders (pharmaceutical manufacturers) due to the lack of specific clinical trials with a given drug. A relatively small target population of people suffering from sarcoidosis may be the cause.

32.2 Clinical Aspects

The off-label use procedure in sarcoidosis treatment is of great clinical significance. The dosing regimen, dose intervals and the required duration of therapy, the route of administration for sarcoidosis are missing. In effect, the therapy usually follows the recommendations from the American and European Respiratory Societies (ATS/ERS), based on the long-term medical research. The unknown is not only the dosing of the drugs currently used off-label in the treatment of sarcoidosis but also their pharmacokinetic parameters. Therapeutic modalities (e.g., mono- or combination therapy) and certain patient characteristics (e.g., age) are not taken into account. A complex problem in the choice of off-label therapy is ensuring the safety of drug use because of the possibility of adverse reactions occurring in the patient, especially those never described before, which may have legal consequences.

32.3 Legal Aspects

Off-label uses of drugs might be viewed as illegal, in a sense. Nonconformity of drug administration with its approval is not equivalent to malpractice. However, we should emphasize the absence of global legal solutions establishing detailed principles of off-label drug use, which shifts more responsibility on physicians towards patients, particularly in the event of adverse reactions.

In Poland, there are no detailed legal acts governing the off-label use. The possibility of using such therapy according to the legal doctrine has been based on the interpretation of Art. 4 of the Act on Medical Doctors and Dentists' Professions, according to which the physician is obliged to practice medicine in a manner complying with, *inter alia*, the guidelines of current medical knowledge (Zimmermann and Zimmermann 2008). Similarly, according to the German law, specifically German National Law on Physicians, doctors have therapeutic freedom and they may prescribe a medicinal product if they feel it is necessary (paragraph 1 Abs. 2). However, the current standard of care must be assured (paragraph 276 of German Civil Code) (Ehlers and Bitter 2003).

In other European countries, states have different policies in regard to the off-label issue, which are often unclear and liable to lead to improper denials. According to the general principles of medical law, off-label therapy is classified as experimental therapy, which has specific legal and economic consequences (Casali 2007).

The patient should be informed of the fact that an off-label procedure will be used in his therapy. The patient must give his informed consent thereto and the consent, as a written statement, is to be kept with the patient's documentation: 'I declare that I understand information concerning the application of the medicine outside the registered indications and have received full and satisfying answers to my questions. I hereby give my informed consent to the therapy with the medicine outside the indications and I am aware that I may discontinue the therapy at any time'.

Practice shows that in European countries off-label uses are often tolerated under restrictions, in spite of the size of the phenomenon, especially in some medical areas (Bernardi and Pegoraro 2008). The drug use should comply with the guidelines of current medical knowledge and evidence of efficacy should be available (Casali 2007). Deciding to use the procedure in question, the physician should be assured that there is no alternative method of treatment or that the alternative method proved inefficient.

In the US, Supreme Court (Evers' case, 643F2d1043) granted the physician the right to prescribe a drug off-label if the manufacturer has not clearly stated that such a procedure is contraindicated. Therefore, the physician does not make a mistake if he decides to use a drug off-label following a detailed analysis of risks and benefits showing that there are evident positive effects of the proposed therapy without significantly increasing the risk of adverse reactions (Henry 1999).

Despite numerous clinical and legal issues, no state attempts to prohibit or encourage to give up off-label drug use in the treatment of a given patient. Off-label drug use is also an issue of ethics and economy in view of the possibility of reimbursement of off-label drug therapy.

32.4 Ethical and Economic Aspects

A physician who undertakes sarcoidosis therapy must make the ethical choice of submitting the patient to an officially unapproved procedure and thus possibly exposing him to danger (Rothberg 2005). Pursuant to the provision of Art. 32 of the Declaration of Helsinki of the World Medical Association: 'If, during the treatment of a patient, proven methods of prevention, diagnostics and treatment are non-existent or ineffective, the physician, subject to the patient's informed consent, must have the freedom of using unconfirmed or novel preventive, diagnostic and therapeutic methods if, in his judgment, they may bring the hope of saving life, restoring health or relieving pain.'

Doctors have been recommended to record in the patient's notes the reason for prescribing outside the license; to explain, where possible, the position to the patient (and carers, if appropriate) in sufficient detail to allow informed consent to be given; and to inform other professionals involved in the care of the patient of such prescribing, so that misunderstandings are avoided.

The position of drug reimbursement bodies (third-party payers) with respect to off-label therapy is autonomous and is not subject to unification procedures in the EU countries. Third-party payers, whether public (national health systems, and the like) or private, may just refuse to reimburse some off-label drugs, at their discretion. In Germany, by resolution of the Federal Court, the possibility of reimbursement of a drug used off-label was limited to strictly defined, scientifically described clinical situations, when it is impossible to use a therapy alternative to off-label therapy. There are drug guidelines (*Arzneimittelrichtlinien*) in which certain accepted off-label uses are listed (Brunne et al. 2004; Brockmeyer et al. 2009). In Poland, to acquire reimbursement of off-label sarcoidosis pharmacotherapy of a hospitalized patient, it is necessary to prove that the drug use is in compliance with the guidelines of current medical knowledge. If the national payer has doubts about the above, he falls

back on the opinion of a consultant in the particular area of medicine. During off-label therapy, it is necessary to monitor the patient's health. In Poland, the treatment of sarcoidosis at an outpatient clinic is 100% payable by the patient (Zimmermann and Zimmermann 2008).

In the United States, due to different requirements of private insurers, the situation varies. Some managed care organizations and private health insurance plans have declined to reimburse the cost of drugs used off-label on the ground that these uses are 'experimental' or 'investigational' (ASCO 2006).

32.5 Conclusions

The issue of off-label drug use is a global concern in contemporary medicine, especially in sarcoidosis therapy. Pharmacotherapy for sarcoidosis is an off-label use procedure what can influence the quality of sarcoidosis treatment. Ignorance of legal, ethical and economic regulations may lead to the physician's accountability, particularly if adverse reactions have occurred. The consequences can be grave, especially for sarcoidosis patients for whom there is no alternative to off-label therapy. Thus, to ensure sarcoidosis patients equal and optimal access to the available pharmacological methods, it would be recommended to suggest introducing such clear and positive systemic solutions for off-label therapy that permit unconditional reimbursement of therapy. It is also indispensable to introduce more legal certainty in the use of off-label medications in sarcoidosis to guarantee maximum safety to patients and medical staff.

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Chapter 33
Invasive Pneumococcal Bacteremia in a 9-Year-Old Boy Caused by Serotype 1: Course, Treatment and Costs

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Abstract *Streptococcus pneumoniae* is a leading cause of bacteremia, sepsis, meningitis, pneumonia, sinusitis, and acute otitis media in young children. Some serotypes are associated with particular disease syndromes, such as complicated pneumonias in children, or with higher rates of hospitalization in children and are consistently responsible for outbreaks in certain populations. In this report we describe a case of a nine-year-old boy who developed an abscess of pleura and invasive pneumococcal bacteremia. The boy was admitted to the hospital with abdominal pain and vomiting, accompanied by mild cough and fever. Chest X-ray revealed lower left lobe consolidation with pleural inflammation and chest CT showed extensive interstitial-alveolar changes in the left lung with atelectasis and pleural effusion causing a reduction in lung volume up to the fourth rib. From the 6th day of hospitalization on, suction drainage and intrapleural administration of alteplase were continued for 5 days. Intravenous antibiotics were administered for subsequent 32 days. The course of disease was complicated with labial herpes and acute adenoviral gastroenteritis. The costs of diagnosis (11.7%), pharmacotherapy (55.2%), hospitalization (30.7%) and additional procedures (2.4%) were about €4,444, while the cost of treatment from the perspective of the National Health Fund was only €1,508. The costs of treating the boy with sepsis caused by *S. pneumoniae* serotype 1 were thus about three times higher than those from the perspective of providers of the National Health Fund. Administration of a new pneumococcal conjugated vaccine containing serotype 1 (PHiD-CV10 or PCV13) could have prevented invasive pneumococcal disease in the described patient.

Keywords Bacteremia • Invasive pneumococcal disease • Serotype 1 • Empyema • Pneumococcal vaccine • Treatment cost

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33.1 Introduction

Streptococcus pneumoniae (*S. pneumoniae*) is still a major cause of serious invasive infections, such as septicemia, meningitis, and bacteraemic pneumonia, associated with high morbidity and mortality, especially among very young children. *S. pneumoniae* is also a leading cause of non-invasive pneumonia, sinusitis, and acute otitis media (Centers for Disease Control and Prevention 2000). *S. pneumoniae* is much more likely to be associated with nasopharyngeal colonisation than to cause invasive disease (Sulikowska et al. 2004).

The bacterial species *S. pneumoniae* consists of 90 immunologically distinct serotypes. Some serotypes seem to be of disproportionate importance as causes of disease in very young infants, in older children, in immunocompromised individuals, or in elderly people. Some serotypes seem to be associated with particular disease syndromes, such as complicated pneumonias in children, or with higher rates of hospitalization in children or mortality in adults, and are consistently responsible for outbreaks in certain populations (Hausdorff et al. 2000).

Invasive pneumococcal disease (IPD) is defined as the recovery of an isolate of *S. pneumonia* from a normally sterile site, such as blood, cerebrospinal fluid (CSF), pleural fluid, joint aspirate, pericardial fluid, or peritoneal fluid. Among all bacteremic infections in hospitalized patients, *S. pneumoniae* etiology constitutes 4–12% cases (Centers for Disease Control and Prevention 2000). The highest incidence of pneumococcal disease occurs in children under the age of 5. Pneumonia, especially pneumococcal pneumonia, is considered one of the major causes of childhood mortality (Williams et al. 2002). In Poland, the incidence rate of IPD is low in all age groups, even when IPD cases identified by polymerase chain reaction (PCR) are included. PCR-based assessments constituted only 7.1% and 6.2% of all IPD cases in 2008 and 2009, respectively. The general IPD incidence rate in Polish children under the age of 5 in 2009 was 2.85/100,000. In children under the age of 5, the most frequently reported isolates belonged to serotypes 14, 6B, and 19 F (52.7% of cases of IPD), and among children 5–14 years old was dominated by serotype 1 (26.8%) (Skoczynska et al. 2011).

Poland is among the countries without mass vaccination against pneumococcal diseases. However, anti-pneumococcal conjugated vaccines are registered and highly recommended. For some risk groups, the vaccine has been free of charge since 2008. It is estimated that about 30% of children have a voluntary (non-refundable) vaccination against pneumococcal (PCV7 or currently PCV13 by Pfizer, and PCV10 by GlaxoSmithKline) (Jackowska and Klyszewska 2010). The objective of this report was to present a case of invasive pneumococcal disease including the costs of therapy.

33.2 Methods

This report describes data collected in accordance with the Declaration of Helsinki for Human Experimentation and it was approved by a local Ethics Committee.

33.2.1 Case Report

We describe the case of a 9-year-old boy who suffered from pneumonia and subsequently developed a pleural empyema and invasive pneumococcal bacteremia. The boy was admitted to the hospital by a surgeon, because of an episode of abdominal pain and vomiting accompanied by a mild cough and

fever. Before admission, the boy was healthy, with occasional respiratory tract infections. He had been vaccinated against tuberculosis, diphtheria, tetanus, pertussis, polio virus, hepatitis B, and measles. Vaccinations against *Haemophilus influenzae, Neisseria meningitidis* and *Streptococcus pneumoniae* were not performed.

The general condition was serious; the patient was dehydrated, in a sitting position (respiratory rate 46/min, pulse 110 bpm, temperature 39.6°C, SaO_2 90%). Laboratory studies found very high rates of inflammation (C reactive protein-CRP – 386.4 mg/L, erythrocyte sedimentation rate, ESR – 140 mm/h, leukocytosis – 30.1 G/L with rejuvenation and a shift to the left – granulocytes clubbed 13, segmented 79), features of hypercoagulability (elevated D-dimer – 2,223 ng/mL and fibrinogen – 496 mg/dL), and the presence of fibrin breakdown products (FBP). Laboratory tests during the disease are shown in Table 33.1. On the lung auscultation, there was dullness below the third rib, and a reduction in the respiratory murmur over the left lung. Abdomen palpation was difficult because of the intensified pain and the patient's defence reaction. A chest X-ray revealed lower left lobe consolidation with symptoms of pleural inflammation.

33.2.2 Course of Disease

After taking a blood culture, antibiotic treatment with cefuroxime and netilmicin was administered. The patient's condition was worsening and we decided to administer intravenous immunoglobulin on the third and fifth day of treatment. On the fourth day, after isolating the *S. pneumoniae* from the blood culture (sensitive to penicillin, erythromicin, clindamycin, ampicillin, amoxicillin/clavulanic acid, trimetoprim/sulphamethoxazole, and vancomycin) benzylpenicillin was added to the therapy, but netilmicin was stopped after 2 days.

The National Reference Center for Bacterial Meningitis in Warsaw, Poland found that the cause was serotype 1 IPD *S. pneumoniae*. Five days after admission, a chest X-ray was performed because of increasing dyspnea (respiratory rate 60/min, pulse 115 bpm, temperature 38.2°C, SaO_2 90%). It revealed significant progression of the inflammatory process in the left lung and pleural effusion. A chest computer tomography (CT) showed extensive interstitial-alveolar changes in the left lung, with atelectasis and pleural effusion causing a reduction in the lung volume up to the fourth rib (Fig. 33.1a).

From the 6th day of hospitalization, pleural suction drainage and intrapleural administration of alteplase, a tissue-type plasminogen activator (Actilise; Boehringer Ingelheim), were instituted and continued for the next 5 days. The patient received 15 alteplase doses in all (three times 10 mg/daily). At the time of pleural drainage, approximately 1,000 ml of purulent liquid was obtained. Intravenous antibiotics were administered for 32 days in total. Benzylpenicillin (15 days) followed by cefotaxime and clindamycin (both for 14 days). A control chest CT, made on the 20th day of treatment, revealed that the fluid in the left pleural cavity had disappeared (Fig. 33.1b). During the whole hospitalization time, physiotherapy was applied. The course of the disease is shown in Fig. 33.2. After 36 days of hospitalisation, the boy was discharged home in a good general condition. The course of the disease was complicated by labial herpes and acute adenoviral gastroenteritis, despite simultaneous treatment with aciclovir since the first day of treatment.

The following final diagnosis was established for this case:

1. Invasive pneumococcal disease *(Streptococcus pneumoniae* serotype 1) presenting as lobal pneumonia complicated by pleural empyema and bacteremia.
2. Labial herpes.
3. Acute adenoviral gastroenteritis.

Table 33.1 Laboratory results in the consecutive days of treatment

Days of treatment	1	6	11	13	16	18	23	31
ESR mm/h (<12)[a]	140	60	155	125	130	–	85	75
CRP mg/L (0.1–5.0)[a]	386	172	75	–	7.8	–	2.3	–
WBC × 10^3/μL (3.5–10.0)[a]	30.1	22.9	16.9	8.8	6.6	7.4	7.0	8.4
Blood smear (only neutrophils)	Band 13, segmented 79	Segmented 84	Meta–myelocyte 1, band 2, segmented 74	Segmented 54	Segmented 52	Segmented 52	Band 3, segmented 46	Segmented 55
Hbg/dL (11.0–16.5)[a]	12.6	11.1	10.1	10.4	10.9	11.1	12.1	11.2
Ht % (35.0–50.0)[a]	36.2	31.6	30.4	30.3	33.2	32.1	36.6	34.4
PLT × (10^3/μL) (150–390)[a]	636	897	1,319	1,191	1,167	665	528	507
Fibrinogen (mg/dL) (169–392)[a]	496	447	378	–	–	–	–	382
D-dimers ng/mL (<500)[a]	2,223	4,333	760	–	–	–	–	548
FBP (negative)[a]	Positive	Negative	Negative	–	–	–	–	Negative

[a]Norm range

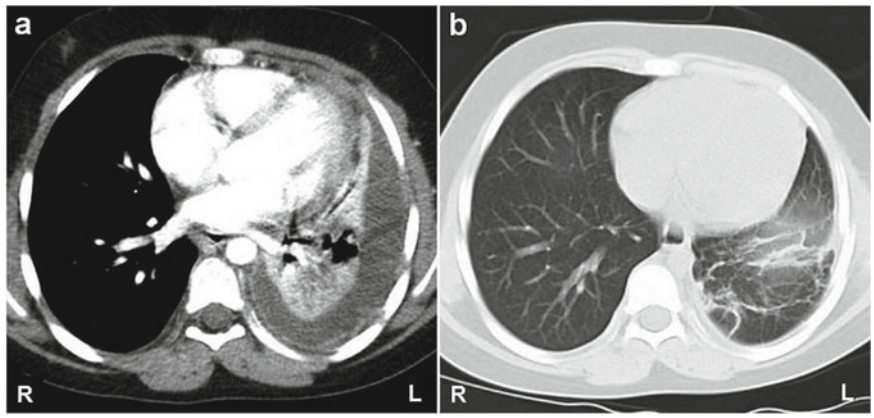

Fig. 33.1 **Chest CT**; (**a**) Extensive interstitial-alveolar changes in the left lung with atelectasis and pleural effusion (Day 5); (**b**) Resolution of changes after 20 days of treatment

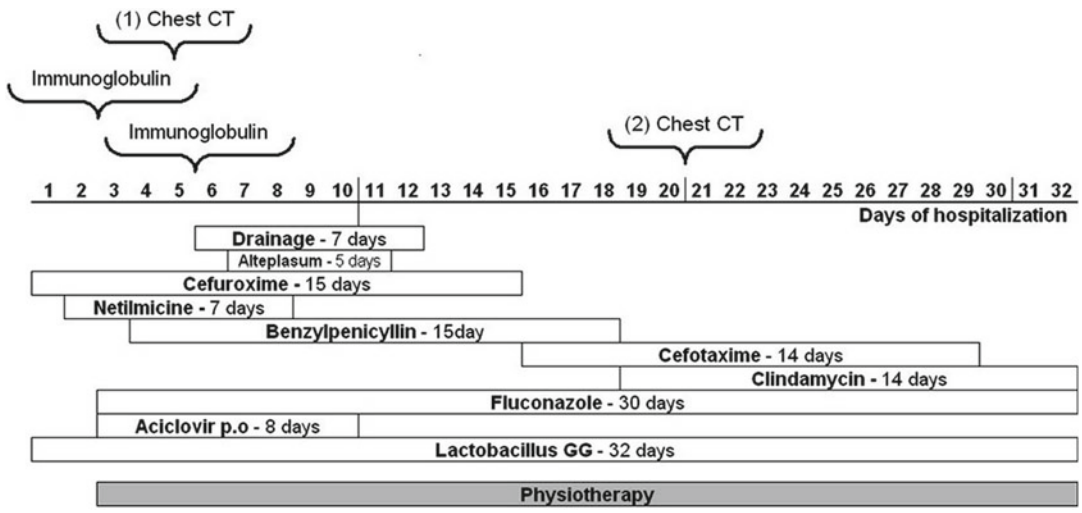

Fig. 33.2 Disease course

33.2.3 Economic Analysis

An in-depth search of literature was conducted to gain a European perspective of resource utilization linked with inpatient treatment of complicated invasive pneumonia. Available costs data were adjusted to 2010 costs using the Consumer Price Index (OECD 2011a) and standardized using the exchange rate to Euro (European Central Bank 2011) and purchasing power parities (PPP) for health (OECD 2011b) (Table 33.2).

The nominal average treatment cost for patients with invasive pneumonia differs among countries being in a range of €2,346–8,052. The level of refunding offered to hospitals in the Polish National Health Fund (NHF) (€1,508) is up to three times lower than that in Belgium, Germany, or Sweden. Nevertheless, NHF reimbursement properly reflects differences in PPP between Poland and other countries. A significant disproportion between the real costs of the described case and the diagnosis-related group (DRG) classification value might be due to a high proportion of spending related to

Table 33.2 Costs of treatment of complicated invasive pneumonia depending on country

Country (Currency/Year)[a]	Definition	Cost (€2010)	Cost (PPP €2008)
Norway (NOK/2004) (Wisloff et al. 2006)	Consolidated Pneumonia	5,856	3,485
Sweden (SEK/2006) (Bergman et al. 2008)	Pneumonia (hospitalized)	3,402	2,652
	Pneumonia (hospitalized) with empyema	6,702	5,225
Finland (€/2004) (Salo et al. 2005)	Pneumonia, inpatient care	2,346	1,988
Belgium (€/2006) (Beutels et al. 2006)	Hospitalised pneumonia	5,830	4,519
Netherlands (€/2009) (Rozenbaum et al. 2010)	Invasive pneumonia[b]	5,142	4,897
Germany (€/2005) (Claes et al. 2009)	Inpatient pneumonia	5,388	5,231
Italy (€/2004) (Marchetti and Colombo 2005)	Inpatient pneumonia	2,557	2,243
	Other pneumococcal IPD[c]	4,278	3,753
Switzerland (CHF/2000) (Ess et al. 2003)	Complicated pneumonia	3,592	2,243
England (£/2002) (McIntosh et al. 2003)	Inpatient pneumonia[d]	3,691	3,858
	Pneumonia with empyema	8,052	8,417
Poland (PLN/2009) (National Health Fund 2011)	Invasive pneumonia (DRG NHF)	1,508	3,136
	Case Report	4,767	9,909

[a]€1 = 9,295 SEK 2006 exchange rate (recalculated)
[b]5–19 age category
[c]According to description this category better reflect invasive pneumonia
[d]Average cost of inpatient pneumonia treatment (recalculated)

Table 33.3 Summary of treatment costs borne by healthcare provider concerning the patient with *Streptococcus pneumonia*-induced sepsis reported in this study

Category	Description	Number (Unit)	Cost (€)	Cost (€) (% of overall cost)
Hospital Stay	Days in ward	32 days	–	1,365 (30.7%)
Diagnostic tests	Diagnostic tests	108 (unit)	–	519 (11.7%)
	Imaging tests	18 (unit)	–	
Pharmacotherapy	Cefuroxime	54 (g)	40	2,454 (55.2%)
	Netilmicin	1.68 (g)	56	
	Immunoglobulin IgG	10 (g)	642	
	Penicillin	90 (MIU)	31	
	Alteplase	0.15 (g)	1,544	
	Cexotaxime	46.20 (g)	28	
	Clindamycin	10.85 (g)	567	
	Fluconazole	4.50 (g)	7	
	Aciclovir	11.75 (g)	32	
	Omeprazole	0.19 (g)	4	
	Others	n/a	14	
Additional procedures	Surgeon consultation	9 (times)	23	105 (2.4%)
	Establishing pleural cavity drainage conditions CBO	1 (procedure)	59	
	Intravenous general anesthesia	1 (procedure)	24	
Overall cost of treatment				4,444 €

pharmacotherapy, which is not susceptible to differences in PPP (a similar nominal level among countries) and low valuation of an additional day of hospital stay in the Polish health care system.

The costs of operations and the cost to suppliers, resulting from the performed treatment are presented in Table 33.3. The costs of hospitalization (30.7%), diagnosis (11.7%), pharmacotherapy (55.2%), and additional procedures (2.4%) were about €4,444, whereas the cost of treatment from the

perspective of the National Health Fund was only €1,508. The breakdown of costs incurred by the hospital to refund the cost of treatment by the NHF leads to the conclusion that the refunding of therapy costs from the public means is far insufficient to cover the real costs of treating a patient with sepsis caused by *S. pneumoniae*.

33.3 Discussion

Invasive pneumococcal disease, caused by *S. pneumoniae*, remains a leading cause of serious illness in children and adults worldwide (Centers for Disease Control and Prevention 2000). In February 2000, the heptavalent pneumococcal vaccine (Prevenar; Wyeth) was licensed for use in the United States for the prevention of invasive pneumococcal disease in children under the age of 5. A total of four doses of PCV7 at the ages of 2, 4, 6, and 12–15 months were subsequently recommended for routine administration in young children by the American Academy of Pediatrics in August 2002 and the Advisory Committee on Immunization Practices (ACIP) in October 2000 (American Academy of Pediatrics 2000). The vaccine was recommended for all children from 2 to 23 months of age, and for children 24–59 months of age who are at increased risk of pneumococcal disease (Advisory Committee on Immunisation Practices 2000). From April 2008, by the decision of ACIP, one dose of PCV7 should be administered to all healthy children aged 24–59 months who have not completed any recommended schedule for PCV7 (CDC 2008). Two new inoculations were registered, in April 2009, PCV10 (GlaxoSmithKline), and in February 2010 PCV13 (Pfizer), including three (1, 5, 7 F) and six (1, 3, 5, 6A, 7 F, and 19A) new serotypes, respectively. Serotype 1 and 5 diseases (serotypes not represented in PCV 7) are important types in older children in industrialised countries and rarely cause mild bacteremias (Hausdorff 2007).

Prognosis of the severity, the incidence of complications, or death from pneumococcal infections is related to the clinical course of the infection, the patient's clinical characteristics, and the type of invasive pathogens (*S. pneumoniae* serotype and degree of susceptibility). The serotype distribution of IPD cases is highly dependent on age. Some serotypes affect only the youngest, while some have a very broad age spectrum. IPD often occurs in children up to 2 years of age, but may also appear in children older than 5. In Poland, pneumococci of serotype 1 were more prevalent in the group of 5–14 years old than in all other age groups (26.8% of all infections caused by pneumococci of serotype 1 occurred among these patients; $p<0.001$) and were responsible more often for bacteremia/sepsis and invasive pneumonia (respectively 15.2% and 13.9% of these infections were due to serotype 1) than for meningitis (1.9% of infections; $p<0.001$) (Skoczynska et al. 2011).

The case presented in the present report indicates that extremely severe pneumococcal infection may be observed, although caused by a serotype associated with less severe course of the disease (serotyp 1). The therapy of severe pneumonia complicated with pleural empyema (besides targeted antibiotic therapy) may be supplemented with the early intrapleural administration of alteplase, which enhanced the efficacy of suction drainage and saves the patient from invasive surgical intervention (Hamblin and Furmanek 2010). At least 40% of all patients with pneumonia will have an associated pleural effusion, although a minority will require an intervention for a complicated parapneumonic effusion or empyema. All patients require medical management with antibiotics. The use of fibrinolytics remains controversial, although evidence suggests a role for the early use in complicated, loculated parapneumonic effusions and empyema (Koegelenberg et al. 2008). However, in our case introduction of alteplase into the treatment regimen (from 7 days) proved to be an efficient intervention, also recommended by other authors as a standard practice for the drainage of complicated parapneumonic effusions (Hawkins et al. 2004).

Serotype 1 is considered to be associated with a better prognosis compared with serotypes 5, 7 F, and 3. The serotypes associated with the highest mortality are 7 F (14.8%), 23 F (8.3%), and 3 (8.3%).

Infection with serotype 7 F is associated with 4.3 times a greater chance of death and 4 times a greater chance of severe infection compared with other serotypes (Ruckinger et al. 2009). In Poland, in children with severe invasive disease, meningitis, complications, and deaths were noted in the case of infections with serotypes 14, 4, 6B, 19 F, and 23 F (Skoczynska et al. 2011).

In the presented case, the prognosis proved successful thanks to intensive therapy (intravenous immunoglobulins, tissue activator plaminogemu, targeted antibiotic therapy, and the use of intensive rehabilitation). However, 35 days of hospitalization with a 7-day pleural drainage was certainly a stressful ordeal. After receiving information that the cause of the disease was vaccinable serotype *S. Pneumoniae*, the parents immediately went for a pneumococcal vaccination with their four-year-old daughter, who received PCV7.

The results of Polish epidemiological studies indicate that the 7-valent pneumococcal vaccine currently provides almost 100% protection against severe cases and deaths associated with invasive pneumococcal disease in children (Grzesiowski et al. 2008). However, the additional coverage offered by the vaccine serotypes 10-valent (Synflorix) or 13-valent (Prevenar-13) represents another step forward in the development of vaccines. One of the priorities of Polish vaccinologists and pediatricians is an urgent inclusion of pneumococcal vaccines in the immunization program. The high cost of vaccines is an understandable obstacle to commencing vaccination of the population. In our case, however, the costs of treating a boy with sepsis caused by *S. pneumoniae* serotype 1 were three times higher than those from the perspective of National Health Fund providers.

Administration of a new pneumococcal conjugated vaccine containing serotype 1 (PHiD-CV10 or PCV13) could have prevented IPD in the described patient. Commencing a population vaccination for each of the registered pneumococcal conjugated vaccine (Synflorix, Prevenar 13) would be an essential step in caring for small children.

33.4 Conclusions

- Invasive pneumococcal disease may appear also in children more than 5 years old.
- Therapy of severe pneumonia complicated with pleural empyema (in addition to targeted antibiotic therapy) may be supplemented with early intrapleural administration of alteplase.
- Intrapleural administration of alteplase enhanced the efficacy of suction drainage and protected the patient from invasive surgical intervention.
- Administration of a new pneumococcal conjugated vaccine containing serotype 1 (PHiD-CV10 or PCV 13) could have prevented invasive pneumococcal disease in the described patient.
- The level of refinancing from public funds of the diagnosis and treatment of patients with sepsis caused by *S. pneumoniae* is highly insufficient to cover the real costs.

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Chapter 34
Nosocomial Rotovirus Gastroenetrocolitis in Children Hospitalized Primarily Due to Respiratory Infections

Aneta Nitsch-Osuch, Ernest Kuchar, Anna Kosmala, Katarzyna Zycinska, and Kazimierz Wardyn

Abstract Rotaviruses are the leading cause of community-acquired and nosocomial gastroenterocolitis in children. There is little data concerning the epidemiology of nosocomial rotavirus gastroenterocolitis (NRVG) in Central European countries. The aim of our study was to analyze the epidemiology of NRVG in a pediatric hospital in Warsaw, Poland, where the majority of children was admitted due to respiratory tract infections. Retrospective chart analysis of 49,697 patients aged 0–18 hospitalized during 2006–2009 was performed. NRVG was defined as acute gastroeneterocolitis (>3 loose stools in 24 h or vomiting), confirmed with A rapid immunochromatographic test, if symptoms developed >48 h after admission. In total, 469 cases of NRVG were diagnosed. The cumulative attack rate of NRVG for the hospital was calculated as 0.97% (CI 0.86–1.02), the cumulative incidence density was 2.07/1000 bed-days (CI 2.01–2.13). The majority of NRVG were diagnosed at the General Pediatrics Ward (206 cases, 44%) and Allergology and Pulmonology Ward (122 cases, 26%), where the mean duration of hospital stay was longer than 5 days (9.9 ± 1.0 and 6.1 ± 0.8 days, respectively). Primary causes of hospitalization of the children with nosocomial rotavirus gastroenterocolitis were respiratory tract infections (including pneumonia, bronchitis, and otitis media) present in 287 cases (61.2%). The nosocomial rotavirus infection was mostly diagnosed among patients aged 6 months – 2 years (201 cases, 42.8%), less common were infections among infants younger than 6 months (133 cases, 28.3%) and children aged 2–6 (115 cases, 24.5%). The mean age of a child with NRVG was 16.2 ± 10.2. In conclusion, rotavirus gastroenteritis is the most important nosocomial infection in children hospitalized due to respiratory tract infections and can prolong their hospital stay.

Keywords Acute diarrhea • Economic burden • Hospital infection • Rotavirus gastroenterocolitis • Nosocomial infections

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34.1 Introduction

Viral gastroenterocolitis in children is caused mainly by rotaviruses, noroviruses, sapoviruses, astroviruses, and enteric adenoviruses (Parashar et al. 2009). Rotaviruses (RVs) are the leading cause of gastroenterolitis in children under 5 years worldwide and the leading cause of nosocomial diarrhea (Parashar et al. 2006). Estimated 72,000–77,000 hospitalizations for community-acquire rotavirus gastroenetrocolitis (CARVG) disease occur annually in the 23 million under-fives living in the European Union, while the median proportion of nosocomial rotavirus gastroenterocolitic (NRVG) among all cases of hospitalization for rotavirus disease is estimated to be 21% (PROTECT 2006).

Data available for seven European countries indicate that 2.5–11.8% of children aged less than 5 may develop NRVG, and the incidence density (RV cases per 1,000 bed-days) ranges from 0.7 to 10 per 1,000 bed-days (PROTECT 2006). Rotavirus gastroenterocolitis has an incubation period of 1–3 days, which is followed by a sudden onset of watery diarrhea, with high risk of dehydration, vomiting, and fever. Symptoms usually last 4–7 days. The seasonal peak of rotavirus infection occurs from November to March in the Northern hemisphere (Cone et al. 1988). The rotavirus is transmitted by feco-oral route or by the direct contact; occasionally it can be transmitted through air-borne droplets. The virus is stable in the environment, transmission occurs through ingestion of contaminated water (or other fluids) and food, and through contact with contaminated surfaces and objects. The hospital environment and health care staff have the potential to become contaminated and serve as reservoir for the virus (Cone et al. 1988; Posfay et al. 2008). Rotaviral infection may be asymptomatic (20–40%), but patients and health care workers with asymptomatic infection may also spread the disease and this may be another reason for difficulties in prevention of rotavirus nosocomial infections and an underestimation of their incidence (Posfay et al. 2008; Gleizes et al. 2006). There is no doubt that nosocomial rotavirus infection is a frequent cause of outbreaks of acute diarrhea in institutions such as hospitals, nursing homes, day-care centers, and schools and causes high direct and indirect costs and may cause severe health complications, including dehydration (Sattar et al. 1986).

Reports on the incidence of NRVG infections are infrequent and the available data have limitations; e.g., different case definitions were used, different time lags from the onset of symptoms, the studies were often performed during the rotavirus season only, and the age groups varied, with the majority of studies concerning children younger than 2–5 years (PROTECT 2006; Gleizes et al. 2006). Also, reports usually describe the epidemiology of community-acquired rotavirus infections. The aim of the present study was to describe the epidemiology of NRVG among children aged 0–18 treated in one tertiary pediatric hospital in Warsaw, Poland during 2006–2009.

34.2 Methods

The retrospective study, performed at The Professor Bogdanowicz Pediatric Hospital in Warsaw, Poland, was in conformity with the 1989 Declaration of Helsinki for Human Research and was approved by a local Ethics Committee. The hospital provides primary, secondary, and tertiary care facilities for about 11,500–12,500 children yearly. It has 250 beds and consists of general pediatrics (47 beds), neonatal pathology (36 beds), pulmonology and allergology (33 beds), ENT (21 beds), neurosurgery (16 beds), neurology (10 beds), traumatic surgery (30 beds), ophthalmology (25 beds) general surgery (30 beds), and ICU (7 beds).

Official statistical data obtained from the hospital records, including the number of hospitalized patients, number of person-days, average duration of hospitalization, and data collected by the Hospital Infection Team, and individual medical files of children aged 0–18 with NRVG were analyzed. The period of analysis covered January 2006 to December 2009.

Gastroeneterocolitis was considered hospital–acquired if symptoms developed >48 h after admission. Acute gastroeneterocolitis was defined as diarrhea (>3 loose or looser-than normal, stools in a 24-h period) or vomiting. Rotaviral infection was diagnosed with a rapid immunochromatographic test (BioMaxima, Poland) characterized by 98% sensitivity and 96% specificity. Stool samples were taken from all symptomatic patients.

To calculate the attack rate (the incidence of NRVG among hospitalized children), the numerator was represented by the reported NRVG cases and the denominator was represented by the total number of patients minus those with community-acquired gastroeneterocolitis. The incidence density was also calculated: the numerator was represented by the number of detected NRVG cases and the denominator was the number of total bed–days spent in the hospital. The 95% confidence interval was calculated on the incidence. We also assessed the difference between the mean duration of hospitalization and that due to NRVG, using a non-parametric Mann–Whitney *U* test.

34.3 Results

The number of children hospitalized during 2006–2009 was 49,697. There were 1,492 cases of community acquired rotavirus gastroenterocolitis (CARVG) and 469 cases of nosocomial rotavirus gastroenterocolitis (NRVG). The incidence density of NRVG ranged from 1.57/1,000 person-days to 2.53/1,000 person-days. The cumulative incidence density was 2.07/1,000 person-days (2.01–2.13, CI 95%). The attack rate of NRVG ranged from 0.8% to 1.07%. The cumulative attack rate of NRVG was 0.97% (0.86–1.02, CI 95%). The median proportion of hospital-acquired rotavirus disease among all cases of hospitalization for rotavirus gastroenetrocolitis was 24% (22.03–25.81, CI 95%) (Table 34.1)**.**

Primary causes of hospitalization of the children with NRVG were respiratory tract infections (pneumonia, bronchitis, and otitis media) in 287 (61%) patients and urinary tract infections in 153 (32.6%) patients. There were also other disorders including: myocarditis (2 cases), meningitis (4 cases), sepsis (8 cases), multiorgan trauma (5 cases), and observational or diagnostic procedures (5 cases).

The majority of both CARVG and NRVG was diagnosed in autumn and winter months of each year, from October to March – 908 cases (60%) and 317 cases (61%), respectively, but the number of cases was also high in the third and second trimester of the year (Fig. 34.1). Most of the children with NRVG infection were hospitalized in general pediatrics – 206 patients (44%), neonatal pathology – 116 (25%), and in pulmonology and allergology wards – 122 (26%), while a minority (5%) was in ENT (11 cases), neurosurgery (6 cases), traumatic surgery (5 cases), ophthalmology – (2 cases), and in general surgery (1 case).

The highest cumulative attack rate and the highest cumulative incidence density were calculated for general pediatrics – 3.0% and 4.7/1,000 person-days, respectively, neonatal pathology – 2.3% and 2.5/1,000 person-days, respectively, and for allergology and pulmonology – 2% and 3.3/1,000 person-days, respectively. The highest incidence rates were noted in the wards in which the average hospital stay was longer than 5 days (Table 34.2).

The nosocomial rotavirus infection was mostly diagnosed among patients aged 6 months – 2 years (201 cases, 43%), less common were infections among infants younger than 6 months (133 cases, 28.3%), and children aged 2–6 (115 cases, 24.5%) (Fig. 34.2). The mean age of a child with NRVG was 16.2 ± 10.2 months. The most common symptoms of nosocomial rotavirus infection were diarrhea, present in 350 patients (75%), vomiting – in 309 patients (66%), and fever – in 295 patients (63%). Three hundred seventy five children (80%) required intravenous rehydration. The mean duration of hospitalization of a child with NRVG was 11.5 ± 0.4 days and the mean duration of non-complicated by NRVG hospitalization was 4.6 ± 0.4 days; the difference between the two was significant ($p < 0.01$).

Table 34.1 Epidemiological data describing community-acquired (CARVG) and nosocomial rotavirus gastroenterocolitis (NRVG) in 2006–2009

	Total number of hospitalizations	Total number of bed-days	Total number of CARVG	Incidence density of CARVG (per 1,000 bed-days)	Total number of NRVG	Incidence density of NRVG (per 1,000 person-days)	Attack rate (% of hospitalized children with NRVG)	% of NRVG among hospitalizations for rotaviral gastroenetrocolitis
2006	12,417	61,674	461	7.47	97	1.57	0.81	17.3
2007	11,577	54,949	291	5.29	123	2.23	1.08	29.7
2008	12,467	54,810	376	6.86	110	2	0.9	22.6
2009	13,236	54,881	364	6.63	139	2.53	1.07	27.6
2006–2009	49,697[a]	226,314[a]	1492[a]	6.59[a]	469[a]	2.07[a]	0.97[a]	23.9[a]

[a]Cumulative numbers and rates

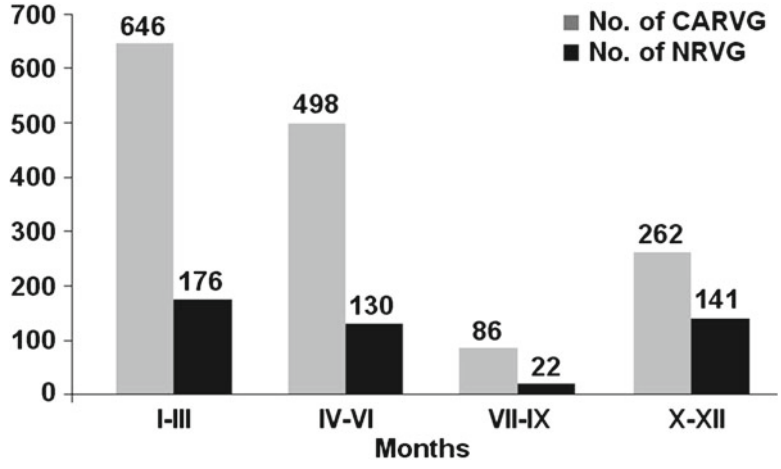

Fig. 34.1 Seasonal distribution of community acquired rotavirus gastroenterocolitis (CARVG) and nosocomial rotavirus gastroenterocolitis (NRVG)

Table 34.2 Distribution of epidemical data: cumulative attack rate and incidence density of NRVG depending on the hospital ward and mean hospital stay

	Cumulative number of patients	Cumulative number of person-day	Cumulative number of NRVG	Cumulative attack rate of NRVG (%)	Cumulative incidence density of NRVG (per 1,000 person-days)	Mean hospital stay (days ± SD)
General pediatrics	8,334	43,351	206	2.47	4.75	9.9 ± 1.0
	6,842[a]			3.01[a]		
Neonatal pathology	8,334	36,378	116	2.27	2.46	5.7 ± 0.6
Allergology and pulmonology	6,004	37,115	122	2.03	3.28	6.1 ± 0.8
ENT	6,798	11,516	11	0.16	0.95	1.7 ± 0.2
General surgery	6,620	194,113	1	0.015	0.05	2.9 ± 0.4
Traumatic surgery	6,245	25,940	5	0.08	0.19	4.1 ± 0.4
Neurosurgery	3,010	15,117	6	0.19	0.39	4.9 ± 0.2
Ophthalmology	5,912	15,387	2	0.03	0.12	2.6 ± 0.6
Neurology	1,280	7,174	0	0	0	4.6 ± 0.3
ICU	387	4,305	0	0	0	4.6 ± 0.4

[a]Cumulative number of patients after exclusion of patients with CARVG

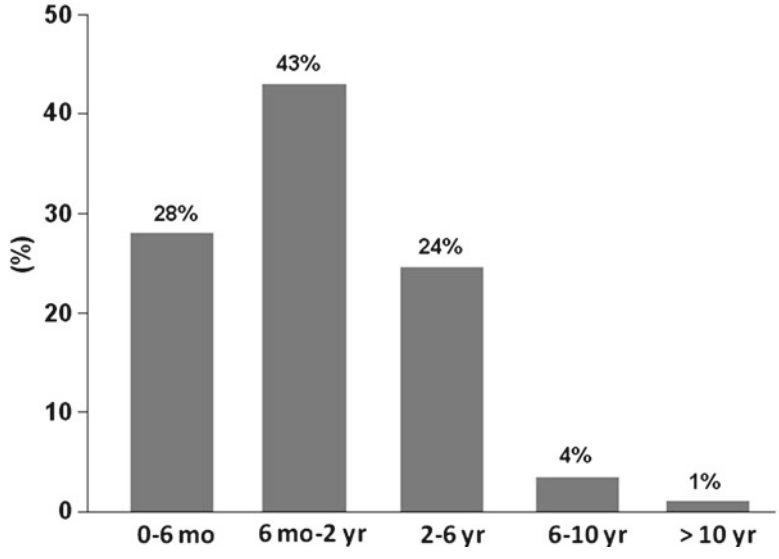

Fig. 34.2 Distribution of nosocomial rotavirus gastroenterocolitis (NRVG) between age-groups of children

34.4 Discussion

Although studies of viral gastroenetrocolitis in children have mainly focused on community-acquired infection, the importance of nosocomial rotavirus gastroenterocolitis and the potential for its prevention has been highlighted in several publications (PROTECT 2006; Gleizes et al. 2006; Cunliffe et al. 2010; Festini et al. 2010). The present study shows that the cumulative attack rate of nosocomial rotavirus gastroenterocolitis was 0.97%. Data concerning the burden of nosocomial rotavirus infections in Poland are limited. A prospective study of Sulik et al. (2004) estimates that 2% of hospitalized children younger than 7 years comes down with rotavirus diarrhea. Noteworthy, in some older Polish studies on the subject, this rate was higher – 4.5–9.0% (Dziechciarz et al. 1997; Mrukowicz et al. 1999).

The results of the present study are similar to those reported in a few other studies on NRVG describing the epidemiological situation in Central Europe. In a Slovakian study, the attack rate of rotaviral nosocomial gastroenterocolitis is 0.65% among children younger than 18 years (Stefcovicova et al. 2008). The attack rate of NRVG in our hospital was in the lower range of those noted in Europe. A 2006 review on the NRVG incidence across Europe reports that NRVG accounts for 0.3–27.7% of all hospital admissions (Gleizes et al. 2006). The results similar to ours were also described by Waisbourd-Zinman et al. (2009) in Israel; NRVG occurred in 1% of all admissions.

The cumulative incidence density of NRVG in our study was 2.07/1000 person days and it was comparable with data from other papers in which the observation period covered the whole year – 1.6–2.6/1,000 bed-days in Austria (Fruhwirth 2001a), 1.6/1,000 bed-days in Germany (Fruhwirth 2001b), 0.7/ bed-days (Switzerland) (Fruhwirth 2001a), or 1.72/1000 bed-days (Slovakia) (Stefcovicova et al. 2008). A 2006 review of NRVG incidence density across Europe reports that NRVG accounts for 1.6–15.8 per 1,000 days of hospital stay (Gleizes et al. 2006).

The median proportion of NRVG among all hospitalized children with rotaviral gastroenteritis in our study was 24%. This figure is slightly higher than the rate typical for European countries – 21% (PROTECT 2006). Previous results from Poland, reported 20 years ago, pointed to a higher rate of 39% (Mrukowicz et al. 1999).

The highest attack rate and the incidence density were reported in the wards where the mean duration of hospitalization was longer than 5 days. It corresponds well with results of previous studies which have proven that the risk of contracting NRVG increases significantly if the child stays in the hospital for more than 5 days (RR 2.8) (Muhsen et al. 2009; Stefcovicova et al. 2008).

In the present study, 67% of NRVG occurred in the autumn and winter season which is comparable with other data available in the literature (Gleizes et al. 2006; Stefcovicova et al. 2008; Gutierrez-Gimeno et al. 2010). This is not a surprising result as rotavirus disease is most frequent in this season of the year in the general population. Since transmission of RV infection occurs mainly by contact, it is essential to insist on correct hand washing by both medical staff and relatives of hospitalized children. Hand hygiene is considered the simplest and most effective measure to prevent cross-transmission of microorganisms, including rotaviruses, but health care professionals appear to have difficulties in performing hand hygiene procedure and compliance below 50% has been reported repeatedly (Posfay et al. 2008). Education and self-screening of family visitors should be also performed in order to avoid transmission of pathogens to patients.

Hospital acquired rotavirus diseases was reported in our study mainly among children aged from 6 months to 2 years, while in the literature we can find an opinion that nosocomial disease is more typical for infants younger than 6 months (Fruhwirth 2001b). However, some authors observed that the mean age of children with NRVG is 9 months or the children with community-acquired rotavirus disease are 9 months older than children with nosocomial infection (Stefcovicova et al. 2008). The reduced incidence of NRVG among children younger than 6 months may be explained by breast-feeding and the presence of transplacental transferred maternal anti-RV antibodies in younger infants

(Stefcovicova et al. 2008). Generally, the peak incidence of NRVG is reported to be less than 2 years of life (Muhsen et al. 2009; Mrukowicz et al. 1999). Symptomatology of NRVG in our patients was typical with predominating symptoms of diarrhea and vomiting. It is noteworthy, however, that 80% of patients required intravenous rehydration which points to the severity of infection and may be source of another hospital acquired infection due to a prolonged use of intravenous access. The longer hospital stay of children with NRVG found in the present study is in accord with other reports – 7.3 days (Stefcovicova et al. 2008), 8.1 days (Gutierez-Gimeno et al. 2010), or 9 days (Waisbourd-Zinman et al. 2009). The prolonged hospital stay of children with NRVG may generate higher costs and influence the quality of life of a hospitalized child.

Our study was a retrospective descriptive study with all inherent limitations characteristic of such studies. Data may be underestimated due to the possibility of asymptomatic nosocomial rotavirus infection and the lack of a follow-up several days after hospital discharge. The proportion of asymptomatic infections is estimated to be 20–40% (Gleizes et al. 2006; Stefcovicova et al. 2008) and asymptomatic patients may spread the disease, but are not included in the statistics. Some patients (up to 30%) may develop symptoms of NRVG after discharge and these cases might be missing in hospital records (Stefcovicova et al. 2008). The results of our study could also be influenced by not accounting for breast feeding. Another limitation may be the lack of information concerning how many children were vaccinated against RV. There is no doubt that vaccination against rotavirus diseases is an effective preventive measure. In 2007 the WHO recommended the inclusion of rotavirus vaccination in the national immunization schedules. In Poland this vaccination is not mandatory, so its coverage remains uncertain. Single studies indicate that RV vaccine coverage may be blow <30% (Pokorna-Kalwak et al. 2009).

34.5 Conclusions

NRVG is a common nosocomial infection in children hospitalized due to respiratory tract infections and can prolong their stay in hospital. The incidence of nosocomial rotavirus gastroenterocolitis in Poland is similar to those in other European countries and increases with the length of children's stay in a hospital. Limiting the number of NRVG may be an important factor to improve patients' safety and to avoid additional health costs. The universal use of rotavirus vaccine should reduce the incidence of nosocomial rotavirus gastroenterocolitis.

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

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Chapter 35
Mental Health of Polish Students and the Occurrence of Respiratory Tract Infections

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Abstract The aim of the paper was to examine the association between the psychological status and the occurrence of respiratory tract infections which constitute the most common group of disorders in the student population. The study comprised 500 Polish students aged 19–21. Two psychological scales were utilized: the Goldberg GHQ-12 scale to examine the general psychological status and the CES-D scale to evaluate the symptoms of depression. In addition a pro-health questionnaire in the examined group of students was performed. We found an increased stress level in 51% of students and the symptoms of depression in 22%. An association between distress and the occurrence of respiratory tract infections was found, based on statistical analyses. The highest stress level and related high distress index were observed in the students suffering from lower respiratory tract infections (7.1 scale value). This group self-evaluated their health status as poor, based on the pro-health questionnaire. In the same group of students, lack of sleep (5.4), lack of regular eating habits (4.2) and lack of physical activity (3.9) were also observed. The study shows that the Polish student population is exposed to increased stress level, which, in turn, increases the occurrence of respiratory tract infections.

Keywords GHQ-12 scale • Mental health • Respiratory infection • Students • Health status

35.1 Introduction

There are a number of psychical disorders and somatic diseases, which may be caused by long-lasting or particularly intense stress. A certain, optimal level of stress (eustress) is needed for the effective functioning of a human being. However, when the stimulation lasts too long or when it is too strong,

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it will always affect the health in a negative way (Chrousos 2009). The kind of stress that is harmful for health and mood is described as distress (damaging stress). It is the cause of many severe disorders in both emotional (neurosis, anxiety, depression) and functional areas (heart disease, circulatory system disease, arterial hypertension, and stroke). Academic students create the environment which is significantly exposed to the negative influence of stress (Dyrbye et al. 2006), which particularly concerns the first year students. It is connected with so-called adaptive disturbances resulting from the change of environment, usually the first attempt of being independent, first obligations, new relationships, separation from the family. It is also intensified by the need of rearrangement of requirements from the ones given in secondary school to those given by the academy, the need of passing exams, etc. Adaptive disturbances, expressed through fears, low spirit or even depression can be factors of pathogenic physiological changes and also can prompt to unhealthy behavior, thereby decreasing the health potential.

The aim of the present study was to examine the association between the mental health status of Polish students and the occurrence of respiratory tract infections.

35.2 Methods

The study was approved by a local Ethics Committee and all subjects gave informed consent. Five hundred first year students of medical and pedagogical studies (315 women and 185 men) from the west part of Poland took part in this study. The mean age was 20.0 ± 0.8SD years. The study was performed in all the students at the same time, before the end of their first academic year, straight ahead of end-of-term examinations.

A shortened version of the Goldberg Depression Questionnaire – General Health Questionnaire (GHQ-12) consisting of 12 questions concerning mental condition with four categories of answers for each of the questions was used to measure the general mental condition. Likert's scaling, assigning wages of 0–1–2–3 to the particular answers (the range of scale from 0 to 36 points) and dichotomized (bi-modal) GHQ scale, 0–0–1–1 (the range of scale from 0 to 12 points) were used for processing the outcome. The index of increased psychic stress (distress) was calculated with the use of the answers in GHQ scale. According to the publications, the occurrence of at least 3 out of the 12 symptoms of worsened psychic mood, i.e., getting more than two points was assumed as the index of increased distress level – distress index. A shortened CES-D scale (Center for Depression Epidemiologic Study Scale) composed of four questions graded from 0 to 3 points (the range of scale from 0 to 12 points) concerning the symptoms of depression, with four answer categories was used for measuring the risk of depression. The occurrence of each of the four symptoms, i.e., getting more than seven points was assumed as the index of the risk of depression – depression index. In both scales the higher is the outcome of the scale, the greater is the escalation of symptoms. The assessment of the mental condition of students in the studied group was supplemented by a subjective index of the poor condition and bad psychic mood. The occurrence of at least 14 'poor' days in last month was assumed as an index of frequent mental health problems (Baldachin et al. 2008).

With the use of the questionnaire there was also collected information concerning the somatic health: the general health (subjective self-evaluation of the health condition, worsening of the health condition in comparison with the previous year) and the respiratory system (frequency and type of the respiratory tract infections, the duration of illness).

The interview was supplemented with the information about the socio-demographic factors (gender, permanent residence, present residence, economic status, family type) and the way of life: addictions (cigarettes, alcohol, drugs, coffee, and energizers), nutrition (regularity of meals, frequency, and quality of meals), sleep duration, physical activity, and leisure time.

One-way analysis of variance was used to analyze the variation of the distress scale in respect to the somatic health, socio-demographic factors, and the way of life. In cases where the assumption of

normality or homogeneity of the variation was not fulfilled, the Kruskal-Wallis Nonparametric test was applied. Backward stepwise regression was used to assess the influence of individual factors (selected independent variables with weak correlation between each other) on the distress level. The above dependences were extended by the analyses for the dichotomized index of increased level of psychic distress with the use of the contingency tables. The nature of the connection between the categories of analyzed variables was estimated with the use of the correspondence analysis. Data were analyzed with the use of packet Statistica 8. The significance level assumed for all analyses was $p<0.05$.

35.3 Results

Increased level of distress was observed in 51% of the students (the mean value of the scale for this group was 6.2 ± 2.7), increased level of the risk of depression – in 22%, increased level of poor psychic mood in the last month – in 16%. Both the index of the risk of depression and the subjective index of the poor psychic mood were highly statistically related with the index of distress. 90% of the students with the symptoms of depression reported the increased level of stress. Students with the index of increased level of psychic distress, with the index of risk of depression and the subjective index of the poor condition made up 16% of the studied group. The mean value of the distress scale for this group was high and amounted to 8.0 ± 3.9 (Table 35.1).

There were marked differences in the distress level observed between genders. Increased level of distress was noted in 57% of the female students (3.9 ± 2.6) and 41% of the male students (2.9 ± 1.9). The highest level of distress was found in the female students of medicine (4.2 ± 2.5) and the lowest level – in the male students of pedagogy (2.0 ± 1.5). The influence of the remaining socio-demographic factors analyzed, i.e., residence during studies and the material conditions, on the stress level was not significant, but higher volumes of distress were observed in the students living in lodgings and dormitories (3.7 ± 3.2) than in those living with families (3.1 ± 2.8) and also in the students with average material conditions (4.5 ± 3.9) and bad material conditions (5.2 ± 4.3) than with good and very good material conditions (3.8 ± 3.5) (Table 35.2).

There was also a relationship between the level of distress and a way of life of the students. The relation between the level of stress and sleep duration, regularity of meals and physical activity turned out to be highly statistically related. Very little time was spent on sleeping in a vast majority of students. 63% sleep less than 6 h a day, whereof 5% only 3–4 h. The association between the small amount of sleep and the distress level is significant (the distress index for this group was high – 5.3 ± 3.8). The level of stress in well-sleeping students was notably lower (2.9 ± 3.1). Higher volumes of distress index were also seen in the students (right up to 63%) who did not train (3.9 ± 3.1) than in those physically active (3.0 ± 2.2) and also in irregularly eating students (57% of the group – 4.2 ± 3.1) than in those eating healthy (3.0 ± 2.1). The analysis of addictions: smoking cigarettes (35% of the group), drinking alcohol (30%), consuming big amounts of coffee and energizers (53%), and taking drugs (24%) did not reveal any significant relations with the distress level (Table 35.3).

Conducted trial proved the existence of strong correlation between distress and somatic health. It concerns both the self-evaluation of the health condition and the infection of the respiratory system. Most of the interviewees positively assessed their health condition (76% of the studied group). They were characterized by significantly lower value of the distress index (2.7 ± 2.2) than the students who assessed their health condition as bad (5.3 ± 3.1). Up to 74% of the students from this category reported worsening of the health condition in comparison with the previous year. The deterioration of the health condition was highly statistically related with the level of distress. The value of mean distress scale of the students reporting worsening of the health condition was 5.0 ± 3.8 and 2.9 ± 1.6 amongst the students, who didn't report such happening (Table 35.4).

Table 35.1 GHQ-12 scores and index of mental conditions

Mental conditions	± SD
Students total	3.7 ± 2.5
Students with risk of distress (GHQ scale)[a]	6.2 ± 2.7
Students with risk of depression (CES-D scale)[a]	6.7 ± 3.2
Students with poor mental self-feeling[a]	7.2 ± 3.5
Students with risk of distress, depression and poor mental self- feeling[a]	8.0 ± 3.9

[a]Explanation in text; means ± SD

Table 35.2 GHQ-12 scores and chosen socio-demographic variables

Socio-demographic variables		± SD
Female	Medical students	4.2 ± 2.5
	Pedagogy students	3.6 ± 2.2
Male	Medical students	3.0 ± 2.9
	Pedagogy students	2.0 ± 1.5
Permanent abode	City	3.6 ± 3.4
	Village	3.8 ± 2.9
Place of living during study	With parents	3.1 ± 2.8
	Without parents	3.7 ± 3.2
Economic status	Very good and good	3.1 ± 2.9
	Average	4.5 ± 3.9
	Bad	5.2 ± 4.3

Means ± SD

Table 35.3 High GHQ-12 scores depending on the selected lifestyle factors

Lifestyle factors		± SD
Sleep	Very little <4 h/24	5.3 ± 3.8
	Little	3.9 ± 3.2
	Enough ≥8 h	2.9 ± 3.1
Eating habits	Regularly	3.0 ± 2.1
	Irregularly	4.2 ± 3.1
Sport	Regularly	3.0 ± 2.2
	Sporadic and not at all	3.9 ± 3.1
Cigarettes	Smokers and ex-smokers	4.7 ± 3.4
	Non-smokers	4.1 ± 2.9
Alcohol	Drinkers	3.9 ± 3.0
	Occasional and non-drinkers	4.1 ± 3.0
Coffee and energizers	Drinkers	4.4 ± 3.4
	Occasional and non-drinkers	3.8 ± 2.7

Means ± SD

The dependence between the stress level and the frequency of respiratory tract infections was also significant. The highest value of the distress index was observed in the students who fall ill "very often" (7.1 ± 4.3) and the lowest value was seen in those who fall ill "almost not at all" (1.4 ± 1.2). The relationship between the duration of infection and the level of stress was found to be not statistically significant, but there was a higher value of the distress index noted in the students with a long course of infection (over 1 week – 3.8 ± 3.1) than with a short course (few days – 3.3 ± 3.2). When the variables were taken into account together (the frequency and the duration of infection), considerable and

Table 35.4 High GHQ-12 scores and somatic condition

Somatic health		± SD
Self-evaluation of health condition	Positively	2.7 ± 2.2
	Negatively	5.3 ± 3.1
Worsening of health condition	No	2.9 ± 1.6
	Yes	5.0 ± 3.8
Frequency of respiratory tract infections	Not at all	1.4 ± 1.2
	Almost not at all	3.1 ± 2.3
	Frequently	4.5 ± 3.2
	Very often	7.1 ± 4.3
Duration of infection	Short	3.3 ± 3.1
	Long	3.8 ± 3.2
Types of diseases	Throat and nose infection	2.9 ± 1.6
	Bronchitis, pneumonia	5.0 ± 3.8

Means ± SD

statistically significant differences between the stress level in the students falling ill often, very often and long (7.2 ± 2.9) and students not falling ill at all, almost not at all and short (1.6 ± 1.2) were observed. It was also noted that the distress level was much lower in the students who most often developed a throat and nose infection (54% of the students) than in those developing infections of the lower respiratory tract: bronchitis, pneumonia – 29% of the students (2.9 *vs.* 5.4).

The model obtained as a result of the backward stepwise regression explained 54% of the variation of student's mental condition ($r^2 = 0.54$). It confirmed the strong relation between the level of the psychic distress among students and respiratory tract infections. Standardized coefficient BETA, showing the force and direction of the correlation, was the highest in case of infection frequency. The following independent variables in this model were also found to be statistically significant: worsening of the health condition, sleep duration, regularity of meals.

35.4 Discussion

Numerous publications report that the incidence of psychic disorders is increasing worldwide. Hence it is important to detect such disorders already during the elementary stage of medical care (Collins and Mowbray 2005; Pokorski and Siwiec 2008; Baldassinet al. 2008). Measuring the mental condition is not easy, but various scales confirm that the psychic condition of the students is worsening. (Rosal et al. 1997; Üner et al. 2008; Stock et al. 2008; Dyrbe et al. 2010). In the present study we confirmed those reports by finding a heightened level of the risk of distress (worsened psychic mood) in over a half of students – 51%. About 16% of the studied group, in whom a synchronous occurrence of symptoms measured by all three indexes with a high level of distress was observed (8.0 ± 2.4), would be classified as particularly endangered.

The GHQ-12 scale used in the present study is not for diagnosing or perceptive psychiatric assessment, but is employed as a screening tool for detection of people with a significant risk of developing the mental health disorders (Goldberg 1978). GHQ has been translated into over 40 languages, including Polish, and it is very scrupulous in cases of short-lasting disturbances, which can run their course untreated. The scale's popularity is an asset, because it allows comparing the individual outcomes with the outcomes of others. On a certain level, the psychological distress have joint features in environments which have otherwise different cultural bases. The scale is of high utility and accuracy, and its short 12-item version is designed in the way that assesses the general mental condition; the score being not affected by somatic diseases (Montazeri et al. 2003; Laranjeira 2008).

The results of the present study reveal a weak psychic condition of Polish students and comparison of these outcomes with reports from other countries show the globalization of this occurrence (Montazeri et al. 2003; Emami et al. 2007; Ozdemir and Rezaki. 2007; Demirüstü et al. 2009). Gender turns out to be a factor that also determines the outcomes of GHQ; the scores are higher for female students (Emami et al. 2007; Stock et al. 2008; Dyrbe et al. 2010). The results of the present study and those of previous studies suggest that psychic distress is more connected with the kind of study (medical training) than personal problems during the first year (Moffat et al. 2004; Rosenthal and Okie 2005; Vaidya and Mulgaonkar 2007; Voltmer et al. 2008).

The problem of mental health remains inseparably related to somatic health. There is a whole series of somatic diseases that may be caused by long-lasting or particularly intense stress or for which the stress is a risk factor (Vitaliano et al. 1988; Stock et al. 2008; Demirüstü et al. 2009). From the contemporary point of view, all diseases are psychosomatic in nature and it is hard to separate the psychosomatic diseases from the somatopsychic ones (Kellner 1994; Stock et al. 2003).

We conclude that the Polish student population is exposed to increased stress level and, as a consequence, to increased occurrence of respiratory tract infections. The first year of study seems the most stressful situation which tapers off in the following year. Promotion of mental health and the ability to deal with stress among university students is required.

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

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Chapter 36
Atherosclerotic Factors in PR3 Pulmonary Vasculitis

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Abstract Autoimmune disease such as systemic lupus erythematosus or rheumatoid arthritis are connected with higher risk of atherosclerosis and cardiovascular complications and mortality. This results from inflammatory damage to the vessel wall by vasculitis. The aim of the present study was to evaluate whether patients with Wegener's granulomatosis (WG) and pulmonary involvement have an increased prevalence of atherosclerotic disease as characterized traditional risk factors. Twenty one patients with WG in remission and 15 control subject were entered to the study. Traditional risk factor for cardiovascular disease such as hyperglycemia, hypertension, smoking, obesity, and dyslipidemia were assessed. Both systolic and diastolic blood pressure were higher in WG patients ($p<0.025$). Total cholesterol, LDL and TG levels were markedly elevated in 18 of the 21 in pulmonary WG patients. Compared with controls, plasma levels of hsCRP were raised in WG patients; 3.68 (0.79–9.75) mg/l *vs.* 0.14 (0.12–0.59) mg/l ($p<0.01$). We conclude that non-pharmacological and pharmacological treatments of traditional risk factors are crucial to prevent cardiovascular disease in WG patients and thus should be part of therapy to control WG activity and damage caused by it.

Keywords Wegener's granulomatosis • Inflammation • Atherosclerosis • Cardiovascular disease • Traditional risk factors • C-reactive protein

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36.1 Introduction

Atherosclerotic vascular disease is an entity in which the artery wall thickens as a result of the accumulation of cholesterol promoted by low-density lipoproteins without adequate removal of fats and cholesterol from the macrophages by functional high density lipoproteins (Booth et al. 2004). Hardening and loss of elasticity of arteries is caused by formation of multiple atheromatous plaques (Finn et al. 2010). Atherosclerosis is a chronic disease and remains asymptomatic for years. Stable atherosclerotic plaques consist of extracellular matrix and smooth muscle cell, while unstable plaques are rich in macrophages and foam cells, and extracellular matrix which separates the lesion from the arterial lumen (fibrous cap) (Benedetto et al. 2008). Ruptures of the fibrous cap expose thrombogenic material, such as collagen, to circulation and induce thrombus formation in the lumen.

Autoimmune disease such as systemic lupus erythematosus (SLE) or rheumatoid arthritis (RA) is connected with a higher risk of atherosclerosis and cardiovascular morbidity and mortality (van Leuven et al. 2003), which results from atherosclerosis and inflammatory damage to the vessel wall by vasculitis. Inflammation also is one of the hallmarks of Wegener's granulomatosis (WG) (Nienhuis et al. 2007; Raza et al. 2000). Therefore, atherosclerosis, endothelial dysfunction, proliferation of smooth muscle cells, and excessive vascular remodeling might be expected in WG patients. Many risk factors for cardiovascular and cerebrovascular disease both traditional and non-traditional are connected with endothelial activation and dysfunction. Traditional risk factors like smoking, hyperglycemia, hypertension and dyslipidemia disturb vascular balance, resulting in endothelial activation (de Leeuw et al. 2005). Furthermore, endothelial activation is caused by antineutrophil cytoplasmic antibodies directed to proteinase-3 (PR3-ANCA), characteristic for necrotizing vasculitis affecting small and medium sized vessels (Cocco and Gasparyan 2010). The aim of the present study was to evaluate whether patients with WG and pulmonary involvement have an increased prevalence of atherosclerotic disease as characterized by traditional risk factors.

36.2 Methods

The study was approved by a local Ethics Committee. Twenty one patients, 11 females and 10 males, the median age 54.5 (27.4–69.8) years with pulmonary WG treated at the Primary Systemic Vasculitis Outpatients Clinic Czerniakowski Hospital in Warsaw, Poland, with biopsy-proven WG were entered the study. WG recognition was established at least 5 years before the study. All patients fulfilled the American College of Rheumatology criteria for classification of WG and the Chapel Hill Consensus Conference definition for WG. Disease activity was confirmed by clinical scoring, laboratory variables and typical imaging procedures. The DEI and BVAS indexes were determined to measure organ involvement and disease activity. The collected data included age, sex, history of hypertension, diabetes, smoking status, body mass index, family history of CVD (first-degree relatives suffered from CVD before 55 years of age), antihypertensive agents, HMG-CoA inhibitors, disease duration, glomerular filtration rate (GFR), and glycemia. Fifteen healthy age and sex-matched volunteers made up a control group.

Hypertension was defined as systolic arterial pressure above 140 mmHg and/or diastolic arterial pressure above 90 mmHg (WHO definition) or a history of hypertensive drug use. Plasma lipid concentration of total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL), triglycerides (TG) was measured by routine techniques. Dyslipidemia was diagnosed if plasma cholesterol exceeded 6.2 mmol/l, LDL cholesterol exceeded 3.3–4.1 mmol/l, triglycerides exceeded 2.2 mmol/l, high density lipoproteins (HDL) were below 1.55 mmol/l, or a subject had a history of lipid-lowering drug using. CRP was measured with an immunoturbidimetry assay (SIMENS ADVIA 1800) and a value greater than 1 mg/l was considered abnormally high.

Data were shown as means ± SE or as median. A Wilcoxon test was used for statistical analysis. $P < 0.05$ was considered statistically significant.

36.3 Results

The patients and controls were similar with respect to age, sex, smoking history, body mass index, prevalence of diabetes, and a positive family history of cardiovascular disease. The characteristics of the WG and control groups are presented in Table 36.1. Both systolic and diastolic blood pressure were higher in the pulmonary WG patients ($p < 0.025$). Seven (33%) patients used antihypertensive drugs and 4 (19%) other patients used HMG-CoA inhibitors in the WG group. The body mass index was higher in the WG patients *vs.,* controls and ranged from 28.6 ± 3 to 23.8 ± 4.

Laboratory data of both WG and control subjects are presented in Table 36.2. Cholesterol, LDL, and TG levels were elevated in 18 out of the 21 WG patients, and in 7 control subjects. The mean total cholesterol, LDL, and TG concentrations were 6.4 ± 1.6, 4.3 ± 1.2, and 2.33 ± 0.8 mmol/l, respectively. The HDL levels were lower in 16 out of the 21 sera WG patients, ranging from 1.2 to 0.45 mmol/l, compared with the control subjects – 12 out of the 15 of them had HDL in the normal range of 2.4 ± 0.76 mmol/l. Renal function was reduced in the WG patients compared with the controls ($p < 0.05$). The plasma levels of hsCRP were higher in the WG patients compared with the control subjects; 3.68 (0.79–9.75) *vs.* 0.14 (0.12–0.59) mg/l, respectively ($p < 0.01$).

36.4 Discussion

Anatomic, physiological and behavioral risk factors for atherosclerosis are known. There are congenital and acquired, modifiable and non-modifiable, traditional and non-traditional risk factors. The risk for atherosclerosis and cardiovascular disease multiply. Hypertension, hyperlipidemia and cigarette smoking combined increase the risk seven times. The most important factors in prevention and prognosis of cardiovascular diseases and events are the modifiable ones: diabetes, impaired glucose tolerance, dyslipoproteinemia, tobacco smoking, hypertension, elevated serum C-reactive protein concentrations, or vitamin B6 deficiency (Libby et al. 2002).

In the present study, the prevalence of traditional risk factors differed significantly between the WG patients and control subject. Patients had higher blood pressure and body mass index, and had a family history of cardiovascular disease. Total cholesterol, LDL, and TG concentrations were all higher and HDL was lower in the WG group.

Atherosclerosis is facilitated by oxidation of LDL, particularly caused by reactive oxygen species. When oxidized LDL comes in contact with an artery wall, a series of immune-related reactions occurs to control the damage (Finn et al. 2010). Lymphocytes T are recruited to absorb the foam cells formed by oxidized LDL. The white blood cells are not able to process the oxidized-LDL and rupture, depositing oxidized cholesterol into the artery wall, causing artery wall inflammation and continuing the

Table 36.1 Characteristics of Wegener's granulomatosis (WG) and control subjects

	WG (n = 21)	Controls (n = 15)	p
Sex (males/females)	10/11	7/8	NS
Median age (range, year)	54.5 (27.4–69.8)	52.4 (25.4–71.4)	NS
Body mass index (kg/m²)	28.6 ± 3	23.8 ± 4	0.01
Blood pressure (systolic/diastolic, mmHg)	150 ±20/85 ± 11	115 ± 17/67 ± 14	0.03
Diabetes (n, %)	5 (24)	4 (27%)	NS
Smoking (n, %)	7 (33)	5 (33%)	NS
Dyslipidemia (n, %)	18 (86)	7 (47%)	0.04
Family history of CVD (n, %)	8 (38)	4 (27%)	0.001
Antihypertensive drugs	7 (33)	4 (27%)	NS
HMG-CoA inhibitors (n)	3 (14)	2 (13%)	NS

Table 36.2 Laboratory data in Wegener's granulomatosis (WG) and control subjects

	WG (n = 21)	Controls (n = 15)	p
hs CRP (mg/l)	3.68 (0.79–9.75)	0.14 (0.12–0.59)	0.01
Total cholesterol (mmol/l)	6.4 ± 1.6	4.5 ± 1.6	0.05
LDL (mmol/l)	4.3 ± 1.2	3.7 ± 0.9	0.02
HDL (mmol/l)	1.20 ± 0.45	2.40 ± 0.76	0.02
Triglycerides (mmol/l)	2.33 ± 0.80	1.98 ± 0.75	0.04
GFR (ml/min)	54.21 ± 13.8	67.8 ± 9.4	0.05

vicious cycle. A cholesterol plaque makes the vessel muscle cells enlarge and forms a hard cover near the affected area, which constricts the artery and reduces blood flow through it. Lowering total and LDL cholesterol seems thus essential in cardiovascular disease protection (Ridker et al. 2002).

It is unknown whether WG is an independent risk factor for the development of atherosclerosis. To resolve the issue prospective studies are needed. Atherosclerosis is considered to be a chronic inflammatory diseases. C-reactive protein is considered a marker of systemic inflammation and a prognostic marker for cardiovascular disease (Albert et al. 2003). In the present study, plasma concentrations of hsCRP in WG patients were increased. C-reactive protein may contribute to atherosclerosis development by inducing the expression of adhesion molecules on the endothelial surface. CRP could thus be a connecting link between an autoimmune disease, such as PR3-ANCA vasculitis, and cardiovascular disease. The proper therapeutic control of pulmonary Wegener's granulomatosis and of traditional cardiovascular risk factors by using dietary management, smoking cessation, and modification of other life style factors, along with antihypertensive and HMG-CoA inhibiting treatment, seem essential to prevent cardiovascular complications.

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Chapter 37
Vagal Heart Rate Control in Patients with Atrial Fibrillation: Impact of Tonic Activation of Peripheral Chemosensory Function in Heart Failure

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Abstract Heart failure (HF) and atrial fibrillation (AF), emerging as two epidemics of the twenty-first century, are commonly associated with each other. Both have been mechanistically linked to changes in cardiac vagal control. The importance of peripheral chemosensors, located in the carotid body, has not been elucidated so far. We therefore investigated whether tonic activation of excitatory chemoreceptor afferents contributes to the altered vagal control in HF patients with a history of AF. In 18 patients (72 ±9 year, 7 male) with sinus rhythm and a history of AF (n = 9, without any evidence of structural heart disease, AF group; n = 9 with structural heart disease and clinical presentation of HF, AFHF group) we investigated the impact of chemosensory deactivation (by breathing 100% oxygen) on heart rate, blood pressure, cardiac output, total peripheral resistance, oxygen saturation and breathing rate. Ten healthy individuals served as a control group. In addition, we performed a deep breathing test demonstrating an impaired heart rate variation in patients with and without HF as compared with controls (expiration/inspiration difference: 23.9 ± 6.9 *vs*. 6.9 ± 6.1 bpm, and 23.9 ± 6.9 *vs*. 7.8 ± 4.8 bpm; $p < 0.05$). In both control and AF groups, heart rate decreased during chemoreceptor deactivation (control: -4.8 ± 3.4%; AF: -5.1 ± 3.0%; $p < 0.05$), whereas heart rate did not change in AFHF patients. This resulted in impaired cardiac chemoreflex sensitivity in AFHF patients (1.9 ± 1.6 *vs*. 0.5 ± 1.2 ms/mmHg; $p < 0.05$). In conclusion, our data suggest that tonic activation of excitatory chemoreceptor afferents contributes to a low vagal tone in heart failure patients with a history of AF (Clinical Trials NCT01262508).

Keywords Atrial fibrillation • Heart failure • Autonomic nervous system • Deep breathing • Hyperoxic chemoreflex sensitivity

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37.1 Introduction

Heart failure (HF) and atrial fibrillation (AF), emerging as two epidemics of the twenty-first century, have been mechanistically linked to changes in cardiac vagal control (de Vos et al. 2008). The pathophysiological relationship between AF and HF has only been partially elucidated, although both entities are commonly associated with each other. Experimental and clinical evidence demonstrates that a relative decrease of vagal tone is common in HF and can precede the onset of AF as characterized by heart rate variability (HRV) at rest and during respiratory maneuvers (deep breathing test). Noteworthy, peripheral chemoreceptors, residing in the carotid body, are well known to modulate vagal heart rate control. High arterial oxygen levels, as achieved by inhalation of pure oxygen, lead to deactivation of these chemoreceptors with a following rise in vagal tone resulting in a decrease of heart rate (Seals et al. 1991). Impairment of this deactivation is supposed to be linked to vagal dysfunction (Ponikowski et al. 1997) and can be quantified by hyperoxic cardiac chemoreflex sensitivity (CHRS) testing. Whether and how peripheral chemosensory function modulates efferent vagal activity within the interaction of both AF and HF is unknown. The aim of the present study was to investigate whether tonic activation of excitatory chemoreceptor afferents contributes to the altered vagal heart rate control in HF patients with a history of AF.

37.2 Methods

37.2.1 Study Design and Patient Selection

The study protocol was approved by the institutional review board of the University of Duesseldorf and all patients gave written informed consent. Hemodynamics, HRV, and blood pressure variability (BPV) at baseline and during chemosensor deactivation by inhalation of 100% oxygen over 5 min were studied in 18 patients with a history of AF and in ten healthy controls. We included two different patient groups: The AF group consisted of nine individuals with a history of AF, but without any evidence of structural heart disease as excluded by coronary angiography. Furthermore, left ventricular dysfunction was excluded either by a levocardiogram or echocardiography. The AFHF group included another 9 AF patients with documented moderately impaired left ventricular systolic function. All patients were in stable sinus rhythm during our experiments. Ten healthy volunteers without any known history of cardiovascular disease served as a control group. AF was defined as recently proposed by the guidelines for the management of atrial fibrillation issued by the European Society of Cardiology (Camm et al. 2010). The diagnosis of HF was based on a documented structural heart disease, as well as clinical appraisal according to the classification of the New York Heart Association (Dickstein et al. 2008). Exclusion criteria were congestive heart failure, with a cardiac ejection fraction of <30%, heart disease associated hypotension, severe cardiac arrhythmias, sleep apnea syndrome, chronic obstructive pulmonary disease and acute inflammation (C-reactive protein >5 mg/l).

37.2.2 Experimental Setup and Autonomic Reflex Testing

All subjects rested in the supine position in a quiet examination room for at least 10 min before testing commenced. To characterize the autonomic cardiovascular reflex control, HRV and BPV were measured at baseline over 5 min (Task Force of the European Society of Cardiology 1996). In addition,

we performed two interventions to investigate the characteristics of vagal tone and vagal reflex control: (i) deep breathing, (ii) pure oxygen inhalation. Both tests were performed in a randomized order. The recovery period between both tests was at least 10 min.

37.2.3 Measurements of Hemodynamics and Blood Parameters

Heart rate, blood pressure, cardiac output, total peripheral resistance, HRV and BPV were measured continuously. We recorded beat-to-beat HR by a two-channel electrocardiogram (ECG), stroke volume by an improved method of impedance cardiography (Gole et al. 2011; Gratze et al. 1998), and blood pressure by a finger cuff the values of which were corrected automatically to the oscillometric blood pressure measured on the contralateral arm (Task Force Monitor (TFM) CNSystems, Graz).

Additionally, the TFM provided data on HRV and BPV calculated from power spectral analysis applying an autoregressive methodology (Gratze et al. 1998, 2005; Task Force of the European Society of Cardiology 1996). The main spectral components were low frequency (LF 0.04–0.15 Hz, HRV and BPV) and high frequency (HF 0.15–0.40 Hz, HRV and BPV) which were calculated in absolute values (HRV: LF-RRI and HF-RRI in ms^2; BPV: LF-sBP and LF-dBP in $mmHg^2$) and were in normalized units (HRV: LFnu-RRI and HFnu-RRI; BPV: LFnu-sBP and LFnu-dBP, %) (RRI- R-R Interval) (Task Force of the European Society of Cardiology 1996).

A standard patient monitor (Philips Intellivue MP50) was used to additionally acquire the following signals: electrocardiogram (at 504 Hz), two photo plethysmograms, one from the ear and one from the finger (at 125 Hz), and a respiration signal (at 62.5 Hz). This system provided HR, respiration rate, perfusion index and oxygen saturation level measured from the ear and finger locations. Signals and data coming from the TFM and the MP50 were synchronized *via* the detected R-R sequences from the ECG signals with an accuracy of less than 0.01 s. Standard clinical blood parameters were analyzed in a central laboratory using standard techniques (Meyer et al. 2010a).

37.2.4 Deep Breathing Test

The test routine consisted of an initial resting phase in which the patients remained recumbent for a period of 10 min in a quite environment. Starting the test, they performed six breathing cycles during 1 min synchronized to an acoustical signal to obtain reproducible results. The expiratory-inspiratory difference (E/I difference) was calculated by subtracting the maximum HR during inspiration from the minimum HR during expiration for each cycle of breathing, and then determining the mean of these differences. The expiratory-inspiratory ratio (E/I ratio) assesses the ratio of the mean of the maximum heart rates and the mean of the minimum heart rates (Hilz and Dutsch 2006).

37.2.5 Hyperoxic Cardiac Chemoreflex Sensitivity Testing

Hyperoxic CHRS testing was performed following an established protocol (Hennersdorf et al. 2001). After a 10 min resting period, patients received 5 l O_2/min *via* a nasal mask over 5 min. No conversation was allowed during this period for minimization of mental influences. A capillary blood sample was taken from the ear lobe at rest and after oxygen inhalation and the partial oxygen and carbon dioxide pressures (pO_2 and pCO_2) were determined using a standardized blood gas analyzer (Radiometer Copenhagen, Denmark). Furthermore, the mean R–R interval out of ten consecutive

R–R intervals (R–R interval preoxygen) was calculated using a two-channel electrocardiogram (TFM) at baseline and after oxygen inhalation. The difference of the R–R intervals before and after oxygen inhalation divided by the difference of capillary oxygen pressure was calculated as the CHRS (ms/mmHg). A CHRS below 3.0 ms/mmHg was defined as pathological (Meyer et al. 2010b; Hennersdorf et al. 2002).

37.2.6 Statistical Analysis

Continuous variables are presented as means ± SD. Univariate correlations were Spearman rank correlations. Analysis of variance ANOVA and a t-test were employed for calculation of significance. $p < 0.05$ was considered to be statistically significant. Statistical analysis was performed using Graphpad Prism 5® (Graphpad Inc., La Jolla, USA).

37.3 Results

The clinical baseline characteristics are shown in Table 37.1. Age, gender and cardiovascular risk factors including smoking, arterial hypertension, dyslipidemia and diabetes did not differ between the AF and AFHF groups. All patients received optimal medication according to current guidelines, resulting in a homogenous pharmaceutical profile of our study groups. Most patients were on a combination of beta blockers, ACE-inhibitors/AT-II antagonists, diuretics, and statines.

Table 37.1 Baseline characteristics

	AF group	AFHF group
n	9	9
Age (year)	71 ± 10	72 ± 9
Sex (male)	4	3
Height (cm)	167 ± 5	166 ± 10
BMI (kg/m²)	28 ± 4	27 ± 5
Current smokers, n	1	0
Past smokers, n	5	3
Diabetes mellitus, n	1	3
Hypertension, n	5	6
Dyslipidemia, n	5	4
CAD, n	7	7
CVD, n	0	0
NYHA class I/II/III/IV, n	0/0/0/0	0/4/5/0
CHADS2 – Score	1 ± 1.2	2 ± 1.3
CHA2DS2-VASc – Score	3 ± 1.9	4.1 ± 2.1
Medication		
Propafenon, n	1	0
Amiodaron, n	0	3
Dronedaron, n	0	1
Beta blockers, n	8	9

(continued)

Table 37.1 (continued)

	AF group	AFHF group
ACE inhibitors/AT-II-antagonists, n	4	6
Ca antagonists, n	1	3
Digitalis, n	2	2
Diuretics, n	4	6
Statins, n	5	4
Oral antidiabetics, n	1	2
Insulin, n	0	1
Phenprocoumon, n	4	6
Blood parameters		
Serum protein (g/l)	7.15 ± 0.58	6.71 ± 0.47
Serum creatinin (mg/dl)	1.13 ± 0.28	1.06 ± 0.23
Erythrocytes (mio/µl)	4.28 ± 0.48	4.20 ± 0.50
Hemoglobin (g/dl)	12.9 ± 1.5	12.3 ± 1.43
Hematocrit (%)	37.5 ± 4.0	37.1 ± 3.33
Total cholesterol (mg/dl)	175 ± 1	187 ± 37
HDL cholesterol (mg/dl)	74 ± 47	65 ± 14
LDL cholesterol (mg/dl)	109.5 ± 2	122 ± 21
Triglycerides (mg/dl)	121 ± 21	131 ± 37
Plasma glucose (mg/dl)	97 ± 26	117 ± 37

BMI body mass index, *CAD* coronary artery disease, *CVD* cerebrovascular disease
All values are means ± SD

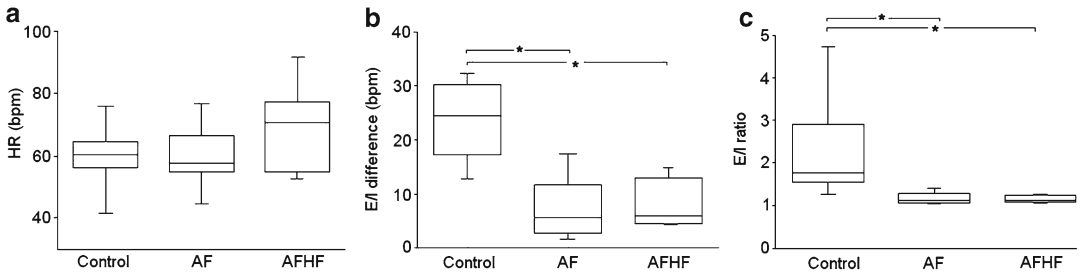

Fig. 37.1 Change in heart rate (HR) during deep breathing. (**a**) Typical pattern of HR variation during deep breathing in the control, AF, and AFHF groups; (**b**) HR variation indexed by expiration to inspiration (E/I) difference; (**c**) HR variation indexed by E/I ratio. Both E/I difference and E/I ratio were lower in the AF and AFHF groups compared with healthy controls (*$p < 0.05$), but there were no differences between the two groups of patients

37.3.1 Heart Rate Variation During Deep Breathing in AF and AFHF Patients

The response to deep breathing was depressed in both groups compared with the healthy controls (Fig. 37.1a). Heart rate variation expressed by the E/I difference was lower in both AF and AFHF groups compared with the healthy controls (6.9 ± 6.1, 7.8 ± 4.8, 23.9 ± 6.9 bpm, respectively; $p < 0.05$), but did not differ between the AF and AFHF patients (Fig. 37.1b). The E/I ratio also was lower in both AF and AFHF groups compared with the healthy controls (E/I ratio: 1.15 ± 0.15, 1.14 ± 0.09, 2.26 ± 1.16, respectively; $p < 0.05$, Fig. 37.1c). E/I ratio did not differ between the AF and AFHF patients.

Table 37.2 Hemodynamics at baseline and after chemosensor deactivation (oxygen)

	AF group	AFHF group	Control
Baseline			
Heart rate (bpm)	63 ± 10	68 ± 12	63 ± 9
SBP (mmHg)	128 ± 29	120 ± 27	124 ± 18
DBP (mmHg)	73 ± 13	72 ± 16	76 ± 11
MAP (mmHg)	86 ± 17	85 ± 20	91 ± 13
Rate pressure product (mmHg/min)	7.7 ± 1.3	8.0 ± 1.6	7.7 ± 1.3
Stroke volume (ml)	83 ± 20	68 ± 16	119 ± 21
Cardiac output (l/min)	5.2 ± 1.6	4.5 ± 0.8	7.4 ± 1.2
TPR (dyne*s/cm^5)	1432 ± 622	1630 ± 517	992 ± 237
Breathing rate (1/min)	16 ± 6	19 ± 3	18 ± 2
Oxygen (5 l/min)			
Heart rate (bpm)	59 ± 9*	67 ± 12	59 ± 9*
SBP (mmHg)	135 ± 24	129 ± 21*	126 ± 18*
DBP (mmHg)	76 ± 12	77 ± 13*	78 ± 11*
MBP (mmHg)	91 ± 16	92 ± 16*	94 ± 14*
Rate pressure product (mmHg/min)	7.7 ± 1.4	8.5 ± 1.2*	7.5 ± 1.2*
Stroke volume (ml)	84 ± 21	66 ± 15	120 ± 21
Cardiac output (l/min)	5.0 ± 1.6	4.3 ± 0.7	7.1 ± 1.3
TPR (dyne*s/cm^5)	1547 ± 671	1835 ± 508*	1073 ± 277
Breathing rate (1/min)	15 ± 6	17 ± 4	14 ± 4*

HF heart failure, *AF* atrial fibrillation, *bpm* beats per minute, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *MBP* mean blood pressure, *TPR* total peripheral resistance
*Significant difference from baseline ($p < 0.05$)

37.3.2 Heart Rate During Peripheral Chemosensor Deactivation in AFHF Patients

No significant changes in systolic blood pressure (SBP), stroke volume (SV) and cardiac output (CO) could be observed. Diastolic blood pressure (DBP) and total peripheral resistance (TPR) increased. Hemodynamic changes during oxygen administration are shown in Table 37.2.

Inhalation of pure oxygen led to a lower breathing rate in every group. However, the dimension of this effect differed between both patient groups as compared with the healthy controls. Both AF and AFHF groups had a lower decrease in breathing rate compared with the healthy controls (change in breathing rate: −10%, −9%, −23%, respectively; $p < 0.05$) and did not differ significantly among one another.

A marked decrease in HR during oxygen administration occurred in the controls (−4.8%, $p < 0.05$) and in the AF group (−5.0%, $p < 0.05$), as opposed to the AFHF group where no significant HR change was present (Fig. 37.2).

37.3.3 Heart Rate Variability During Peripheral Chemosensor Deactivation

In the control group, high frequency bands in normalized and absolute values increased during oxygen administration compared with baseline (HFnu-RRI +18.3%, HF-RRI +96.7%, $p < 0.05$), whereas the LF/HF ratio decreased (−20.8% ± 29, $p < 0.05$). By contrast, in both AF (+3.1%) and AFHF (+5.26%) patients no significant changes in high frequency bands and in LF/HF ratio were observed. Peripheral chemosensor deactivation did not change the low frequency bands of BPV (LF-sBP, LF-dBP) either in the healthy controls or in the AF or AFHF patients.

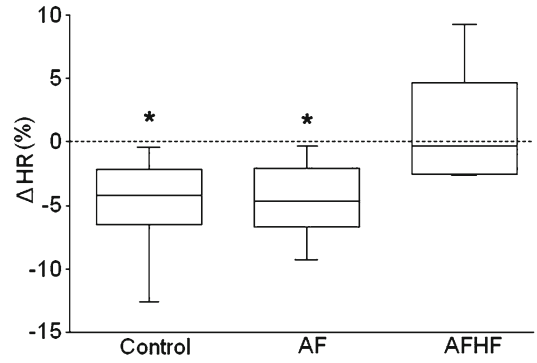

Fig. 37.2 Changes in heart rate (HR) after chemosensor deactivation. A marked decrease in HR during inhalation of 100% oxygen occurred in controls (−4.8%) and in AF patients (−5.0%, *p < 0.05), as opposed to AFHF patients in whom no change in HR was seen

Table 37.3 Blood gas analysis at baseline and after chemosensor deactivation with oxygen

	AF group	AFHF group	Control
RRI (ms)			
Baseline	988 ± 157	954 ± 146	984 ± 162
Oxygen (5 l/min)	1041 ± 147*	970 ± 146	1037 ± 175*
pO_2 (mmHg)			
Baseline	72 ± 8#	65 ± 3#	91 ± 10
Oxygen (5 l/min)	115 ± 40*	104 ± 28*	123 ± 20*
pCO_2 (mmHg)			
Baseline	35.07 ± 4.11	37.38 ± 3.80	38.56 ± 3.3
Oxygen (5 l/min)	35.11 ± 4.24	37.03 ± 5.00	39.16 ± 3.64
pH			
Baseline	7.44 ± 0.01	7.46 ± 0.03	7.43 ± 0.02
Oxygen (5 l/min)	7.44 ± 0.03	7.47 ± 0.03	7.43 ± 0.02

HF heart failure, *AF* atrial fibrillation, *RRI* RR-interval, pO_2 partial pressure of oxygen, pCO_2 partial pressure of carbon dioxide
*$p < 0.05$ *vs*. corresponding baseline values
#$p < 0.05$ *vs*. control values.

37.3.4 Chemoreflex Sensitivity in Atrial Fibrillation Patients with Heart Failure

None of the patients were hypoxemic at baseline with oxygen saturation values ranging 94–100%. Every subject reached an oxygen saturation value more than 99% during inhalation of pure oxygen (controls: 100 ± 0%; AF group: 99.9% ± 0.02%; AFHF group: 99.8% ± 0.3%, p = ns). Baseline oxygen saturation and HR did not differ in the AF and AFHF patients as compared with the healthy controls. Baseline pO_2 values were lower in both AF and AFHF patients as compared with controls ($p < 0.05$), whereas pO_2 values during oxygen inhalation did not differ between both patient groups (Table 37.3). During inhalation of oxygen, the pO_2 of all subjects increased (controls: +35%, AF: +65%, AFHF: +60%, $p < 0.05$). In the healthy controls, the increase in pO_2 correlated with the decrease in HR during inhalation of oxygen ($r = 0.9$; $p < 0.05$), while in the AF and AFHF groups this could not be observed. Corresponding to the changes in HR the RR-interval increased in the AF patients (+4.9%, $p < 0.05$) and in the controls (+5.2%, $p < 0.05$), but not in AFHF patients. This resulted in an impairment of CHRS in both AF and AFHF patients. CHRS was lower in the AFHF patients than that in AF patients (Fig. 37.3).

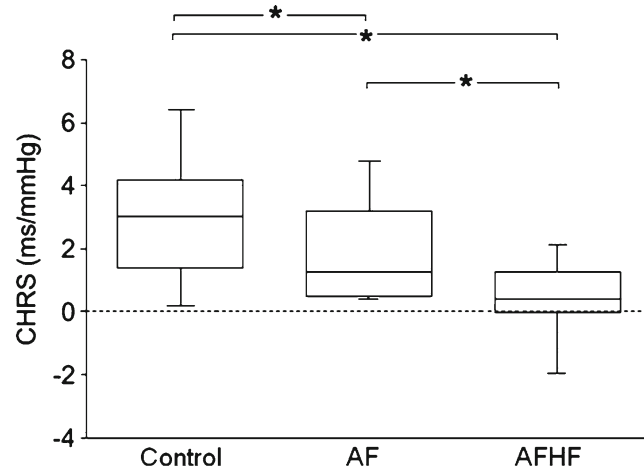

Fig. 37.3 Impairment of hyperoxic cardiac chemoreflex sensitivity (CHRS) in AF and AFHF patients. CHRS was lower in AFHF patients than in AF patients (*$p < 0.05$)

37.4 Discussion

In the present study we assessed the impact of heart failure on peripheral chemoreflex control in patients with a history of atrial fibrillation. The key findings of the present study are as follows: (i) AF patients with and without HF show a comparably low heart rate variation during deep breathing and (ii) disturbance of chemoreflex sensitivity in AF patients is advanced in patients with heart failure. Our findings indicate that tonic activation of peripheral chemoreceptors in AF patients contributes to a lower vagal tone in patients with heart failure that might be influenced by spontaneous breathing characteristics.

The role of autonomic dysregulation in patients with atrial fibrillation has been discussed for several years (Bettoni and Zimmermann 2002; Chen et al. 1998). Deep breathing is an established test in clinical measurement of autonomic nervous function and therefore numerous studies propose deep breathing for early detection of cardiovagal dysfunction (Blumenthal et al. 2005; Shields 2009; van den Berg et al. 2001; Wheeler and Watkins 1973). In our study we found lower values in deep breathing indexes in AF patients compared with healthy subjects. Corresponding to these results we suspect a lower vagal tone in AF patients, which is in line with previous reports (Chen et al. 1998; de Vos et al. 2008). Importantly, this might be partly explained by a decrease of sinus arrhythmia with increasing age (Low et al. 1997; O'Brien et al. 1986). Van den Berg et al. (2001) have taken the E/I difference of more than 15 bpm for the norm and claim a marginal decrease in heart rate variation, whereas Hilz and Dutsch (2006) defined a cut-off level at five beats per minute below which the E/I difference would have been abnormal in persons older than 50 years. Therefore, the interpretation of heart rate variation during deep breathing has to be done with caution. However, in our population there were no differences in deep breathing measurements between AF patients with and without HF. Consequently, we suppose that the two groups do not vary in basal vagal tone of efferent fibres innervating the sinus node.

It is well known that inhalation of pure oxygen leads to a decrease of HR in healthy subjects (Gole et al. 2011). This can be an expression of the physiological mechanisms of peripheral chemoreceptors. These receptors respond primarily to changes in the partial oxygen pressure. High arterial oxygen levels lead to deactivation of peripheral chemoreceptors. Consequently, excitatory receptor afferents evoke a rise of vagal tone resulting in a decrease of heart rate (Thoren 1979). This is supported by our findings in healthy controls who showed an obvious decrease in HR and thus no pathological CHRS values.

In addition the high frequency band of HRV, representing parasympathetic activity, rose during administration of oxygen.

Corroborating a previous study we found a decreased CHRS in AF patients (Budeus et al. 2003). Furthermore, Hennersdorf et al. (2001) have demonstrated that patients with HF have a reduced CHRS as well. Yet, there exists no study that has investigated the effect of inhalation of pure oxygen in patients with a combined history of AF and HF. Here we could demonstrate unchanged HR during administration of oxygen in AF patients with HF, indicating a lower CHRS compared with the AF patients without HF. According to these results we assume that tonic activation of chemoreceptors contributes to a lower vagal tone in AF patients with HF.

Considering critically our assumption, other underlying mechanisms could have played an important role or influenced the measurements. HF is characterized by increased sympathetic activity (Schwartz and De Ferrari 2011). Esler and Kaye (2000) have detected higher levels in plasma catecholamines in HF patients. This might have increased vagal activity during deactivation of chemoreceptors ("accentuated antagonism"). Nevertheless, the fact that all patients were on highest tolerable beta-blocker doses should have kept this influencing parameter at bay. Furthermore, unchanged values in the low frequency bands of BPV (LF-dBP and LF-sBP) in AF patients substantiate our assumption that the observed effects were predominantly modulated by parasymphathetic and not sympathetic activity, which is in line with previous reports (Gole et al. 2011; Seals et al. 1991).

Inhalation of oxygen produced a reduction of respiratory rate and a prolongation of expiratory time. This leads to a reduced activation of pulmonary stretch receptors resulting in increased vagal tone (Zuperku et al. 1982; Schelegle and Green 2001). It is possible that this respiratory phenomenon contributes to the decrease in heart rate. This limits the interpretation of our data because decreasing HR might not only reflect the dysfunction of one reflex arch, but the interaction of two mechanisms: deactivation of peripheral chemoreceptors and diminution of the respiratory rate with reduced activation of pulmonary stretch receptors. Despite this possibility we preclude an essential role of respiratory mechanisms. In all subjects the breathing rate decreased. Despite this decrease, heart rate did not change in AF patients with HF, whereas in healthy controls and in AF patients without HF heart rate HR clearly decreased. This fact underlines a low contribution of decreased respiratory rate to heart rate changes.

Schwartz and De Ferrari (2011) have highlighted the clinical relevance of our results stating that whenever vagal activity (tonic or reflex) is decreased, cardiac mortality increases. Accordingly, we submit that quantification of peripheral chemosensor function might be a useful tool to improve the evaluation of vagal heart rate control in some patients. A combination of different non-invasive autonomic function tests (e.g., cold pressure, cold face, or handgrip test) might additionally be useful for specifying autonomic dysfunction in AF patients with heart failure.

37.5 Conclusions

Our data suggest that tonic activation of excitatory chemoreceptor afferents contributes to a low vagal tone in heart failure patients with a history of AF. Quantification of deactivation characteristics of peripheral chemoreceptor function might be useful to characterize cardiac vagal control in patients with a history of atrial fibrillation during the development and progression of heart failure. This might improve heart failure management in the future.

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

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Chapter 38
Pulmonary Arterial Hypertension in Patients with Sarcoidosis: The Pulsar Single Center Experience

Stefan Pabst, Christoph Hammerstingl, Natalie Grau, Jens Kreuz, Christian Grohe, Uwe R. Juergens, Georg Nickenig, and Dirk Skowasch

Abstract Sarcoidosis is a systemic granulomatous disease with unknown etiology. Lungs and lymph nodes are commonly affected. Also, cases of pulmonary hypertension (PH) and pulmonary arterial hypertension (PAH) are described. However, the exact prevalence of PAH in patients with sarcoidosis is unclear. A 111 patients with proven sarcoidosis were recruited from January 2010 to October 2010. All patients were studied prospectively by transthoracic echocardiography (TTE) for the presence of PH. In assumed PH, a right heart catheterization (RHC) followed if there were no other reasons for PH. In 23 of the 111 patients (21%) PH was assumed in TTE. Three patients presented with severe mitral insufficiency III° and IV°, in eight patients PH was supposed to be caused by chronic heart failure or relevant diastolic dysfunction>II°, two patients declined undergoing RHC. Of the ten patients investigated with RHC, four showed a precapillary pulmonary arterial hypertension and in one patient a postcapillary hypertension was diagnosed. All four patients with precapillary PH had a radiologic stage III and IV. In three of the four patients a significantly reduced transfer factor for carbon monoxide (TLCO) <50% was found. All patients with precapillary PH had a chronic course of sarcoidosis lasting ≥13 years. This is the first study which prospectively investigated a large cohort of patients with sarcoidosis for the prevalence of PH and PAH. The prevalence of precapillary PH was found to be at least 3.6% (4/111) and therefore exceeds the prevalence of PAH in the normal population by far. A chronic and progressive lung involvement due to sarcoidosis seems to be the most evident risk factor for developing a sarcoidosis PH.

Keywords Pulmonary arterial hypertension • Heart failure • Lung • Transthoracic echocardiography • Sarcoidosis

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38.1 Introduction

Sarcoidosis is an inflammatory granulomatous multisystem disorder, primarily affecting the lung and lymph nodes. Other organs, including skin, heart and liver may also be afflicted. The disease is characterized by noncaseating granulomas and an exaggerated cellular immune response caused by increased inflammatory activity of macrophages (Iannuzzi et al. 2007). Sarcoidosis manifests itself in a wide variety of clinical symptoms as the acute disease, including Löfgren´s syndrome to persistent and progressive stages. The course of most sarcoidosis patients is short and favorable, but about 20% develop a chronic and prolonged disease, requiring treatment with corticosteroids. Up to 5% of all patients suffer severe complications such as lung fibrosis and cardiac involvement. The etiology remains unclear. Evidence however suggests that it is the product of an unknown exogenous antigenic stimulus and an endogenous genetic susceptibility (Statement on sarcoidosis 1999). Several investigators have described pulmonary hypertension (PH) and pulmonary arterial hypertension (PAH) in patients with sarcoidosis (Rizzato et al. 1983; Sulica et al. 2005; Baughman et al. 2006, 2010; Handa et al. 2006; Bourbonnais and Samavati 2008).

PH is a hemodynamic and pathophysiological state found in a range of clinical conditions and is characterized by an increase in the mean pulmonary arterial pressure (mPAP ≥25 mmHg); a rare subgroup of PAH is defined by the additional criterion of a pulmonary arterial wedge pressure (PCWP) ≤15 mmHg (Galiè et al. 2009). The different forms of PH have been classified into five clinical groups with specific characteristics (Galiè et al. 2009; Simonneau et al. 2009). Group 1 consists of the major forms of PAH (idiopathic, heritable and associated with connective tissue disease, and congenital heart disease, etc.). A diagnosis of PAH requires the exclusion of all other causes of PH, and specific treatments are available. Group 2 describes PH due to left heart disease. Group 3 PH is due to lung diseases and/or hypoxia, and Group 4 is chronic thromboembolic pulmonary hypertension (CTEPH). Group 5 consists of PH with unclear and/or multifactorial mechanisms. Sarcoidosis-associated PH is included in group 5, because it can be provoked by various conditions as fibrotic destruction of the vessels and direct compression of the blood vessels by adenopathy (Nunes et al. 2006). Recently, it could be demonstrated that the survival of patients with sarcoidosis-associated PH dramatically is impaired compared to sarcoidosis without PH (Baughman et al. 2007).

Because there are no prospective studies investigating the prevalence of PH/PAH in sarcoidosis patients we have initiated the PULSAR study (PULmonary Hypertension in SARcoidosis) and screened our large outpatient cohort by transthoracic echocardiography (TTE) and right heart catheter (RHC) for the prevalence of sarcoidosis-associated PH and the clinical risk factors that might be involved.

38.2 Methods

38.2.1 Patients

This was a prospective, single center study conducted at the University of Bonn, Germany. Local ethics committee approval was obtained prior to the inclusion of any patient in the study and the study was conducted according to the Declaration of Helsinki. A 111 consecutive outpatients with sarcoidosis diagnosed according to the current ATS/ERS/WASOG guidelines (Hunninghake et al. 1999 - Statement on Sarcoidosis) were assessed for pulmonary hypertension. Sarcoidosis was diagnosed by typical chest X-ray (posterior-anterior and lateral) abnormalities and confirmed by biopsy with evidence of noncaseating epitheloid cell granulomas. The following assessments were undertaken in all patients: transthoracic echocardiography (TTE) with estimation of systolic pulmonary arterial pressure (PAPsyst), medical history (including exact data concerning immunosuppressive medication and other

medication); clinical examination, including height, weight, blood pressure; standard 12-lead-electrocardiography (ECG); lung function testing (body plethysmography and transfer factor for carbon monoxide (TLCO)); laboratory investigations including blood count, and potassium, sodium, aspartate aminotransferase/alanine aminotransferase (AST/ALT), creatinine, angiotensin converting enzyme (ACE) and soluble interleukin-2 receptor (s-Il2-R).

38.2.2 Right Heart Catheterization

Patients with elevated PAPsyst in TTE (≥50 mmHg + estimated central venous pressure or ≥30 mmHg + estimated central venous pressure and dyspnea) underwent RHC. PH in RHC was defined as the mean pulmonary arterial pressure (mPAP) ≥25 mmHg regardless of the pulmonary capillary wedge pressure (PCWP). If mPAP was ≥25 mmHg and PCWP was ≤15 mmHg, the diagnosis of precapillary PH was made. In case of precapillary PH, a complete work-up (including chest computer tomography scan, ventilation-perfusion scan, sleep apnea screening, ultrasound of the liver and laboratory testing) was performed to verify or exclude PAH. Vasoreactivity testing (inhaled iloprost 5 μg; iNeb, Philips Healthcare, Eindhoven, Netherlands) was performed in case of precapillary PH/PAH. Positive vasoreactivity was defined as a decrease of mPAP ≥10 mmHg to reach ≤40 mmHg with a stable cardiac index (CI) (Galiè et al. 2009). Cardiac index was measured by direct Fick method.

38.2.3 Statistical Analysis

A German version of SPSS V17.0 (IBM, Munich, Germany) was used as a database and for statistical analysis. Data are expressed as means ± SD and as a percentage for categorial parameters. Differences between groups were compared with a *t*-test. Statistical significance was set at $p < 0.05$.

38.3 Results

38.3.1 Study Population

From January 2010 to October 2010, a 111 consecutive patients with confirmed diagnosis of sarcoidosis were screened by transthoracic echocardiography (TTE) as presented in Fig. 38.1. Of these 111 patients, 20.7% (23/111) showed elevated PAPsyst ≥30 mmHg (+ estimated CVP) and dyspnea or a PAPsyst ≥ 50 mmHg (+ estimated CVP) without dyspnea. Ten patients underwent RHC. In 13 patients, RHC was not performed due to the following reasons: declined participation (n = 2), LVEF <50% in TTE (n = 3), evidence for diastolic dysfunction ≥ II° (n = 5), severe mitral insufficiency III°-IV° (n = 3). The patients' characteristics and differences between suspected PH and no PH are presented in Table 38.1.

38.3.2 Prevalence of Precapillary and Postcapillary PH

PAH was observed in four patients, one patient had a postcapillary PH, in five patients PH/PAH could be excluded. None of the four patients was vasoreactive to inhaled iloprost. The clinical and hemodynamic

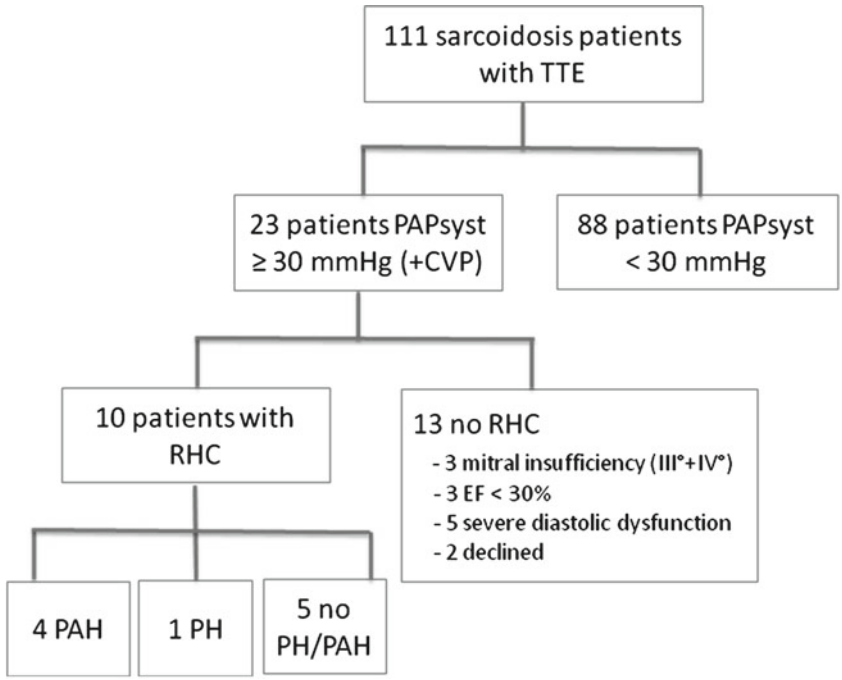

Fig. 38.1 Patient recruitment and results

Table 38.1 Baseline characteristics of all patients, patients with no suspicion of pulmonary hypertension (PH) and patients with suspicion of PH

	All sarcoidosis patients (n = 111)	No suspicion of PH in TTE (n = 88)	Suspicion of PH in TTE (n = 23)	*t*-test[a] suspicion *vs.* no suspicion
Age (year)	52.2 ± 14.9	49.8 ± 13.9	61.4 ± 15.3	**p = 0.001**
Sex (m/f)	65/56	40/48	15/8	p = 0.093
PAPsys (TTE) (mmHg)	24.3 ± 9.6	20.7 ± 1.4	39.5 ± 12.0	**p < 0.001**
s-IL2-R (pg/ml)	694.0 ± 301.3	660.2 ± 277.6	822.4 ± 357.3	**p = 0.027**
ACE (units/l)	39.1 ± 23.6	41.3 ± 24.2	30.5 ± 19.3	p = 0.059
EF (%)	63.4 ± 10.5	63.8 ± 8.7	62.3 ± 15.8	p = 0.541
$TLCO_{SB}$ (%)	72.2 ± 19.3	73.8 ± 17.6	66.3 ± 24.1	p = 0.205

ACE Angiotensin converting enzyme, *EF* left ventricular ejection fracture, PAP_{sys} systolic pulmonary arterial pressure, *sL2-R* soluble interleukin-2 receptor, $TLCO_{SB}$ transfer factor for carbon monoxide in single breath technique in percent of estimated, *TTE* transthoracic echocardiography

[a]Significant associations are printed in bold

profiles of the four patients with precapillary PAH are displayed in Table 38.2. Further diagnostic workup according to clinical guidelines (Galiè et al. 2009), including chest CT-scan, ventilation-perfusion-scan, sleep apnea screening, ultrasound of the liver and laboratory testing, did not reveal any further reasons for PAH. Thus, prevalence of precapillary PH was 3.6% (4/111) sarcoidosis patients.

It is evident that patients with sarcoidosis-PH have a chronic course and a progressive pulmonary involvement of the lungs with an advanced radiologic stage and a reduced lung function with impairment of TLCO.

Table 38.2 Characteristics of the four patients with precapillary pulmonary hypertension

PAH patient	1	2	3	4
Age (year)	60	73	59	73
Duration of sarcoidosis (year)	18	15	8	14
PAP_{syst} (mmHg)	68	80	30	40
PAP_{mean} (mmHg)	49	49	27	25
PAP_{diast} (mmHg)	30	34	22	17
RAP (mmHg)	12	9	10	8
PCWP (mmHg)	14	12	12	13
PVR (dyn sec cm^{-5})	667	1,233	250	209
TPG (mmHg)	35	37	15	12
CI (l/min)	2.2	1.3	2.4	2.4
CO (l/min)	4.2	2.4	4.8	4,6
6MWT (m)	420	300	450	480
$TLCO_{SB}$ (%)	13	49	66	41
Radiological stage	IV	III	III	III
s-IL2-R (pg/ml)	1,675	1,076	368	832

6MWT six minute walk test, *diast* diastolic, *CI* cardiac index, *CO* cardiac output, *PAP* pulmonary arterial pressure, *PCWP* pulmonary capillary wedge pressure, *PVR* pulmonary vascular resistance, *RAP* right arterial pressure, *s-IL2-R* soluble interleukin-2 receptor, *syst* systolic, $TLCO_{SB}$ transfer factor for carbon monoxide in single breat technique as percent of estimated, *TPG* transpulmonary gradient (PAP_{mean} *minus* PCWP)

38.4 Discussion

This is the first study prospectively investigating a large cohort of patients with sarcoidosis for the prevalence and possible causative factors of sarcoidosis-associated PAH. The detected prevalence for precapillary PH was 3.6% (4/111) and therefore dramatically exceeds the prevalence of PAH in the general population of 15–50 per million adult population (Galiè et al. 2009; Humbert et al. 2006).

The prevalence for sarcoidosis-associated PH in TTE was 20.7% (23/11). This epidemiological data lets us conclude that sarcoidosis itself is a trigger for the development of precapillary PAH in predisposed patients, analogous to connective tissue disease, HIV, or portal hypertension. The predisposing factors for precapillary PH in our study are: older age, longer duration of the disease, and advanced lung involvement with impairment of TLCO. However, according to other sarcoidosis phenotypes (Pabst et al. 2010), probably also genetic susceptible factors are at play.

The prevalence of 3.6% sarcoidosis-associated precapillary PH reported in the present study is not very high comparing this data to other studies, where sarcoidosis-associated PH has been found in up to 50% of all sarcoidosis patients (Sulica et al. 2005; Handa et al. 2006; Nunes et al. 2006, 14. Baughman 2007; Baughman et al. 2007; Preston et al. 2001). But it should be noted that (postcapillary) PH and (precapillary) PAH associated with sarcoidosis are different entities and in most studies no RHC was used to asses hemodynamics invasively. Therefore, the strength of our study is the prospective design and the invasive measurement of hemodynamics in most patients with suspicion of PH in TTE. We were able to distinguish between precapillary and postcapillary PH in sarcoidosis patients. Perhaps we also would have found a higher prevalence of a precapillary PH, had two patients not declined participating in the study. Furthermore, because not all sarcoidosis patients regardless of PAPsyst measured in TTE were investigated by RHC, we do not know how many false negative TTE results we had.

The pathophysiology of PH related to sarcoidosis seems to be complex, with multiple mechanisms contributing to its pathogenesis (Corte et al. 2011). Possible triggers for developing sarcoidosis-associated PH are destruction of the pulmonary vascular bed due to lung fibrosis, extrinsic compression of pulmonary vessels caused by lymphadenopathy, or pulmonary veno-occlusive disease (PVOD) (Nunes et al. 2006). We can only assume which are the causes for sarcoidosis-associated precapillary PH in our cohort, especially as PVOD only can be assured *post mortem*. Regarding the advanced radiographic stages with fibrosis but no hilar lymphoma in three of the four patients in our study with precapillary PH, we think that in our cohort the obliteration of the vascular bed by parenchymal fibrosis is the most possible factor. This finding is in accordance to others (Nunes et al. 2006), although cases of sarcoidosis-associated PH without lung fibrosis also are described (Shorr et al. 2005).

Treatment regimens were not assessed in our study. Therefore, the question how best to treat patients with sarcoidosis-associated PH remains unresolved. Although information on specific PAH treatment or clinical outcome would be of interest, it would necessitate a controlled, prospective study analyzing clinical end-points with specific PAH treatment and would require a follow-up period of several years and the recruitment of a large patient cohort. Several case series describe a benefit of treatment with intravenous epoprostenol (Fisher et al. 2006), inhaled nitric oxide (NO) (Preston et al. 2001), and the endothelin receptor antagonist bosentan (Foley and Metersky 2008; Sharma et al. 2005; Pitsiou et al. 2009). Also, the phosphodiesterase-5-inhibitor sildenafil is improving hemodynamics and the clinical outcome (Milman et al. 2008; Barnett et al. 2009). However, even under specific therapy the patients with sarcoidosis-associated PH have a high mortality.

In conclusion, this study provides evidence that precapillary PH/PAH is a rare but underestimated co-morbidity in sarcoidosis patients. Careful screening in patients with sarcoidosis should be warranted, especially when the patients report dyspnoea. In cases of doubt, always a RHC should be performed to measure hemodynamics invasively.

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Chapter 39
Cutaneous Changes: An Initial Manifestation of Pulmonary Wegener's Granulomatosis

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Abstract Cutaneous vasculitis can occur as an isolated dermatologic disorder or as manifestation of a potentially life-threatening systemic vasculitis such as Wegener's granulomatosis (WG). The aim of the study was to characterize cutaneous lesions in 66 WG patients (30 female, 36 male) and to assess the viability of skin biopsy the diagnosis of WG. Skin involvement was observed in 21 (32%) WG patients; in 14 (21%) patients as an initial manifestation and in other seven during the diagnosis establishment. Cutaneous lesions included palpable purpura (n = 10), subcutaneous nodules (n = 4), hemorrhagic bullae (n = 3), ulcers (n = 2), pustules (n = 1), pyoderma gangrenosum (n = 1). The patient with pulmonary WG can present initially with cutaneous symptoms and positive PR3-ANCA serologic test results. Leukocytoclastic vasculitis (LCV) was the predominant histopathologic pattern.

Keywords Wegener's granulomatosis • Pyoderma gangrenosum • Skin biopsy • Cutaneous vasculitis • Leukocytoclastic vasculitis

39.1 Introduction

Cutaneous vasculitis can be found in a diverse group of primary and secondary systemic vasculitis and it presents as a mosaic of clinical and histological findings due to varied pathogenic mechanisms. These entities do not correlate precisely with any constellation of morphological signs (Carlson and Chen 2006). In combination other symptoms, laboratory and histopathologic findings, the presence of cutaneous vasculitis can help not miss the clinical diagnosis. Wegener's granulomatosis (WG) is a multi-system PR3-ANCA vasculitis characterized by a necrotizing disease of different organs. WG most commonly involves the upper, lower respiratory tract, and kidneys, but may affect any organ system (Brons et al. 2001). Skin lesions occur in 15–50% of patients and are a presenting sign in 10% of them. Cutaneous manifestations of this disease are non-specific. Lesions often take the form of papulonecrotic changes distributed symmetrically over the elbows, knees, and sometimes the buttocks (Carlson et al. 2005).

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Skin involvement includes subcutaneous nodules, palpable purpura, hemorrhagic bullae, pustules, papules, macules, vesicles, petechiae, pigmentary changes, and ulcerating lesions (pyoderma gangrenosum) (Kuchel and Lee 2003). A definitive diagnosis requires a histological confirmation. A histopathologic interpretation pointing to vasculitis is dependent on the type of biopsy, the age of the cutaneous lesion sampled, and the experience of a pathologist. The most common skin lesion specific for WG is palpable purpura and histopathologic correlates of leukocytoclastic vasculitis (LCV). The aim of the present study was to characterize cutaneous lesions in WG patients and to assess the viability of skin biopsy for the diagnosis WG.

39.2 Methods

The study was approved by a local Ethics Committee. Sixty six patients, 30 females and 36 males, the mean age 65.6 ± 3.5SD years, from the Primary Systemic Vasculitis Outpatients Clinic Czerniakowski Hospital in Warsaw, Poland, with biopsy-proven WG were recruited for the study between January 2003 and December 2009. All patients fulfilled the American College of Rheumatology criteria for the classification of WG and the Chapel Hill Consensus Conference definition of WG. Disease activity was confirmed by clinical scoring, laboratory variables, and typical imaging procedures (CT of the nasal cavity, sinuses, and lungs). The DEI and BVAS indexes were used to measure organ involvement and disease activity. Furthermore, collected data included the age at the onset of skin symptoms, actual skin symptoms, history of skin biopsy, dermatoscopic examination, phototherapy, and the local and systemic immunosuppressive treatment. Patients with skin involvement underwent skin biopsy (n = 15) during an active phase of the disease. All biopsies were taken from active lesions, legs (n = 9), arms (n = 4), abdomen (n = 2), torso (n = 1), buttocks (n = 1), and lips (n = 1) and stained according to the protocol outlined below. After local anesthesia with lignocaine, a 3–4 mm punch biopsy was obtained from a skin lesion within 48 h of its development. Chronic skin changes, lasting for more than 48 h, observed in six patients, were not biopsied. All biopsies were snap frozen in liquid nitrogen and stored at −80°C until further use. Light microscopy was performed in hematoxylin–eosin stained and paraffin embedded sections.

39.3 Results

Cutaneous lesions included palpable purpura (n = 10), subcutaneous nodules (n = 4), hemorrhagic bullae (n = 3), ulcers (n = 2), pustules (n = 1), and pyoderma gangrenosum (n = 1). The time from the onset of a skin lesion to systemic manifestations of the disease ranged from 5 to 32 days. Eighteen patients had positive findings for PR3-ANCA and 3 for MPO-ANCA. Light microscopic examination showed leukocytoclastic vasculitis in nine patients, granulomatous inflammations with nodule in three patients, non-specific inflammation in two cases, and mucosal vasculitis in one patient. Skin involvement and biopsy results are presented in Table 39.1. Fibrin deposits were observed in all cases. Typical active vasculitis was observed in 11 patients: angiocentric and angioinvasive inflammatory infiltrates, disruption and destruction of a vessel wall by inflammatory infiltrates, and intramural or/intraluminar fibrin deposits of fibrin (fibrinoid necrosis), and nuclear dust (leukocytoclasia) and endothelial swelling, suggestive of vasculitis. There also were signs of red blood cell extravasation (petechiae, purpura, hematoma), necrosis, or infarction. We observed chronic signs of vasculitis in 4 patients: lamination (onion-skinning) of vessel wall constituents (concentric proliferations of pericytes and smooth muscle cells), luminal obliteration, segmental or complete loss of elastic lamina in medium vessels associated with acellular scar tissue and reactive angioendotheliomatosis.

Table 39.1 Skin involvement and cutaneous histopathologic findings in Wegener's granulomatosis

Case	Cutaneous lesions	Location of cutaneous lesions	Cutaneous histopathologic findings
1	Palpable purpura	Legs, abdomen	Bullous LCV
2	Subcutaneous nodules	Upper and lower extremities	Granulomatous vasculitis
3	Pyoderma gangrenosum	Legs	Mucosal vasculitis and granulomatous inflammation
4	Palpable purpura	Torso, abdomen	Non-specific vasculitis
5	Ulceration	Buttocks	Bullous LCV
6	Subcutaneous nodules	Upper extremities, buttocks	LCV
7	Hemorrhagic bullae	Manus	LCV
8	Ulceration	Lips	LCV
9	Hemorrhagic bullae	Left foot	Non-specific
10	Subcutaneous nodules	Lower extremities	Granulomatous vasculitis
11	Palpable purpura	Ankles	LCV
12	Palpable purpura	Ankles, elbows	LCV
13	Subcutaneous nodules	Upper and lower extremities	Granulomatous vasculitis
14	Palpable purpura	Ancles	LCV
15	Palpable purpura	Upper and lower extremities	LCV

LCV leukocytoclastic vasculitis

39.4 Discussion

Skin involvement due to primary and secondary vasculitis presents as a mosaic of clinical and histological findings. The triggers for cutaneous vasculitis often are the following: infections, chronic inflammatory disease, carcinomas, immunodeficiency states, vaccines drug exposure, silica, solvents and petroleum products exposure, allergies or PR3-ANCA synthesis. The interval between the onset of cutaneous symptoms and signs of systemic disease can vary from days to months, the mean is 6 months (Crowson et al. 2003; Carlson et al. 2006). Three patterns of disease occur in cutaneous vasculitis:

- single acute, self-limited episode (resolved in <6 months), typically associated with a drug or infectious factor (60% cases);
- relapsing disease with symptom-free periods usually found in patient with Henoch- Schönlein purpura (HSP) or connective tissue disease (CTD) (20% cases);
- chronic, unremitting disease often associated with cryoglobulinemia and malignancy (20% cases).

Physical signs of vasculitis include urticaria, palpable purpura, purpuric papules, infiltrated erythema, ulceration, infarct, livedo reticularis, pustules, and papules that affect the skin with varying intensity, depth, range, and distribution. Palpable purpura may be the first clinical sign of WG vasculitis in a patient at risk for life-threatening diffuse alveolar hemorrhage (DAH), rapidly progressive glomerulonephritis (RPGN), and nervous system involvement (Rosthak and Pittelkow 2008).

The type of clinical lesion and of pathologic assessment has a great impact on the diagnostic area of cutaneous biopsies. The essential factor, however, is the timing of a skin biopsy. If it is performed over more than 48–72 h after the since skin lesion had appeared, the pathological features of vasculitis may be lost (Comfere et al. 2007). A punch biopsy of a lesion will enable histological confirmation of most small vessel vasculitides. Purpuric lesions acquired in the first 24 h are characterized by fibrin deposits and neutrophilic infiltration of the wall. After 24 h, neutrophils are replaced by lymphocytes and macrophages. Biopsy of lesions older than 48 h may show lymphocyte-rich infiltrates.

Biopsies should be taken from non-ulcerated sites or from the edge of an ulcer. Histopathologic interpretation for vasculitis also depends on prior local and systemic treatment and pathologist experience (Gupta et al. 2009).

Active WG vasculitis is typically associated with an acute phase response C-reactive protein and PR3-ANCA titers. However, the presence of ANCA is not diagnostic of systemic vasculitis, as up to 60–70% of patients with cutaneous leukocytoclastic have positive PR3-ANCA tests (Gibson et al. 2003; Csernok and Gross 2000).

A distinction between cutaneous (localized) *vs.* systemic vasculitis is the most crucial point in predicting the patient's outcome; the mortality rate varies from 4 to 40%, respectively. A biopsy confirmation of cutaneous vasculitis is crucial for the diagnosis and separating true vasculitis from its mimics. The majority of cutaneous vasculitis cases will present as leukocytoclastic vasculitis (neutrophilic small vessel vasculitis), rarely as lymphocytic vasculitis or as chronic vessel damage in the form of endarteritis obliterans. Our study demonstrates that patients with Wegener's granulomatosis can present initially with cutaneous symptoms of palpable purpura and leukocytoclastic vasculitis as the predominant histopathologic hallmarks.

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

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Chapter 40
Posturography in Differential Diagnosis of Normal Pressure Hydrocephalus and Brain Atrophy

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Abstract Differentiation between normal pressure hydrocephalus (NPH) and brain atrophy is difficult in clinical practice. The purpose of this paper was to apply two advanced statistical, pattern recognition methods: discriminant analysis (DA) and k-nearest neighbour (K-NN) for the classification of NPH and atrophy patients to approach computer aided differential diagnosis. The classification is based on a few measures of the center of foot pressure (COP) movements (radius, area, and length). The posturography method gives a measure of current postural stability by a quantitative evaluation of postural sways. Measurements have been performed in the standing upright position in two conditions: with eyes open (EO) and closed (EC). The study comprises 18 patients (mean age 64 ± 13 years) diagnosed as normal pressure hydrocephalus and qualifying for shunt implantation. The patients were evaluated by static posturography twice: before and after surgery. The NPH patients were compared with 36 atrophy patients (mean age 64 ± 13 years) and 47 healthy persons (mean age 60 ± 7 years). There were two basic dissimilarities in the NPH patients before surgery in comparison with the other groups: very large sways and their independence from vision. Over 90% of the NPH cases both before and after surgery were correctly classified. There also were over 90% of correctly classified patients if we compared the before surgery NPH and atrophy patients. Further posturographic measurements and data collection are needed to verify these results.

Keywords Hydrocephalus • Atrophy • Body balance • Posturography • Pattern recognition • Discriminant analysis

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40.1 Introduction

Differentiation between the processes of normal pressure hydrocephalus (NPH) and brain atrophy encounters great difficulties in clinical practice (Tans 1979; Galia et al. 2005). The consequences of the wrong diagnosis can be quite serious and cause a steady search for new non-invasive or minimally-invasive methods to ascertain the true diagnosis.

The most important, but of limited success, method is by far an infusion test (Czernicki et al. 1984; Sliwka et al. 1984; Czosnyka et al. 1988). The test consists of the measurement of cerebrospinal intracranial fluid pressure with simultaneous infusion of physiological saline in L4 and S1 region. The presence of ventriculomegaly is essential, but not a prerequisite, for the positive test result indicating NPH. Another non-invasive method of differential diagnosis of NPH and brain atrophy is a morphometric evaluation of CT images. The method allows determining the volume and distribution of cerebrospinal fluid in intracranial spaces (Jurkiewicz 1996). The appearance of the Hakim triad of symptoms (Hakim and Adams 1965) is considered complementary, but has an already established value, similarly to neuropsychological elements related to dementia, accompanying both NPH and brain atrophy patients (Iddon et al. 1999) and being quite similar to those in Alzheimer's disease.

The evaluation of gait, a third element in the Hakim triad, relates to postural stability in the upright standing position. Gait disturbances, characteristic of NPH, consisting of a shuffling manner of walking, moving with a dragging, scraping step without raising the feet are with high probability relevant to the overall lack of stability while standing. The measurement of center of foot pressure (COP) movements has become a quantitative evaluation of postural sways and thus posturography can be treated as a measure of stability and the current state of the balance system. It should be mentioned that enlarged sways are not specific. Postural balance can be impaired in individuals with numerous pathologies, including vestibular and cerebellar disorders, ataxia (Mohan et al. 2009), Parkinsonism (Bloem et al. 1995; Jagielski et al. 2006), alcohol dependence (Wöber et al. 1998), multiple sclerosis (Kessler et al. 2011), or normal pressure hydrocephalus (Szczepek et al. 2008; Czerwosz et al. 2008, 2009). Postural balance also may be distorted in muscle fatigue and in old age in otherwise healthy people (Blaszczyk and Michalski 2006). Posturographic measurements can change day-to-day. Correct performance of a balance test is difficult in itself, it needs maximum stillness of a patient for eliminating any external stimuli abstracting patients and provoking involuntary moves toward sound or light sources. The elimination of such interferers is particularly important in advanced NPH patients.

The purpose of the present study was an attempt to differentiate normal pressure hydrocephalus and brain atrophy by means of advanced computer aided statistical approaches: discriminant analysis (DA) and k- nearest neighbour method (K-NN) of the pattern recognition theory; both based on posturographic tests in the standing position with eyes open and closed.

40.2 Methods

40.2.1 Patients

The study was performed in conformity with the Declaration of Helsinki (1989) for Human Experimentation and the protocol was approved by a local Ethics Committee.

Eighteen patients (mean age 64 ± 13, range 32–82 years) diagnosed as normal pressure hydrocephalus were qualified for shunt implantation with the following inclusion criteria: (i) ventriculomegaly seen on CT or MR – Evans' ratio above 0.3 (Evans 1942), (ii) neurological symptoms (Hakim triad–minimum two of three symptoms), (iii) mean intracranial pressure above 10 cmH_2O, and (iv) resorption resistance R ≥11 mmHg/ml/min. In all cases posture imbalance and severe

impairment of gait was observed. Posturographic tests were performed before shunt implantation and early, within 7 days, after the surgery. The patients formed two groups/classes: NPH BEFORE and NPH AFTER.

The ATROPHY group has been formed from 36 patients (mean age 64 ± 13, range 32–82 years) with the following inclusion criteria: (i) ventriculomegaly seen on CT or MR (Evans' ratio above 0.3), (ii) both subcortical and cortical atrophy, (iii) no characteristic neurological symptoms, (iv) mean intracranial pressure below 10 cmH_2O, and (v) resorption resistance R <11 mmHg/ml/min. Balance disturbances and some impairment of gait were observed in all cases in this group as well. The CONTROL group consisted of 47 healthy volunteers (mean age 60 ± 7, range 50–59 years).

40.2.2 Statistical Analysis

Two advanced statistical methods were used in the current paper: discriminant analysis (DA) and k- nearest neighbour method (K-NN) (Devijver and Kittler 1982; Duda et al. 2001). DA calculations were performed using a statistical package for the social sciences (IBM SPSS Statistics). A computer program made by Adam Jóźwik was used for K-NN calculations (Sokolowska et al. 2009; Jozwik et al. 2011).

40.2.2.1 Statistical Classes and Sets of Classes

The results of posturographic measurements obtained in the classes investigated: NPH BEFORE, NPH AFTER, ATROPHY, and CONTROL were classified into two combinations:

1. NPH BEFORE – NPH AFTER,
2. NPH BEFORE – ATROPHY – CONTROL.

The first set allows distinguishing posturographic outcomes measured in the NPH patients in two states: before surgery and after shunt implantation. The latter set allows comparing two usually difficult to identify brain diseases: NPH and atrophy. It was additionally possible, using both statistical methods, to classify all cases from NPH AFTER group to one of the three groups: NPH BEFORE, ATROPHY, and CONTROL. This classification was performed in accordance with the classification rule obtained from the training phase.

40.2.2.2 Features

Posturografic measurements were performed in the standing upright position in two conditions: eyes open (EO) and closed (EC). There are three kinds of measures that can be calculated for each posturographic trajectory:

- R, average center of foot pressure (COP) sway radius,
- A, area of developed surface of COP trajectory,
- L, length of COP trajectory.

We tested several optional sets of features both with DA and K-NN methods. A set of features represents a case in the classification procedure. Six raw parameters – outcomes of EO and EC measurements constituted a basic set of features assigned to every case.

- Radiuses measured with eyes open and closed: R_{EO} and R_{EC},
- Areas measured with eyes open and closed: A_{EO} and A_{EC}
- Lengths measured with eyes open and closed: L_{EO} and L_{EC}.

Subsequently sums EO+EC and differences EC-EO; according to formulas (40.1) and (40.2) below were calculated. The primary alternative set of six features contained:

$$\text{Sums: } SR = R_{EC} + R_{EO} \quad SA = A_{EC} + A_{EO} \quad SL = L_{EC} + L_{EO} \tag{40.1}$$

$$\text{Differences: } DR = R_{EC} - R_{EO} \quad DA = A_{EC} - A_{EO} \quad DL = L_{EC} - L_{EO} \tag{40.2}$$

Then, the vision indices related to Radius, Area, and Length of sways were calculated accordingly to formulas (40.3):

$$IR = DR / SR * 100\% \quad IA = DA / SA * 100\% \quad IL = DL / SL * 100\% \tag{40.3}$$

Indices are non-dimensional and are expressed as per cent. The secondary alternative set of six features contained vision indices together with adequate sums. Thus, the parameters analyzed made three sets of features as follows:

1. R_{EC}, R_{EO}, A_{EC}, A_{EO}, L_{EC}, L_{EO} – six EO&EC features**.**
2. DR, DA, DL, SR, SA, SL – six D&S features**.**
3. IR, IA, IL, SR, SA, SL – six I&S features**.**

A detail list of various combinations of features was given below in the results section. Usually, we force-entered into the analysis a whole previously planned set of features, but an automatic selection of features was also allowed in stepwise procedures.

40.2.2.3 Comparison of Classifications

A percentage value showing the level of correctly classified cases was the most important result of each analysis for both classification methods: DA and K-NN. This percentage was calculated on the basis of the number of cases correctly classified to each of groups/classes knowing the true group affiliation of all cases. In both methods, there were training and classification phases. Each case was in sequence temporarily removed from the analysis, then the other cases were used for training of the classifier, and then the removed case was classified on the basis of the training. The percentage of correctly classified cases gives the efficiency of dichotomization, i.e., the distinction of classes. It also determines distances between classes. The percentage depends on the efficiency of the classification algorithm, but the upper limit of this efficiency does exist, within some assumed sets of features. Within some frames, the classification cannot be better, independently of the classification method. The level of classification relates only to the differences in classes, but not to classification quality. Our goal was to approach this level as closely as possible, but one could never be sure if any other algorithm which emerged would not have done better.

40.3 Results

40.3.1 Raw Posturographic Parameters – EO&EC Features

Figure 40.1 presents raw values of average sway radiuses measured in the EO and EC conditions in the study groups. Group differences were easily observable: the NPH patients before surgery (NPH BEFORE) had the largest sways, with both EO and EC. Both parameters exhibited large and uncorrelated variability; the radiuses R_{EC} and R_{EO} did not correlate. The control group (CONTROL) exhibited much smaller radiuses of sways, with both EO and EC and the radiuses R_{EC} and R_{EO} did

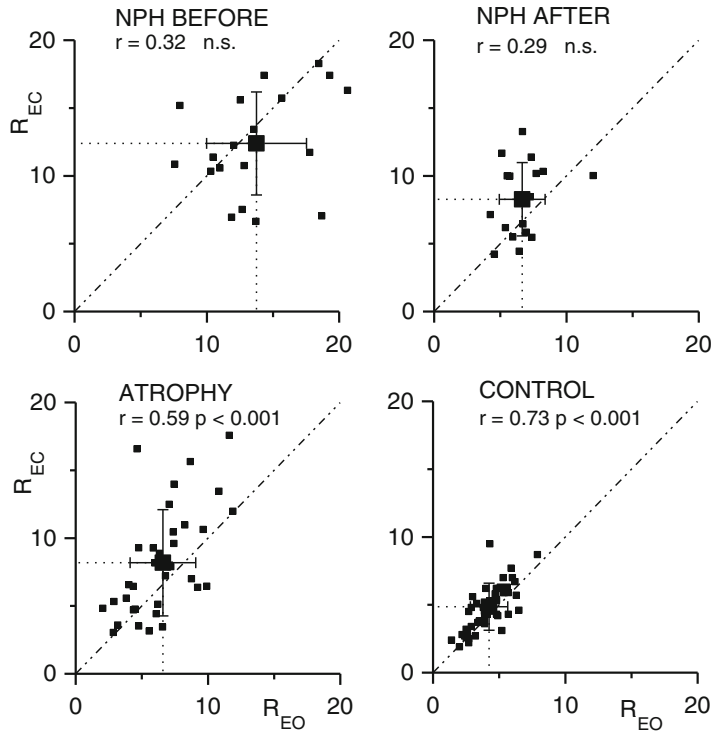

Fig. 40.1 Raw data taken from four groups: NPH BEFORE, ATROPHY, CONTROL, and NPH AFTER. Only two variables – the sway radiuses are presented on each scattergram: R_{EC} *vs.* R_{EO}. Centroids of each group are shown – the *crosses* represent means ± SD of R_{EC} and R_{EO} in each group. Bisector of the *right angle* is shown in each scattergram to *emphasize* that most of the points are located above the line

Table 40.1 Means ± SD of raw parameters: R_{EC}, R_{EO}, A_{EC}, A_{EO}, L_{EC} and L_{EO} in the investigated groups

Parameter \ Group	NPH BEFORE	ATROPHY	CONTROL	NPH AFTER
R_{EO} [mm]	13.8 ± 3.8	6.6 ± 2.5	4.2 ± 1.4	6.7 ± 1.7
R_{EC} [mm]	12.4 ± 3.8	8.2 ± 3.9	4.8 ± 1.7	8.3 ± 2.7
A_{EO} [cm^2]	50.2 ± 32.7	17.9 ± 26.5	4.3 ± 3.2	12.1 ± 5.5
A_{EC} [cm^2]	45.3 ± 28.7	34.5 ± 56.2	7.2 ± 7.2	25.4 ± 24.9
L_{EO} [mm]	1124 ± 551	735 ± 734	296 ± 140	586 ± 235
L_{EC} [mm]	1127 ± 541	1074 ± 1024	233 ± 279	842 ± 546

correlate (r = 0.73), the correlation was here best in the groups compared. The brain atrophy (ATROPHY) and the NPH patients after surgical treatment (NPH AFTER) demonstrated a medium level of sways compared with those in the NPH BEFORE and CONTROL groups.

The sway radius measured with eyes closed, R_{EC}, was slightly bigger than that with eyes open, R_{EO}, in most persons in the ATROPHY, CONTROL, and NPH AFTER groups; the scattergram point laid above the bisector of the right angle ($R_{EC} = R_{EO}$). As already said, there was no such relation in the NPH BEFORE group.

These observations were confirmed through statistical calculations performed on every raw parameter: R_{EC}, R_{EO}, A_{EC}, A_{EO}, L_{EC}, and L_{EO}. The mean values are displayed in Table 40.1 for all the groups. Statistics related to comparison of the means and to comparison of EO and EC for sway Radius and Area have already been published elsewhere (Czerwosz et al. 2009).

The observations of raw data and statistical analysis indicate differences in postural stability between then groups investigated with eyes open or closed. The large magnitude of sways is the first basic dissimilarity between the NPH BEFORE and all the other groups.

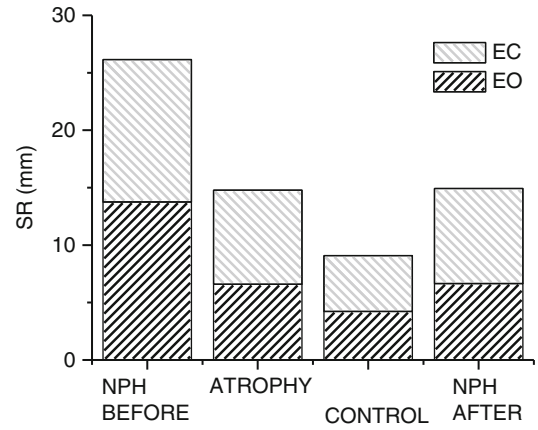

Fig. 40.2 The way of summing of results obtained with eyes open and closed accordingly to formula (40.1). Sway radius is shown as an example: $SR = R_{EC} + R_{EO}$

Table 40.2 Means ± SD of sums of radiuses SR, areas SA, and lengths SL calculating accordingly to formula (40.1) from components measured with EO and EC

Parameter \ Group	NPH BEFORE	ATROPHY	CONTROL	NPH AFTER
SR [mm]	26,1 ± 6.2	14.7 ± 5.7	9.1 ± 2.9	14.9 ± 3.6
SA [cm^2]	95.5 ± 47.6	52.4 ± 81.6	11.5 ± 97.0	37.5 ± 28.3
SL [mm]	2252 ± 968	1817 ± 1732	729 ± 402	1428 ± 740

40.3.2 Calculated Variables

Using the transmutation (formula 40.1 outlined above) we are getting the sums of R, A, and L variables. Figure 40.2 shows the mean values of the sums of the radiuses SR and their components R_{EC} and R_{EO} in the groups investigated. Table 40.2 gives the mean values of the sums of: Radiuses – SR, Areas – SA, and Lengths – SL in all the groups.

Differences in sway radiuses (DR) obtained with EO and EC in the groups investigated are shown in Fig. 40.3a. The differences in Areas (DA) and Lengths (DL) came out analogously; all these data are detailed in Table 40.3. These differences should be considered as zero values in the NPH BEFORE group because of the large scatter of individual results. In the other groups, the differences were significant ($p < 0.05$). The differences in DR are equal in the ATROPHY and NPH AFTER groups and they are two-times bigger than those in the CONTROL group.

Vision indices related to the radius of sways (IR) in the groups investigated are shown in Fig. 40.3b, and those related to Area (IA) and Lengths (IL) came out analogously; all these data are detailed in Table 40.4. The values of vision indices of Radius, Area, and Length, similarly to the differences above detailed, should be considered as zero in NPH BEFORE in contrast to the other groups. The average values of respective indices are statistically equal in the ATROPHY, CONTROL, and NPH AFTER groups. Vision indices, but also simple differences between raw EC and EO data, indicate a second basic dissimilarity of the NPH BEFORE group from the other groups, in particularly from the NPH AFTER group.

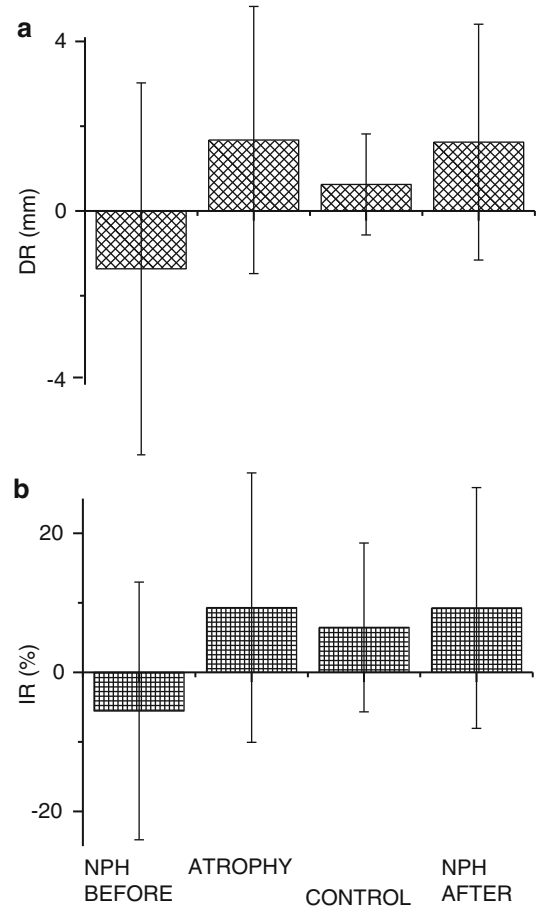

Fig. 40.3 **(a) Average differences (DR) of sway radiuses** calculated according to formula (40.2) in four groups; **(b) average vision indices (IR) of radiuses** calculated according to formula (40.3). *Vertical bars* are SD

Table 40.3 Sway radiuses DR, areas DA, and lengths DL differences between EC and EO conditions

Parameter \ Group	NPH BEFORE	ATROPHY	CONTROL	NPH AFTER
DR [mm]	−1.4 ± 4.4	1.7 ± 3.2*	0.6 ± 1.2*	1.6 ± 2.8*
DA [cm^2]	−5.0 ± 39.0	16.5 ± 33.4*	3.2 ± 5.6*	13.3 ± 22.4*
DL [mm]	4 ± 508	330 ± 469*	137 ± 182*	257 ± 401*

*Denotes that a quantity of a difference significantly differs from zero ($p < 0.05$)

Table 40.4 Sway radiuses IR, areas IA, and lengths IL vision indices

Parameter \ Group	NPH BEFORE	ATROPHY	CONTROL	NPH AFTER
IR [%]	−5.5 ± 18.5	9.3 ± 19.4*	6.5 ± 12.1*	9.3 ± 17.3*
IA [%]	−4.1 ± 34.1	22.1 ± 28.2*	19.8 ± 23.5*	15.6 ± 37.7*
IL [%]	−0.0 ± 10.7	16.3 ± 15.3*	15.5 ± 13.4*	13.3 ± 16.1*

*Denotes that an index significantly differs from zero ($p < 0.05$)

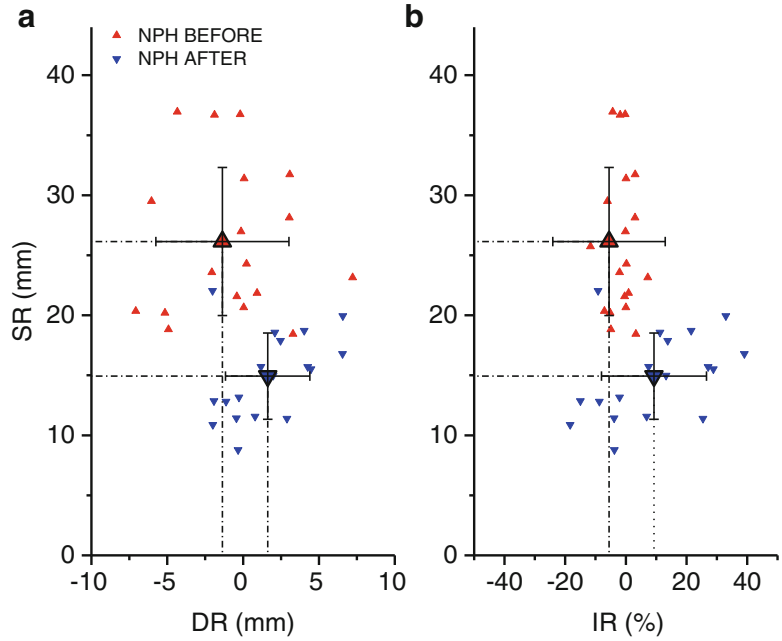

Fig. 40.4 Scattergrams presenting all cases in two groups: NPH BEFORE and NPH AFTER in **(a)** the SR *vs.* DR coordination system and **(b)** the SR *vs.* IR system. Centroids of the groups are shown

40.3.3 Scattergrams in SR vs. DR and SR vs. IR Coordination Systems

The analysis outlined above tackled only single features, but it allowed us to make a statement that there were significant differences in the postural stability between:

- NPH patients before and after surgery treatment.
- NPH and atrophy patients.

Further analysis shows that a more effective way of differentiation consists of taking into account two variables simultaneously. Figure 40.4a shows individual values of differences (DR) and sums (SR) of the sway radiuses for all cases in the NPH BEFORE and NPH AFTER groups in the SR *vs.* DR coordination system, whereas individual values of the vision indices (IR) and sums (SR) for the same groups in the SR *vs.* IR coordination system are shown in Fig. 40.4b. Centroids of the groups are shown on both scattergrams.

Figure 40.5, on the other hand, shows three groups: NPH BEFORE, ATROPHY, and CONTROL in the same coordination systems. The panels indicate that it was possible to separate patients from the NPH BEFORE and ATROPHY groups, but ATROPHY cases were intermingled with the CONTROL ones.

40.3.4 Classification of NPH BEFORE and NPH AFTER Groups

In the initial analysis, all features R_{EC}, R_{EO}, A_{EC}, A_{EO}, L_{EC}, L_{EO}, SR, SA, SL, DR, DA, DL, IR, IA, IL were subjected to one-feature classification. Table 40.5 shows features used for the classification (F) and DA and K-NN classification results as percent of correctly classified cases.

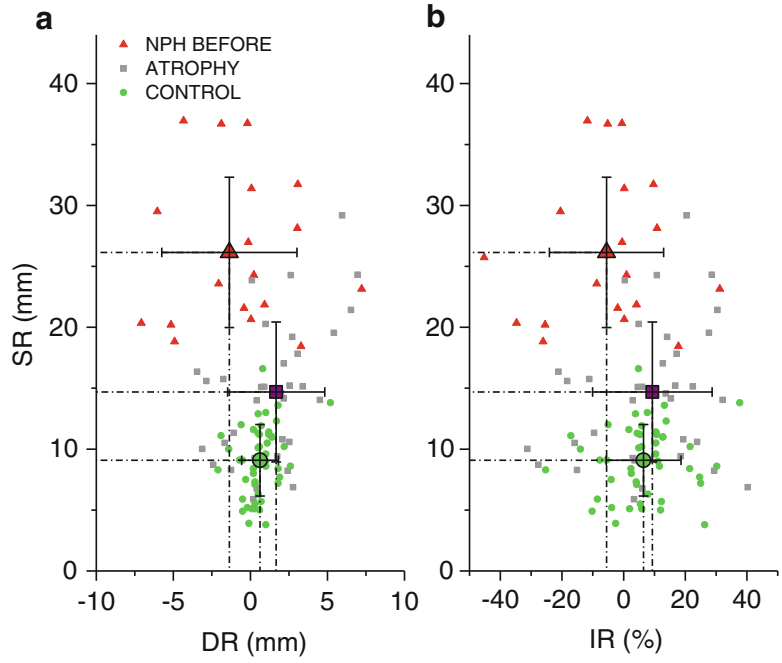

Fig. 40.5 Scattergrams presenting all cases in three groups: NPH BEFORE, ATROPHY, and CONTROL in **(a)** the SR *vs.* DR coordination system and **(b)** the SR *vs.* IR (Index Radius) coordination system. Centroids of three groups are shown

Table 40.5 Comparison of 15 DA classifications of NPH BEFORE and NPH AFTER groups/classes and 15 K-NN classifications

F	P-DA	P-KNN	F	P-DA	P-KNN	F	P-DA	P-KNN
R_{EO}	91.9%	91.9%	A_{EO}	86.5%	83.8%	L_{EO}	70.3%	73.0%
R_{EC}	78.4%	78.4%	A_{EC}	64.9%	70.3%	L_{EC}	67.6%	73.0%
SR	86.5%	89.2%	SA	75.7%	78.4%	SL	75.7%	75.7%
DR	67.6%	73.0%	DA	51.4%	75.7%	DL	48.6%	73.0%
IR	67.6%	67.6%	IA	64.9%	64.9%	IL	59.5%	62.2%

All features have been used separately. Portions of correctly classified cases as a percentage of all grouped cases are presented as P-DA – percentage obtained in DA, and as P-KNN – percentage obtained in K-NN method. F means feature

The sway radius with EO (R_{EO}) showed the best separation power. With only one feature applied to DA or K-NN classifier, both methods gave an almost equal result; they both classified correctly 91.9% cases, when R_{EO} was used. The features related to Area emerged to be a little bit worse (A_{EO}: 86.5%) and those related to Length were much worse. Classification power of vision indices was rather poor; the best was the radius vision index: 67.6%.

Table 40.6 contains the outcomes of two-class and two-feature classification. Features were entered into the analysis in pairs: (EO and EC) or (sum and difference) or (sum and index). The features related to Radius, Area, and Length were paired separately. The best results were obtained when applying features related to Radius – 91.9% in DA and even 94.6% in KNN. It is worth noting that there was no difference in the classification level among pairs (R_{EC}, R_{EO}), (SR, DR) and (SR, IR). The efficacy of DA classification was almost the same as that of K-NN.

We also performed a multi-feature analysis by K-NN method. A six-feature classification with all features forced to enter the analysis resulted in 89.2% of correctly classified cases, but the same set of

Table 40.6 Comparison of nine DA classifications of NPH BEFORE and NPH AFTER groups/classes and nine K-NN classifications

F1	F2	P-DA	P-KNN	F1	F2	P-DA	P-KNN	F1	F2	P-DA	P-KNN
R_{EO}	R_{EC}	91.9%	94.6%	A_{EO}	A_{EC}	83.8%	83.8%	L_{EO}	L_{EC}	73.0%	73.0%
SR	DR	91.9%	91.9%	SA	DA	83.8%	78.4%	SL	DL	73.0%	72.7%
SR	IR	91.9%	91.9%	SA	IA	86.5%	83.8%	SL	IL	73.0%	70.3%

Two-features sets used with forced inclusion into the analysis. Portions of well classified cases as a percentage of all grouped cases presented as P-DA – percentage obtained in DA, and as P-KNN – percentage obtained in K-NN method. F1 and F2 mean a priori selected features

Table 40.7 Comparison of nine classifications of NPH BEFORE, ATROPHY and CONTROL classes by means of DA and K-NN

F1	F2	P-DA	P-KNN	F1	F2	P-DA	P-KNN	F1	F2	P-DA	P-KNN
R_{EO}	R_{EC}	75.5%	75.5%	A_{EO}	A_{EC}	67.6%	72.5%	L_{EO}	L_{EC}	67.6%	71.6%
SR	DR	75.5%	76.5%	SA	DA	67.6%	73.5%	SL	DL.	67.6%	74.4%
SR	IR	73.5%	74.5%	SA	IA	67.6%	66.7%	SL	IL	64.7%	73.5%

Two-features sets used with forced inclusion into the analysis. Portions of well classified cases as a percentage of all grouped cases presented as P-DA – percentage obtained in DA, and as P-KNN – percentage obtained in K-NN method. F1 and F2 mean a priori selected features

features after selection yielded 94.6%; the selected features were SR and IA. Therefore, there are many ways to distinguish the NPH BEFORE and NPH AFTER groups efficiently and there are many feature sets giving similar results.

40.3.5 Three-Group Classification of NPH BEFORE, ATROPHY, and CONTROL

Three-group classification (NPH BEFORE, ATROPHY, and CONTROL) using single features did not give satisfactory results with either DA or K-NN method. The best result concerned A_{EO} and was 77.4% of correctly classified cases; a rather mediocre score (data not shown).

It is worth noting that the SR feature enabled to classify properly a 100% of cases from NPH BEFORE and CONTROL groups in the two-group K-NN sub-classifications that were performed as part of the three-group parallel classification procedure. Differentiation between the NPH BEFORE – ATROPHY or ATROPHY – CONTROL groups was worse. Table 40.7 shows the outcomes of the three-class and two-feature classifications. Features were entered into the analysis in pairs: (EO and EC) or (sum and difference) or (sum and index) as outlined above for the two-class analysis. Again, there was no difference between the classification level among pairs (R_{EC}, R_{EO}), (SR, DR), and (SR, IR). DA classification was almost the same as K-NN.

Six-feature analyses were performed using three sets of features. These results are given in Table 40.8. The table rows marked 'All' contain the results of all (six) features forced into the analysis. The rows marked 'Sel DA' contain DA classification results and those marked 'Sel KNN' contain KNN classification results; both with a feature selection which was different in each method.

Forced entering of 15 features into the analysis ended up with a good performance; DA – 78.4% and KNN – 79.4% of correct classification. Stepwise DA correctly classified 80.4% of cases when R_{EO} and L_{EC} were selected from among 15 features the result similar to that with a six-feature selection (Table 40.8). The K-NN method with feature selection classified correctly 85.3% of cases and eight features were selected as valid: R_{EO}, R_{EC}, L_{EO}, DR, DA, DL, IA, and SR, which however makes the interpretation difficult.

Table 40.8 Comparison of DA and K-NN multi-feature classifications

	F1	F2	F3	F4	F5	F6	P-DA	P-KNN
All	R_{EO}	R_{EC}	A_{EO}	A_{EC}	L_{EO}	L_{EC}	78.4%	73.5%
Sel DA	R_{EO}	–	–	–	–	L_{EC}	80.4%	–
Sel KNN	R_{EO}	R_{EC}	A_{EO}	A_{EC}	L_{EO}	–	–	82.3%
All	SR	DR	SA	DA	SL	DL	78.4%	74.5%
Sel DA	SR	DR	–	–	–	–	75.5%	–
Sel KNN	SR	DR	–	DA	SL	–	–	81.4%
All	SR	IR	SA	IA	SL	IL	79.4%	73.5%
Sel DA	SR	IR	–	–	–	–	73.5%	–
Sel KNN	SR	–	–	IA	SL	–	–	79.4%

Features were grouped in three sets. Basically all features have been forced to enter the analysis (rows with "All", DA and K-NN results are in the same row). Selection of features was allowed – the results are in separate rows with "DA Sel" or "KNN Sel" – selected features are listed with percentage of cases correctly classified

Parallel sub-classifications demonstrated the following:

- 100% for NPH BEFORE and CONTROL with the selection of only one feature – SR;
- 94.6% for NPH BEFORE and ATROPHY with the selection of three features: R_{EO}, DA and DL; this is evidence for the existence of a difference in the body balance between NPH and brain atrophy patients; the difference embedded in sway amplitude and the responses recorded with eyes open or closed;
- 85.3% for ATROPHY and CONTROL with the selection of four features: R_{EC}, L_{EC}, DR and IA. Here, the brain atrophy results were close to the control ones.

40.3.6 Classification of NPH AFTER Cases Into One of the Groups: NPH BEFORE, ATROPHY, or CONTROL

Table 40.9 shows the results of classification of NPH AFTER cases (true class) by a standard (not parallel) K-NN classifier with leave one method. Each object was assigned to only one of the three classes: NPH BEFORE, ATROPHY, and CONTROL. Before performing the classification, the algorithm was trained during six-feature, three-class analysis. IR, SR, and SL features were selected from IR, IA, IL, SR, SA, and SL during training and used for the classification. The results were lucid, all cases after surgery were classified as ATROPHY or CONTROL cases and none was classified as NPH BEFORE case.

40.4 Discussion

In this study we attempted to find the best features distinguishing patients with normal pressure hydrocephalus and brain atrophy. We addressed the issue by using advanced statistical algorithms consisting of discriminant analysis (DA) and k- nearest neighbour method (K-NN) of the pattern recognition theory. The major result of the analyses performed was that both methods gave similar results for most of the classifications. This was rather a surprise, knowing that the methods differ substantially. DA is

Table 40.9 Results of classification by standard (not parallel) K-NN classifier with leave one method

		Voting		
Case	Assigned to	NPH BEFORE	ATROPHY	CONTROL
1	ATROPHY	5	7	2
2	ATROPHY	1	12	1
3	ATROPHY	2	8	4
4	ATROPHY	3	9	2
5	CONTROL	0	5	9
6	CONTROL	0	3	11
7	CONTROL	0	6	8
8	CONTROL	0	1	13
9	ATROPHY	1	10	3
10	ATROPHY	2	10	2
11	ATROPHY	2	10	2
12	CONTROL	0	2	12
13	ATROPHY	1	11	2
14	CONTROL	2	5	7
15	CONTROL	0	3	11
16	CONTROL	1	6	7
17	CONTROL	0	6	8
18	ATROPHY	1	8	5

Features used in classification: IR, SR, and SL

a parametric method closely related to a linear combination of features, represented by ANOVA and the analysis of variance. A fundamental assumption of the method is that independent variables have to be normally distributed which, if violated, makes the DA outcome not reliable. By contrast, the K-NN method does not rely on the normality of distribution. The close results we obtained in this study using both methods indicate that these results may be judged solid. From the other side, however, the number of NPH cases we had was rather low for making stable classifiers which could be applied in future computerized NPH diagnostic paradigms.

The hypothesis that we set forward that the two groups: NPH BEFORE and NPH AFTER would be identical may be rejected on the basis of standard tests only. In current study, both DA and K-NN showed the possibility of classifying of 91.9% of cases using only a single feature – the sway radius measured with open eyes: R_{EO}. The efficiency of DA or K-NN classifiers is not improved after adding a second feature: R_{EO}.

One-feature classifications with the use of vision indices were rather poor. The best was IR – 67.6% (DA and K-NN). In classical statistics, IR showed a difference between NPH BEFORE and NPH AFTER; for a paired *t*-test $p < 0.007$, for a non-parametric Wilcoxon test $p < 0.008$. It should be noted that in these two groups there were the same NPH patients at two stages: before and after surgery. The same groups were compared by a non-paired *t*-test ($p < 0.017$), but a non-parametric Kolmogorov-Smirnov test for independent groups demonstrated no significance.

One can note the equal efficiency of pairs of features: (R_{EO} and R_{EC}), (SR and DR), and (SR and IR) were concerning both NPH BEFORE–NPH AFTER (Table 40.6) and NPH BEFORE–ATROPHY–CONTROL (Table 40.7) classifications. This means that there is the same information included within each pair of features. In fact, the pairs are related to each other by simple transmutations: addition, subtraction, and normalization. One can relate this to the similarity of topologies of both panels in Figs. 40.4 and 40.5. The pairs of Areas and Lengths are analogously equivalent to each other.

40.5 Conclusions

- The classification methods allow distinguishing NPH and Atrophy patients with high accuracy – over 90% of correctly classified cases.
- NPH patients after surgery differ from the state before surgery – over 90% of correctly classified cases.
- There are many equivalent combinations of features giving similar results of classification.
- Further posturographic measurements and data collection is needed to enlarge the groups and check if our results would be stable.

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Chapter 41
Psychological Background of Pro-health Behavior

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Abstract In this study, psychological conditions of pro-health lifestyle behavior have been analyzed. A first research group consisted of 88 healthy people (44 males, 44 females) aged 19–39. Psychological analysis showed a positive correlation between the internal locus of control and adherence to healthy diets; a correlation extending to the knowledge about healthy food. Social exclusion appeared to reduce the possibility of reaping new knowledge about healthy diets and was negatively correlated with the tendency of using healthy diet or dietary supplements. A second group consisted of 70 women aged 20–65. The subjects in this group were oriented towards using a diet which reduces body mass; pro-health both physical and psychological objectives other than body mass reduction were secondary in this study. General self-esteem and physical self-esteem were found to be positively correlated with the involvement in physical activities and satisfaction from dietary intervention. These outcomes were negatively correlated with body mass. The study shows that the efficiency of prevention is related to the locus of control, self-efficacy expectation, faith in the result, and self-esteem. The information about the interconnections among these variables may be useful in building preventive behavioral programs.

Keywords Diet • Health prevention • Locus of control • Self-esteem • Social exclusion

41.1 Introduction

Pro-health behavior consists of conscious activities undertaken by a human being in order to increase the potential of their health and to minimize the risk of illness development. In preventive practice this means the behavior that allows avoiding the development of a degenerative disease (including cardiovascular system diseases, nervous system diseases, cancer, and others) by means of minimizing the negative influence of an array of genes and the environmental impact. Such activities include

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Table 41.1 Prognosis for incidence of diseases for the next decade in Europe and the whole world (WHO-Global Forum for Health, Geneva, 2010)

	1990	2020
Coronary heart diseases[a]	3.4	5.9
Perinatal complications[a]	6.7	5.7
Psychiatric disorders[a]	3.7	5.7
Cerebrovascular diseases[a]	2.8	4.4
Tuberculosis	2.8	3.1
Lower respiratory tract infections	8.2	3.1
Gastrointestinal diseases	7.2	2.7

Numbers are in DALY (disability-adjusted life year) which is a measure of overall disease burden, expressed as the number of years lost due to ill-health, disability, or early death

[a]Diseases associated with diet – in particular with dietary fat intake

both taking care of your body (proper nutrition, physical activity) and of your emotional well-being (mental tension monitoring).

The return in preventive medicine to mutual interactions between the 'body and mind' aspects has been reflected in the present definition of human health provided by WHO which reads as follows: 'It is not only the lack of illness or disability, but also the condition of a full physical, mental, and social well-being' (http://www.who.int/en/). The definition emphasizes the mutual relations between emotional and physical condition and social functioning. An appropriate lifestyle, diet, and physical activity, thinking and coping with emotions, especially with emotional burdens which we take up every day, are stressed by WHO to be essential in preserving health. The Global Health Forum in Geneva in 2010 discussed the prognoses for the incidence of diseases for the next decade in Europe and the whole world (http://www.ghf10.org/). The specialists predict that the first place will be taken by degenerative diseases connected with the cardiovascular system and mental illnesses (Table 41.1). The results of the latest research verifying the evolutionary diet/tissue hypothesis point out that susceptibility to the majority of contemporary non-communicable diseases has a common source, first of all, in improper diets (De Meester 2009; Wilczynska et al. 2010, 2011).

The objective of the present study was to test to what extent psychological and social conditions influence the acquisition of knowledge about essential eating habits and its active inclusion in human pro-health programs.

41.2 Mental Tension Monitoring

In the field of the recommended pro-health activities, the researchers emphasize the importance of the type of behavior-related to psycho-social functioning, such as receiving and providing social support, minimizing the stress influence and effective coping with situations causing tension. One of the methods recognized in the past decade by the research team of the Center of Chronobiology in Minneapolis, which is used to diagnose the influence of psycho-social phenomena on our health, is the examination of the variability of vascular rhythms enabling the measurement of a 24 h tension affecting a person during a weeks-long time (circaseptan). This diagnostic procedure shows a body strain connected with the environmental factors and its possible role in the development of degenerative diseases (Halberg et al. 2003).

In a yearlong chrono-psychological follow-up study carried out under supervision of the Halberg Chronobiological Center of the University of Minnesota, Minneapolis, it was demonstrated that

psychological (self-assessment of stressful situation and the coping with stress) and psychosomatic data are compatible with strain detected through a continuous 7/24 h blood pressure monitoring (Wilczynska et al. 2010).

41.3 Diet Being the Source of Health

Proper nutrition keeps a human being in physical and mental fitness. Despite the inevitability of aging, there is more and more evidence that a proper diet constitutes one of the key determinants to maintain health and prolong human life. According to the Columbus Concept (De Meester 2009), returning to the original balanced (1:1) ratio of polyunsaturated fatty acids (PUFAs) and to a corresponding 25% proportion of ω6 highly unsaturated fatty acids (HUFAs) in serum total lipids (ω6:ω3 PUFAs = 1:1 and %ω6 in HUFAs = 25) can possibly reduce the risk of developing chronic degenerative diseases to zero at the population level.

The literature presents the results of the world clinical research which show that the diet has a direct influence on brain functioning, emotional, and cognitive aspects of human activity, and general psychosomatic conditions (De Lorgeril and Salen 2000; Vaddadi 2006). Increased intake of refined grains and fast foods is associated with lower intake of ω3 fatty acids, leading to a sequence in the emergence of chronic diseases of affluence: obesity, diabetes, metabolic syndrome, heart attack, and bone and joint diseases (Kartikey et al. 2010).

Studies on the evolutionary aspects of diet clearly show that human beings evolved on a diet that was balanced in the omega-6 and the omega-3 fatty acids (ω6:ω3 PUFAs ~ 1:1) (Simopoulos 2001). The Lyon Heart Study was the first clinical intervention trial that paid attention to the ratio of omega-6 to omega-3 fatty acids and had a dietary ratio of omega-6:omega-3 of 4:1 for the secondary prevention of coronary heart disease (CHD). The results were very impressive because over a 2-year period, there was a 70% decrease in mortality from CHD and there were no sudden deaths (De Lorgeril and Salen 2000).

Omega-3 long PUFAs are implicated in the development of several human conditions and diseases, including dementia, schizophrenia, and depression (Horrobin et al. 2002). Omega-3 treatment of these diseases shows positive effects (Freeman 2000; Hakkarainen et al. 2004; Silvers et al. 2005; Stoll et al. 1999).

41.4 Pro-health Behavior Conditions

Undertaking pro-health activities to maintain health and prevent degenerative disease is related to the qualities of a person embarking on a healthy lifestyle. The present study focuses on the identification of psychological social determinants related to dieting. Nowadays, application of proper nutrition is connected with a cognitive effort aiming at the selection of a proper diet satisfying a person's need for necessary nutrients. Food industry takes advantage of the possibility of advertising in the media in order to maximize their profits from sales of various products. Thus, selection of a proper way of nutrition out of many diets offered on the market requires from an average individual certain knowledge and directional motivation to gain such knowledge, which is linked with an array of psychological features of a human being.

One of the psychological constructs conditioning the effective and consistent efforts to achieve a certain goal is the notion of a sense of self-efficacy developed in psychology by Bandura (1977). The author defines the sense of self-efficacy as the assessment of one's own capabilities to organize and realize sets of activities aiming at the pre-set goal. Furthermore, faith or the expectation of certain

results also is single out as another essential factor in achieving one's goals. The expectations of self-efficacy and pre-set results may influence the undertaking of pro-health activities. Bandura (1986) suggested that self-efficacy should not be limited to a generalized means, as it is a dynamic property changing from task to task. Many other researchers following this path have also avoided the definition of a generalized sense of self-efficacy (GSE, General Self-Efficacy), perceiving it as inaccurate, in contrast to the specific, situation-based measurements of specific self-efficacy in the precise areas of life (SSE, Specific Self-Efficacy) (Eden and Aviram 1993). The authors suggested that in order to examine human efficacy in particular areas one should apply the scales which include statements relating to this specific field. Caplan et al. (1989), e.g., created a scale of the sense of self-efficacy in the situation of searching for a job, while Gist et al. (1989) conducted measurements of the sense of self-efficacy in the scope of knowledge and skills of computer operation, especially with reference to a specific computer application.

A factor deemed to be significant in undertaking conscious and target-oriented activities is 'the sense of locus of control' (LOC), which plays a decisive role in a decision-making process based either on acquired knowledge or on verified experience (Balch and Ross 1975).

People with an external locus of control are more susceptible to persuasion, especially when the information comes from the source of a subjectively estimated high prestige. People with an internal locus of control are guided more by the accuracy of the information content than by the source prestige. An important feature that differentiates people with an external and internal locus of control is the way of searching for information. In comparison with the people who believe that a chance or coincidence, or other people's intervention influences the course of events, people who perceive the events being under their control are prone to search for information in a more active personal way. More extensive knowledge of a given subject enables people with an internal locus of control to control the situation in a fuller way. The research conducted by Seeman and Evans (1962) gives a good example. They found that patients with an internal LOC wanted to know more and in fact knew more about the condition of their health as well as made contact with the hospital personnel more often than patients with an external LOC, which positively influenced the former's health condition.

In the context of undertaking pro-health activities, it is self-assessment that also plays a significant role. Self-assessment has been defined as 'an individual's affective response to oneself'. Self-assessment can be treated as a relatively permanent quality of a person, or as a condition and motivation of a person. Self-assessment is described in three chief dimensions: height – high self-assessment is displayed by a person who thinks about himself positively; clarity – people having a high self-esteem are usually convinced of the rightness of this belief, in contrast to people having a low self-esteem who are not sure what they are like and cannot take an explicit attitude towards themselves; constancy in time – influencing a particular person's behavior in a considerable way (Wojciszke 2004). It is worth mentioning that a high self-assessment correlates positively with both the clarity of self-assessment and its constancy in time. Hence, a person having a positive opinion about him is certain of this belief and such beliefs are relatively permanent. What is more, self-assessment influences considerably the functioning of an individual in many areas of their life. It includes task-related, emotional, and social spheres.

41.5 Research Problems

The research consisted of two parts. The first part of the tests included participants who did not apply any specific diets. The subjects in this group represented the population of young adults, aged 19–39 (average age of 28 years). In total, 88 people were examined (44 men, 44 women), among which 40 people met the criteria of being exposed to social exclusion (long-term unemployment). The main

Table 41.2 Assessment of body mass

BMI	No. of persons	Percent
<18.5	4	5.7
18.5–24.9	47	67.0
25.0–29.9	13	18.6
>30.0	6	8.6

objective set in this part of the study was to determine if in a group of young people there any preventive methods were used to counteract the possibility of a development of degenerative diseases. The issue of an interest also was to determine to what extent the factors connected with an array of psychological traits affect the decision to undertake pro-health activities. We also were interested whether social factors, such as exposure to social exclusion, could be of any significance to pro-health activity.

The second part of the tests included 70 women aged 20–65 (average age 34 years). The analysis of these subjects' body mass (Table 41.2) revealed that there were 23 women whose body mass could be judged as improper; 4 were underweight, 13 who were overweight, and 6 women were obese. The ratio of body mass to height in the remaining women was correct.

The following research questions were raised:

1. What are the motives of diet searching and its application in a given group?
2. Is there any relationship between self-efficacy, self-assessment, and satisfaction from the effects of the diet applied?
3. Is there a difference between the professionally active group and a group with a risk of social exclusion?

41.6 Research Tools

The study was in conformity with the Declaration of Helsinki of 1989 for Human Experimentation of the World Medical Association and was approved by a local ethics Committee.

We used the Delta Questionnaire developed by Drwal (1979) to test the locus of control, perceived as a personality dimension. This questionnaire relates to general beliefs about the possibility of controlling one's own fate in daily situations. To examine 'self-efficacy expectation' we used a questionnaire developed for the purposes of this research, measuring individuals' knowledge and conviction about one's own abilities to apply it in the scope of dieting. The subjects were asked if they were going to have a status Omega-6 test done in the nearest future, on the basis of blood sampled from a finger, to determine a risk of the development of a degenerative disease. Moreover, the subjects were asked if they would declare to implement a proper diet supporting the prevention of the development of civilization diseases.

In the second part of the study, we used the Questionnaire of Self-Assessment (Bargiel-Matusiewicz et al. 2010) and the authors' original survey including questions concerning age, height, weight, a subjective assessment of body mass, motivation to take up a diet, efficacy of the applied diets, and physical activity. The questionnaire allows determining the level of self-assessment in the subjects in four domains: – physical properties (Physical Self), emotional properties (Emotional Self), interpersonal properties (Social Self), and properties revealed in action (Target-Oriented Self). Reliability of the scale measured by α-Cronbach coefficient equals 0.87.

Pearson's correlation was used to assess associations between the variables studied. Statistical elaboration was conducted with the use of a commercial SPSS statistical package.

41.7 Results and Discussion

We found no significant relation between the LOC control and the declaration of undergoing a preventive test of a risk of developing civilization diseases ($r=-0.03$, $p=0.77$). However, a significant relationship was found between LOC and the declaration of applying a proper diet ($r=-0.52$, $p<0.01$), meaning that the lower the LOC score, the more often the subjects declared a diet application. A similar significant correlation was revealed between LOC and the sense of specific self-efficacy/gained knowledge ($r=-0.53$, $p<0.01$). Also, the association between knowledge (self-efficacy expectation) and faith (result expectation) was significant ($r=0.88$, $p<0.01$). Similar correlations were identified between searching for the knowledge of healthy nutrition and the declaration to apply a proper diet (or its supplements) ($r=0.85$, $p<0.01$).

No significant correlation was found between the social exclusion and the declaration to undergo a preventive test of a risk of developing civilization diseases ($r=0.11$, $p=0.30$). However, social exclusion was associated with a smaller knowledge of healthy nutrition ($r=-0.43$, $p<0.01$) and the lack of readiness to apply a certain diet ($r=-0.54$, $p<0.01$). The dependence between particular variables was presented in Fig. 41.1.

The first stage of this study was to determine if young adults who do not show any clinically diagnosed symptoms of a generative disease would be interested in undertaking pro-health activities. To this end, we examined the factors related to the socio-economic status of the subjects and their individual characteristics, such as the locus of control, specific self-efficacy expectation, and faith in the expected result. The results revealed promising relations between the sense of specific self-efficacy, faith in the expected result of a diet, and the internal LOC. This outcome is in accord with other studies which have found that the internal LOC is a significant factor in a pro-health decision-making process (Cardarelli et al. 2007; Wu et al. 2004). We found, however, that the internal locus of control was not straight connected with making a decision to undergo a preventive test of a risk of developing degenerative disease. The subjects who declared applying a pro-health diet were often uninterested in its influence on human health. We interpreted this outcome as the fear of receiving information about the risk of falling ill or the apprehension of revealing that the applied diet was improper.

The results highlighted the knowledge gap between the group of people exposed to social exclusion and the group of working people. This outcome provides alarming information about an unequal access to the data resources (such as the Internet, educational meetings, etc.) pointing out to the need of equal pro-health education in the whole society.

In the second part of the study conducted in a group of 70 women, it was found that the desired values of body mass differed from their actual values, on average, by 6.3 kg. A majority of the subjects

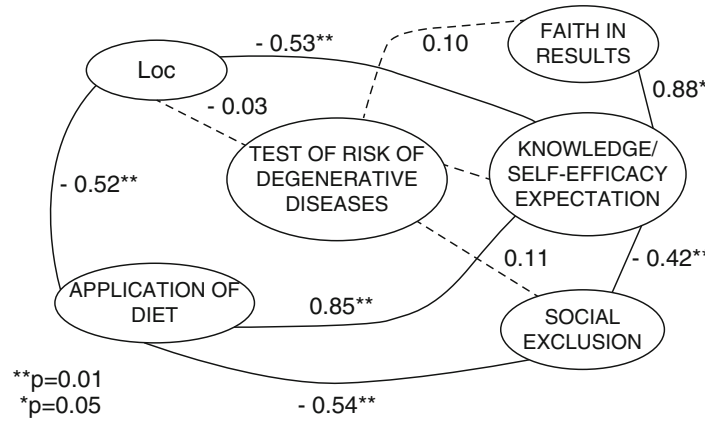

Fig. 41.1 Correlations between variables (Pearson's – *r*) in a group of persons who do not apply any diets

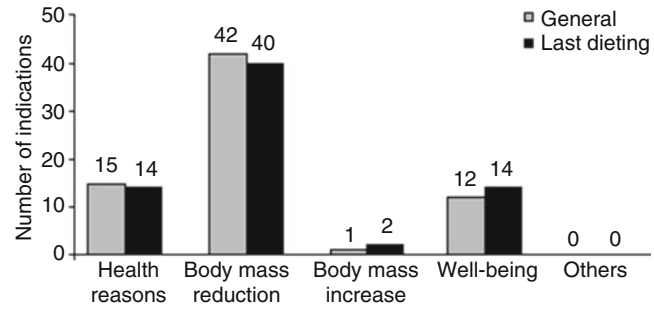

Fig. 41.2 Motivation for dieting; in general and during the last dieting episode

Table 41.3 Correlations between each variable of self-assessment and the achieved results of dieting, frequency of undertaking physical activity, and body mass (n = 70)

Variables	Positive effects of dieting	Physical activity	Body mass
General self-assessment	0.26*	0.25*	−0.25*
Physical self	0.29*	0.32**	−0.49**
Emotional self	0.17	0.05	−0.14
Target-oriented self	0.18	0.06	0.04
Social self	0.08	0.11	−0.12

*p < 0.05; **p < 0.01

declared the desire to reduce their body mass or to maintain it at a constant level, which was also the main motivation, aside from health issues and the desire to improve mod, to go on a diet. The results concerning the motivation of the subjects to apply diets are presented in Fig. 41.2. The need to reduce body mass by 1–5 kg was expressed by 40 women, by 5–15 kg by 23 women, and the remaining seven subjects wanted to lose more than 15 kg. After relating these values to BMI, it turned out that five women wanted to reduce their weight to the degree of being underweight. Only two women, who belonged to the underweight lot, expressed the wish to increase their weight by 5 kg.

The relationships between each variable of self-assessment and satisfaction from the effects of dieting, undertaking physical activity, and body mass are shown in Table 41.3. The domains of General Self-Assessment and Physical Self, which have to do with the evaluation of one's appearance and physical fitness, turned out the most important in this context. Both variables correlated positively with the results of dieting and undertaking physical activity while on a diet, and negatively with body mass. The inference is that increased body mass may contribute to decreased General Self-Assessment, particularly within the scope of Physical Self. Anyhow, it appears that positive self-assessment contributes to undertaking physical activity and increases satisfaction from the results of dieting.

As above mentioned, the prevailing motive for going on a diet was the desire for weight reduction. The subjects also declared the desire to improve their health and well-being. A study of O'Brien et al. (2007) provided generally similar results showing that the main aim of dieting was health (50%), appearance (35%), and frame of mind (15%) improvements. That study also showed that people who went on a diet to improve their health condition defined themselves as happier and had a higher self-assessment than those motivated to go on a diet due to other reasons. The lowest level of self-assessment was shown by people who went on a diet to improve their frame of mind. It should be noted that that study was conducted in a group of overweight people, so the majority of answers relating to health improvement could result from the fact that obesity is now considered as an illness (Tsigos et al. 2009). Our results also are in line with those of Jankauskiene and Kardelis (2005) who showed that the major motive of undertaking restrictive diets is the need to reduce body mass and increase the assessment of body image.

In the research presented, at the moment of examination, over half of the respondents expressed the need for dieting, but did not actually apply it, while 17% of the subjects were in the middle of dieting. It also turned out that 74% of the subjects assessed their weight as a little big or considerably too big. It is worth mentioning that only 27% of those feeling overweight had factual reasons for making such an assessment on the basis of their BMI. Wong and Huang (1999) and Strauss (1999) reported that even women whose BMI classifying them as underweight often declare their willingness to lose weight and over half of the subjects having a correct body mass see them as overweight or obese.

41.8 Conclusions

The study points to substantial inequality in accessibility to knowledge on healthy nutrition to the disadvantage of people socially excluded compared with professionally active ones. Such outcome reveals the need for a wider pro-health education in society. The results also show that the efficiency of health prophylaxis is connected with the locus of control, the sense of self-efficacy, faith in the expected result and self-assessment. The undertaking actual pro-health activities can be mostly expected in people with the internal locus of control. Psychological assessment should be taken into consideration in preventive program.

Conflicts of interest: No conflicts of interests were declared by the authors in relation to this article.

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Chapter 42
Cardiovascular Effects of the Valsalva Maneuver During Static Arm Exercise in Elite Power Lifting Athletes

Aleksandra Zebrowska, Zbigniew Gasior, and Dariusz Jastrzebski

Abstract The objective of the study was to investigate whether a blood pressure increase during static exercises might affect the left ventricular function and whether a possible pressure overload might decrease cardio-respiratory adaptation to aerobic exercise in power lifting athletes. Nine resistance-trained athletes and ten age-matched untrained men participated in high intensity isometric exercise performed during the Valsalva maneuver and in an incremental arm cranking test. All subjects underwent echocardiographic evaluation. The combine effect of exercise and increased intrathoracic pressure due to the Valsalva maneuver was a significant increase in systolic blood pressure in the athletes compared with controls. Echocardiography demonstrated significant differences in left ventricular mass and left ventricular mass index; both being higher in the athletes than in controls. The intraventricular septum diameter and left ventricular posterior wall thickness were significantly greater and the myocardial performance index was lower in the athletes compared with controls, indicating a better left ventricular function in the athletes. A cumulative effect of mechanical compression of peripheral blood vessels by contracting muscles and intrathoracic pressure increase during the Valsalva maneuver did not compromise myocardial contractility and cardiorespiratory adaptation to incremental arm exercise in power lifting athletes.

Keywords Left ventricular hypertrophy • Myocardial performance index • Respiration • Resistance training • Static exercise

42.1 Introduction

Morphological and functional cardiac changes in response to resistance training, such as weight or power lifting, may result in myocardial growth potentially associated with increased arterial pressure resulting from mechanical compression of peripheral vessels by contracting muscles (Wernstedt et al.

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2002; Khamis and Mayet 2008). Static arm exercise causes peripheral vasoconstriction induced by parallel activation of the arterial baroreflex and muscle mechanoreceptors. As a result, arterial blood pressure and left ventricular (LV) wall stress are increased (Secher and Volianitis 2006; Calbet et al. 2007; MacDougall et al. 1992). Pressure overload can also be induced voluntarily due to the elevation of intrathoracic pressure during the Valsalva maneuver (Lentini et al. 1993; MacDougall et al. 1985). The maneuver and high levels of muscle tension required to lift heavy weight may result in dramatic changes in physiological responses to resistance training. These mechanisms cause a greater rise in blood pressure compared with other exercises performed at equivalent oxygen uptake (Newcomer et al. 2004; Volianitis and Secher 2002). In athletes who rely heavily on the upper body musculature for sport performance with predominantly arm exercise, a significantly greater pressure overload of the heart may lead to concentric ventricular hypertrophy (Pelliccia et al. 1991; Gates et al. 2003).

Recent investigations suggest that athletes engaged in the same sport discipline for many years may develop different types of cardiac remodeling (Urhausen and Kindermann 1999; Fagard 2003; Rich and Havens 2004). Purely power-oriented training involves several repetitions of maximum muscle contractions and eccentric contractions with relatively long periods of recovery. Therefore, the peak blood pressure in response to the Valsalva maneuver persists for a short period during the training session (Haykowsky et al. 2001; Pelliccia et al. 1993). The results of Lentini et al. (1993) and Haykowsky et al. (2001) suggest that increased intravascular pressure during resistance exercise is secondary to intrathoracic pressure elevation associated with a brief Valsalva maneuver; pressure overload of the heart was lower than that predicted by the intravascular pressure alone. A potentially positive effect of the above mentioned heart-lung interactions during resistance exercise on left ventricular function might protect resistance-trained athletes against the risk of ventricular dysfunction (Haykowsky et al. 2002; MacDougall et al. 1985). Therefore, the objective of the present study was to investigate whether a rise in blood pressure during static exercises might have an effect on the left ventricular systolic and diastolic functions and whether pressure overload might indicate a decrease of cardiorespiratory adaptation to aerobic exercise in power lifting athletes.

42.2 Methods

42.2.1 Subjects

The study protocol was approved by the Ethics Committee of the Academy of Physical Education in Katowice, Poland and conforms to the standards set by the Declaration of Helsinki for Human Experimentation. The subjects were nine resistance-trained (RTr), power lifting athletes. Ten age-matched healthy, not specifically trained men, served as the control group. The athletes underwent medical evaluation at the beginning of the pre-season training, including clinical history, echocardiography, and physical examination. The experimental procedures and possible risks were explained to all participants verbally and in writing; the participants gave informed written consent. Age of participants and their anthropometric characteristics are displayed in Table 42.1.

42.2.2 Exercise Protocols

Maximal muscular strength was assessed as voluntary one-repetition maximum (1 RM). All subjects performed a set of 8–10 repetitions of an isometric exercise test (bench press) with weight 50–60% and 80% of 1 RM. The subjects then completed one repetition set of 90–100% of individual maximum intensity. Each set of isometric exercise was performed with a brief Valsalva maneuver. Heart rate (HR)

Table 42.1 Anthropometric variables in resistance-trained athletes and control subjects

	Athletes (n = 9)	Controls (n = 10)
Age (year)	23.0 ± 1.8	21.4 ± 0.5
Height (cm)	172 ± 5	177 ± 5
Weight (kg)	77 ± 5	72 ± 6
BMI (kg/cm^2)	26 ± 2	22 ± 1
Training status (year)	6 ± 2	0

Values are means ± SD

was continuously monitored using a PE-3000 Sport-Tester (Polar Inc., Finland). Systolic (SP) and diastolic blood pressures (DP) were measured before and within half a minute after exercise with a sphygmomanometer.

The participants' cardiopulmonary adaptation to exercise and aerobic efficiency was measured during an incremental arm cranking test (ergometer-based on a commercial device; Monark, Sweden). The test started at a power output of 30 W, with 15 W increments every 3 min until voluntary exhaustion. We analyzed the maximal power output (W_{max}), maximal oxygen uptake (VO_{2max}), ventilation threshold (V_ET) (Schneider et al. 1993) and oxygen deflection point (ODP) (Zoladz et al. 1998).

42.2.3 Echocardiography

M-mode and two-dimensional Doppler-echocardiography was performed in all subjects using a Hewlett-Packard Image Point HX ultrasound system equipped with standard imaging transducers. All echocardiographic analyses were carried out according to the guidelines of the American Society of Echocardiography (Sahn et al. 1978). The left ventricular (LV) systolic function based on left ventricular ejection fraction (LVEF), stroke volume (SV), peak velocities of early (E) and late (A) diastolic filling, the E/A ratio, deceleration time, isovolumic contraction time (IVCT), isovolumic relaxation time (IVRT), and ejection time (ET) were all determined. The Tei-Index, a combined myocardial performance index (isovolumic contraction time plus isovolumic relaxation time divided by ejection time) (myocardial performance index) was calculated by subtracting ejection time from the interval between cessation and onset of the mitral flow (Tei et al. 1997).

The left ventricular muscle mass (LVM) was derived according to Devereux and Reichek (1997). LVM = 1.04[(LVEDd + IVSDd + LVPWTd)^3-(LVEDd)^3]–13.6 g, where LVEDd is left ventricular end-diastolic internal diameter, IVSDd is interventricular septum diameter in diastole, and LVPWTd is left ventricular posterior wall thickness in diastole. The left ventricular mass index (LVMI) was calculated with a correction for body surface area. Left ventricular hypertrophy was identified when LVMI was equal to or greater than134 g/m^2 (Levy et al. 1997).

42.2.4 Statistical Evaluation

Data are presented as means ± SD. The echocardiographic data were analyzed with two-factor (group and exercise) repeated measures ANOVA followed by the Student-Newman-Keuls test when appropriate. Intergroup correlation coefficients were determined with Pearson's rank order test. All were performed using Statistica v. 7.1 software package (StatSoft, Tulsa, OK). Statistical significance was set at $p < 0.05$.

42.3 Results

The combined effect of high intensity isometric exercise and increased intrathoracic pressure due to the Valsalva maneuver increased SP significantly more in the RTr athletes than in the control subjects ($p<0.05$) (Table 42.2). The RTr athletes also demonstrated a significantly higher 1 RM and maximal power output during isometric exercise ($p<0.001$). Heart rate, particularly the resting heart rate, was lower in the athletes.

Echocardiography demonstrated significantly greater left ventricular mass, left ventricular mass index, intraventricular septum diameter in diastole ($p<0.001$ for all), and left ventricular posterior wall thickness in diastole ($p<0.01$) in the RTr athletes compared with the control subjects; pointing to cardiac hypertrophy, confirmed by an increase of hypertrophy index (IH) ($p<0.05$) (Table 42.3).

Resistance training had a significant effect on stroke volume (SV) and myocardial performance index (Tei-index) (Fig. 42.1a, b, respectively). The Tei-index was significantly lower in the athletes compared with the control subjects ($p<0.05$), indicating better LV systolic and diastolic functions.

Table 42.2 Responses to maximum isometric exercise in resistance-trained athletes and control subjects

	Athletes (n = 9)	Controls (n = 10)
RM (kg)	138 ± 16***	87 ± 13
HR_{rest} (beats/min)	66 ± 1*	71 ± 8
HR_{max} (beats/min)	161 ± 6	165 ± 8
SP_{rest} (mmHg)	118 ± 8	116 ± 7
DP_{rest} (mmHg)	70 ± 5	68 ± 4
SP_{max} (mmHg)	181 ± 4*	174 ± 12
DP_{max} (mmHg)	90 ± 7	92 ± 7

Vales are means ± SD.

RM-voluntary one-repetition maximum to measure muscle strength, *HR* heart rate, *SP & DP* systolic and diastolic pressures, respectively, and their resting levels and maximal levels in response to isometric exercise

*$p<0.05$; ***$p<0.001$ for differences between the two groups

Table 42.3 Echocardiographic variables in resistance-trained athletes and control subjects

	Athletes (n = 9)	Controls (n = 10)
LVM (g)	288 ± 17***	218 ± 25
LVMI (g/m^2)	148 ± 19***	107 ± 14
IVSDd (cm)	1.3 ± 0.2***	0.9 ± 0.2
LVPWTd (cm)	1.2 ± 0.2**	0.9 ± 0.1
LVEDd (mm)	53 ± 2	52 ± 2
IH	0.6 ± 0.1*	0.4 ± 0.1
LVEF%	62 ± 5	64 ± 4
E/A	1.7 ± 0.2	1.8 ± 0.3

Values are means ± SD

LVM left ventricular mass, *LVMI* left ventricular mass index, *IVSDd* interventricular septum diameter in diastole, *LVPWTd* left ventricular posterior wall thickness in diastole, *LVEDd* left ventricular end-diastolic internal diameter, *HI* hypertrophy index, *LVEF%* left ventricular ejection fraction, *E/A* ratio of peak velocities of early (E) and late (A) diastolic filling

*$p<0.05$; **$p<0.01$; ***$p<0.001$ for differences between the two groups

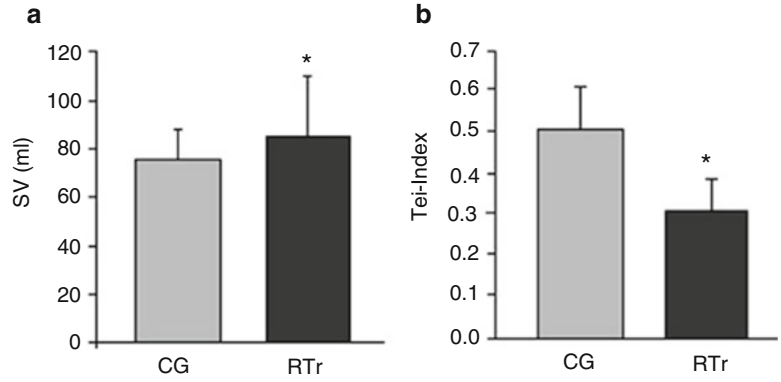

Fig. 42.1 **(a)** Stroke volume (SV) and **(b)** Myocardial performance index (Tei-index) in resistance-trained athletes and control untrained subjects; *p<0.05 the differences between the two groups

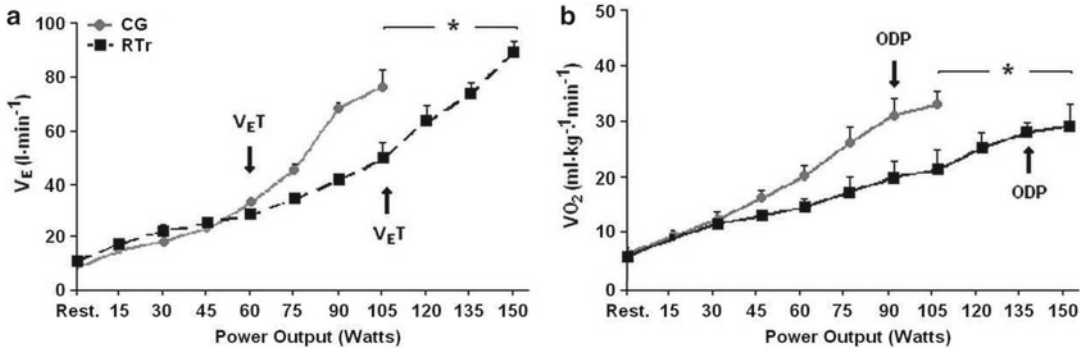

Fig. 42.2 **(a)** Pulmonary minute ventilation (V_E) and ventilation threshold (V_ET) and (**b**) Oxygen uptake (VO_2) and oxygen deflection point (ODP) in resistance-trained athletes and control untrained subjects; *p<0.05 the differences between the two groups

Compared with untrained subjects, the athletes had a significantly higher ventilation threshold (V_ET), implying a better tolerance to endurance arm exercise (Fig. 42.2a). We also found that oxygen deflection point (ODP) was higher in the RTr athletes compared with controls and it was achieved with a lower level of oxygen uptake ($p<0.05$) (Fig. 42.2b). We noted positive correlations between LVM and maximal power output during arm incremental exercise (W_{max}) ($r=0.5$; $p<0.05$) and between the hypertrophy index and W_{max} ($r=0.6$; $p<0.01$). We did not observe any significant influence of arterial blood pressure increase and post-exercise pressure overload on the echocardiographic variables either in the athletes or control subjects.

42.4 Discussion

Data concerning the effect of resistance training on LV systolic and diastolic functions are scarce. Most studies report the development of concentric cardiac hypertrophy without ventricular dysfunction or cavity reduction (Fagard et al. 1997; Pelliccia et al. 1993; Barauna et al. 2007; Gates et al. 2003). There are also reports showing no change in LV mass expressed per unit of body size (Haykowski et al. 2000; Urhausen and Kindermann 1999; Bell 2008). However, a rise in arterial blood pressure (300 mmHg), and wall stress associated with long-term strength training may increase the

threat of pathological heart hypertrophy, which is an established risk factor for heart failure (Williams et al. 2007; Crowley et al. 2006; Bertovic et al. 1999). The results of the present study demonstrate that LV hypertrophy in resistance-trained athletes was not associated with alterations in left ventricular systolic function. Moreover, the Tei-index, which incorporates elements of both systolic and diastolic phases in the assessment of global ventricular performance (Tei 1995; Libonati et al. 2001), was lower in the athletes than in control subjects.

The present study demonstrates significant differences in left ventricular mass (LVM), interventricular septum thickness, and left ventricular posterior wall thickness between resistance-trained athletes and untrained sedentary controls. Left ventricular mass index was equal to or greater than 134 g/m^2 and LVEDd was within the normal range for male subjects (Savage et al. 1987). Although all echocardiographic data were clearly suggestive of adaptive, i.e., physiological heart hypertrophy, a significant increase of the hypertrophy index might indicate concentric heart hypertrophy. These results are consistent with previous observations that static exercise may result in left ventricle enlargement, with a reduction of its internal dimension (Crowley et al. 2006; Fleck 1988). According to the literature (Colan 1992; Bertovic et al. 1999; MacDougall et al. 1985; Makan et al. 2005), a rise in arterial blood pressure during perfusion pressure decrease in exercising muscles contributes to the effects outlined above. Pressure overload during the Valsalva maneuver (forcible exhalation against the closed glottis) might also be contributory. The maneuver markedly elevates intrathoracic pressure and affects venous return, myocardial contractility, vasomotor tone, and baroreceptor heart rate control. The hemodynamic response to the Valsalva maneuver has four distinct phases: phase 1 – a rise in arterial pressure, phase 2 – a rapid decrease in arterial pressure and tachycardia, phase 3 – a reduction in arterial pressure upon the sudden termination of breath holding, and phase 4 – a brief overshoot in arterial pressure accompanied by a slowing of heart rate (Lu et al. 2001). Isometric effort considerably enhances a pressure load on the heart through combining the effects of vasoconstriction, increased cardiac output, and disproportionate SP and DP elevation associated with an increase in peripheral resistance.

The present study also revealed significant differences in systolic blood pressure between athletes and untrained subjects; however, no correlations were found between arterial pressure and LVM or LVMI. Moreover, comparable DP values obtained for all participants seem to confirm the hypothesis that left ventricular hypertrophy is not linked to changes in hemodynamics of the circulatory system. These observations are in agreement with those of Lentini et al. (1993) who have demonstrated that positive swings in intrathoracic pressure are transmitted directly to the arterial vasculature as an increase in systolic pressure; however, the pressure to which the heart is actually exposed is not elevated above the resting level.

Additionally, we used the Tei-index to assess the combined systolic and diastolic left ventricular function (Tei 1995) based on the analysis of the systolic and diastolic sub-phases of the heart cycle. According to previous studies (Bruch et al. 2000; Tei et al. 1997; Kacikciogli 2004), the method might be used as complementary or alternative to separate assessment of the LVEF, SV, E/A, IVRT, and IDT indices. We therefore decided to use the Tei-index while investigating the role of static exercises in the regulation of left ventricular function in resistance-trained athletes. The results reveal that the trained athletes with left ventricular hypertrophy had lower values of the Tei-index compared with the non-hypertrophic untrained participants or with normal ranges for untrained individuals (0.39 ± 0.05), which indicates a better LV function.

42.5 Conclusions

The study indicates differences in myocardial structure and contractility depending on the pressure overload during static exercise in male power lifting athletes. However, a cumulative effect of mechanical compression of blood vessels and intrathoracic pressure increase during the Valsalva maneuver did not

compromise myocardial contractility and cardiorespiratory adaptation to incremental arm exercise in power lifting athletes.

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Chapter 43
Computer Games and Fine Motor Skills

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Abstract The study seeks to determine the influence of computer games on fine motor skills in young adults, an area of incomplete understanding and verification. We hypothesized that computer gaming could have a positive influence on basic motor skills, such as precision, aiming, speed, dexterity, or tremor. We examined 30 habitual game users (F/M – 3/27; age range 20–25 years) of the highly interactive game *Counter Strike,* in which players impersonate soldiers on a battlefield, and 30 age- and gender-matched subjects who declared never to play games. Selected tests from the Vienna Test System were used to assess fine motor skills and tremor. The results demonstrate that the game users scored appreciably better than the control subjects in all tests employed. In particular, the players did significantly better in the precision of arm-hand movements, as expressed by a lower time of errors, 1.6 ± 0.6 *vs.* 2.8 ± 0.6 s, a lower error rate, 13.6 ± 0.3 *vs.* 20.4 ± 2.2, and a shorter total time of performing a task, 14.6 ± 2.9 *vs.* 32.1 ± 4.5 s in non-players, respectively; $p < 0.001$ all. The findings demonstrate a positive influence of computer games on psychomotor functioning. We submit that playing computer games may be a useful training tool to increase fine motor skills and movement coordination.

Keywords Fine motor skills • Video games • Movement coordination • Psychomotor functioning – Young adults

43.1 Introduction

Investigations on the influence of computer games on neuropsychological health have brought inconsistent results. The psychological effects on the players of video games are usually in the focus of interest. The studies report that using the computer games may have both negative and positive influence on the players (Ferguson 2007). Playing games may increase the incidence of depression, overweight (Weaver et al.

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2009), or may give rise to gender stereotypes (Behm-Morawitz and Mastro 2009). Games also are subject to polemics, as being associated with violence, isolation, or addictiveness (Ferguson 2007; Barlett et al. 2007), all of which may have an impact on the psychological maturation of children and adolescents (Gibb et al. 1983; Kastenbaum and Weinstein 1985; Hastings et al. 2009). On the other side, games are considered a valuable addition to the programs enhancing general health, physical fitness, psychomotor functioning (Papastergiou 2009), therapy and rehabilitation procedures (Yong Joo et al. 2010; Peretz et al. 2011).

Computer-based rehabilitative treatment is perhaps most widespread in neuropsychology in the form of game-like programs and tests used in neuropsychological diagnosis and therapy (Blumen et al. 2010). Neuropsychological tools seem advantageous in decreasing neurological impairment in such disorders as attention deficit hyperactivity disorder or brainstem encephalitis (Hou et al. 2008; Hauke et al. 2011). A positive influence of video games also applies to overall motor functioning in strokes and other brain injuries (Lange et al. 2009). Moreover, most patients find the games enjoyable, which increase motivational aspects on the side of users. However, most studies in this area refer to general motor skills, despite the fact that the therapeutic potential of gaming also may concern fine motor skills which are of notable importance not only in adult brain disorders, but also in the child's development. Yet the influence of games on fine motor skills is an area of limited understanding. Therefore, in the present investigation we seek to determine whether spontaneous non-structured computer gaming would be associated with better performance in fine motor skills tasks in healthy individuals. We addressed the issue by examining such skills as precision of aiming, arm-hand coordination and speed of movement, and tremor in young habitual video game users and comparing them with those in never game users.

43.2 Methods

43.2.1 Subjects

The study was performed in accordance with the Declaration of Helsinki for Human Experimentation and the study protocol was approved by an institutional Research Review Board. Participants, who volunteered for the study, gave informed consent after being informed about the aim and method of the study. No incentive was offered for enrolment into the study.

Thirty video game users (F/M-3/27; age range 20–25 years) were enrolled into the study who confirmed regular use of the *Counter Strike* game, an on-line multiplayer game set on a virtual battlefield, with the players impersonating soldiers from the first person perspective. The enrolment citerion was that the subjects played for at least three times a week, a minimum of 2 h a day, and for at least 6 months prior to the study; they were referred to as habitual game players. The control group consisted of 30 non-players (F/M-4/26; age range 20–25 years) who declared never to play games for at least 2 years prior to the study. The tests were conducted at the Institute of Psychology of Opole University in Opole, Poland. All participants were university students. The players used a standard PC computer with a keyboard and mouse as the main accessories for game playing and they declared using the multiplayer mode to interact throughout the game with other players. Data presented in this report are part of a wider investigation performed in the same subjects which concerned social and personal functioning of young video game players. Changes in fine motor skills are considered a separate ramification of neuropsychological effects of using computer games and as such are presented herein.

43.2.2 Measurement Tools

Cognitive functions were assessed using subtests of Vienna Test System version six (Dr. G. Shuhfried GmbH, Mödling, Austria; www.schuhfried.com). The Schuhfried VTS enables computer-assisted application of a number of diverse psycho-diagnostic tests and measuring procedures. These tests

are well standardized and sanctioned computerized paradigms used for the assessment of mainly executive motor functions. Specifically, Motor Performance Series (MLS) by Shoppe (1974) and Hamster (1980) was used to assess the precision of aiming, tremor, coordination of arm-hand movements manual, and the wrist speed ability. Tests were taken from the short form of Sturm & Büssing (seven tests were performed). The testing set consisted of the Work Panel, two styli and a set of pins used by the subjects to perform various tasks on the panel.

The Work Panel featured holes of different sizes placed symmetrically on left and right sides (each size appears twice on each side) for tremor assessment, a curvy groove for precision of arm-hand movements, 2×20 contact points for aiming, 25 additional holes placed on both sides for inserting pins, two metal plates for tapping. In every test requiring the use of a stylus, the goal of a task was to perform an action (aiming, moving a stylus, keeping a stylus in one position) inside the groove or hole in a given order and time without touching the panel. All tasks are relatively simple and natural. The following tests were used to assess each skill: aiming (1 test), tremor (1 test for speed, i.e., for the total time required to accomplish the task and 1 for the error rate), precision of arm-hand movement coordination (1 for the summed time of errors in line tracking tasks, 1 for the error rate for line tracking, and one for the total time of performing a task), wrist speed ability (1 test for tapping). Participation in all tests and tasks was anonymous and voluntary. The subjects were surveyed in groups of three and were assisted by the same examiner. The time to fulfill each test varied from 1 to 5 min, which was in accord with the specific instructions.

43.2.3 Data Evaluation

Data were presented as means ± SD. For the precision of aiming and the wrist speed ability, the data were presented in points (computed indexes). For the total time of errors and the total time required for performing a task in the arm-hand movement coordination, the data were presented in seconds. Differences in the scores between the players and non-players were compared using one-way ANOVA. The distribution of the subjects between slow and fast task performers, concerning the tremor level, in the two population groups were compared with Pearson's Chi-square test.

43.3 Results

The mean results of the tests employed in players *vs.* non-players are depicted in Table 43.1. The players had a significantly better score in aiming; 9.2 ± 0.9 *vs.* 5.0 ± 0.8 points in non-players, $p < 0.001$. The assessment of tremor or steadiness consisted of two tests: one that assessed the number of errors

Table 43.1 Fine motor skill in video game players compared with non-players assessed in MLS Motor Performance Test System

Test	Players	Non-players
Aiming (point index)	9.2 ± 9.0*	5.0 ± 0.8
Steadiness (tremor)	6.5 ± 0.6*	8.9 ± 0.8
No. of errors		
Precision of arm-hand movements		
Total time of errors (s)	1.6 ± 0.6*	2.8 ± 0.6
No. of errors	13.6 ± 0.3*	20.4 ± 2.2
Total time of task (s)	14.6 ± 2.9*	32.1 ± 4.5
Wrist speed ability (point index)	228.2 ± 7.3*	183.27 ± 9.9

Values are means ± SD

*$p < 0.001$ for players *vs.* non-players

made by the subject and the other that assessed the total time required accomplishing a task; the latter was analyzed in the present study as distribution of the subjects between slow and fast task performers in the two groups. The players performed better in both tests, making fewer errors, 6.5 ± 0.6 *vs.* 8.9 ± 0.8 in non-players. There also was a significant difference in the distribution of the subjects between fast and slow task performers, to the advantage of the players who were significantly faster task performers; $\chi^2 = 57.3$, $p < 0.001$ (These last results are not included in the results table). The players did significantly better in the coordination of arm-hand movements, as expressed by a lower time of errors, 1.6 ± 0.6 *vs.* 2.8 ± 0.6 s, a lower error rate, 13.6 ± 0.3 *vs.* 20.4 ± 2.2, and a shorter total time of performing a task, 14.6 ± 2.9 *vs.* 32.1 ± 4.5 s in non-players, respectively; $p < 0.001$ for all. Finally, the video game players also did better on the wrist speed ability, 228.2 ± 7.3 *vs.* 183.3 ± 9.9 points in non-players, $p < 0.001$.

43.4 Discussion

The results of the present study consistently indicate that the habitual use of video games exerts positive effects on fine motor skills of those who play. The players scored better in all tests employed in this study to assess their motor skills. The assessment concerned a wide range of hand-arm movements and coordination and the players were capable of using their motor skills more effectively than non-players.

In this study we chose the Vienna Test System which is based on the Fleishman analysis of fine motor skills (Fleishman and Mumford 1991) such as the precision of aiming, tremor, coordination of arm-hand movements, and the wrist speed ability. This assortment of the motor skills was investigated in relation to the *Counter Strike* video game due to its wide popularity among young adults and its interactive character consisting of the players' perception of the battlefield-like conditions from the first person perspective, which emulates the subject's involvement into various military actions requiring instantaneous reaction.

The findings of the study are of relevant practical values. Motor skills may be impaired due to many pathological reasons; irrespective of which the harm ensues regarding everyday life performance. Correction of a disabled ability to perform quick and accurate arm-hand coordinated actions is of special attention in therapy plans. When we know what effects computer gaming exerts on fine motor skills in healthy individuals we would be able to proceed onto experimental testing in patients with different motor disorders to find a supportive rehabilitation tool. To judge the usefulness of the video games in improving fine motor skills, the long-term effects of such training in both healthy and diseased individuals in various age-groups ought to be known. Boot et al. (2008) showed that the long-term (years) gaming experience predicts superior performance in cognitive tasks far better than a short-term training of non-players. Yet that study was limited to specific cognitive tasks (attention, spatial cognition) and the method used did not distinguish the kind of motor skills. The lack of separation of different motor skills may be less relevant in cognitive studies, but appears essential in arm-hand coordination training which employs a variety of accessories. Furthermore, it is unclear whether gaming causes an increase of cognitive functioning or the players were just recruited from more 'cognitively developed' individuals or both.

Another issue which requires exploration is the transfer of the improvement in fine motor skills gained in front of the computer screen to real-life tasks. There is evidence for a substantial improvement in hand dexterity of laparoscopy surgeons who were experimentally 'trained' in video gaming, which implies that fine motor skills can also be enhanced by a short-term training and the improvement holds when performing not game-related tasks (Rosser et al. 2007). Since video games improve cognitive and coordination functioning in healthy young individuals, the plausibility arises that the same effects might occur in other age-groups and at various stages of motor impairment.

Different games affect different cognitive functions (Boot et al. 2008). The same may be true for fine motor skills. The improvement in motor skills noted in the present study was achieved by players who used an ordinary keyboard and mouse. It seems a reasonable assumption that the use of different types of game and more complex accessories would lead to different changes in motor skills. Such nuances may be of significance, similarly to switching from handwriting to keyboard use as shown by Sulzenbruck et al. (2011). The type of accessory seems an important factor, as shown in a study of patients subjected to post-stroke rehabilitation (Yong Joo et al. 2010). In that study the authors have used a set of accessories of the modern game console Nintendo Wii in upper limb rehabilitation of stroke patients and observed improvement. The console enforces movements of a whole body (imitates sports) which makes it unique among other gaming accessories. This promising evidence should now be extended by search for the effects concerning specific motor skills. Nevertheless, that study makes the use of video games in stroke patients the best established yet.

There are other studies which show improvement of fine motor skills due to computer game training. Games are successfully used in motor therapy of children with dyspraxia, a major problem in developmental coordination disorder (Rodger et al. 2003). It may be posited that video games targeting the fine motor skills might be a useful adjunct to anti-aging computer-based psychotherapy employed in the aged healthy individuals to counteract the decline in their motor abilities. Moreover, video games may become a rehabilitation tool in brain neurodegenerative diseases, particularly of the Parkinsonian type in which tremor affecting the forearms and disordered aiming, tapping, and pronation-supination movements, leading to difficulties in the initiation of motor activity, are cardinal symptoms (Ringendahl 2002). Further studies are needed to evaluate these predictions.

In conclusion, the findings of this study demonstrate an enhancement of fine motor skills in young healthy individuals who persistently use video games. We submit that playing computer games may be a useful training tool in preventive or rehabilitative programs devoted to perseverance or improvement of psychomotor functioning.

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Chapter 44
Toward the Clarification of Ideas: Medical Futility, Persistent/Obstinate Therapy and Extra/Ordinary Means

Leslaw Niebroj, Kamilla Bargiel-Matusiewicz, and Agnieszka Wilczynska

Abstract Despite reluctance of a part of medical society to accept the moral and/or legal permission to euthanasia, there is seemingly a common agreement on the need to resolve the problem of excessive therapy. Several ethical concepts are used to justify decisions to withhold/withdraw such treatment. Three of them are of particular value. The ordinary-extraordinary means distinction has a long tradition deeply-rooted in the Catholic medical ethics. During the last decades the concept of futile (or pointless) treatment has reached popularity within bioethical discourse. Also, slightly less common in use, the term 'obstinate therapy' and the relative concept seems to provide interesting insights into ethical debate. What is however to be emphasized is the ambiguity of meanings attached to these terms/concepts which prompt many bioethicists to reject these terms in favor of other concepts. In the present study a PubMed literature database review is done in order to recognize and then to classify the different ways of interpretation of the three concepts related to withholding/withdrawing excessive treatment. Retrieved interpretations of these concepts are evaluated in the light of an integrated model of moral justification. The undertaken analyses permit reaching the conclusion that the concepts which are the subject matter of this article can be properly defined and used only within the context of the so called holistic ethics and as an example of such i.e., a holistic approach to bioethics, the life's programs approach to bioethics is given.

Keywords Bioethics • Euthanasia • Medical ethics • Futile treatment • Thomism • Therapy

44.1 Introduction

There seems to be contradictory opinions on how to properly describe the relationship between (traditional) medical ethics and bioethics (also called 'biomedical ethics') (Curran 1976). The former makes of appeals to the Hippocratic tradition, the latter is commonly viewed as a relatively young

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discipline that got started in the 1970s of the past century. Is bioethics nothing more than the simple continuation of medical ethics and the very terms 'bioethics' and 'medical ethics' are synonymous? Or should bioethics be seen rather as a discipline which evolved from and replaced medical ethics? Medical ethics would be then antecedent to bioethics which builds up on what its precursor's knowledge has introduced into the medico-moral debate. There is however also a third option that should be taken into consideration. In this view bioethics is clearly recognized as a discipline that started and has been developing in opposition to medical ethics. If so, medical ethics and bioethics are in fact two concurrent ethical systems dedicated to identifying and resolving moral problems in medicine.

A closer look at the contemporary meta-ethical debate permits to sustain that this last opinion is not only the most commonly shared but it also helps to interpret and explain two other opinions on medical ethics – bioethics relationship (Baker and McCullough 2007). In fact, assuming that bioethics is contra proposition to medical ethics does not exclude that the new discipline builds on terminology, concepts and methods known from the Hippocratic tradition. Moreover, bioethics is fully aware that its own intellectual background is imbued with ideas which have been originally elaborated in the domain of the traditional medical ethics (Beauchamp and Childress 2009). It is no wonder that bioethics is seen as a successor or as a discipline which has evolved (and replaced) medical ethics. Although the sense of the term 'successor' and 'evolutionary character of changes' need to be addressed here with great caution. The departure from traditional medical ethics, i.e., the starting point of bioethics, is to be described rather in terms of revolutionary than evolutionary changes. The terms, concept, and ideas taken from medical ethics were decontextualized and then recontextualized in bioethics (Baker and McCullough 2007). Consequently, their meaning (including the key terms as for example 'autonomy') has changed significantly (Niebroj et al. 2007).

Undoubtedly success of bioethics measured in the ever-growing number of publications, proliferation of graduate programs, and the huge amount of influence that bioethics exercises over the social and political life, does not mean that traditional medical ethics simply disappeared from intellectual life and moral discourse (De Vries 2004; Kahn 2006; Lopez 2004). Moreover, from the point of view of those who work in traditional medical ethics, bioethics is just a new term to describe the long-time tradition of moral inquiry.

Both traditional medical ethics and bioethics can be described as 'comprehensive doctrines', in the sense given to the term by John Rawls (1993), i.e., as doctrines which provide coherent systems of beliefs, practical rules and which are open to change on the basis of its own standards and norms. In the case of medical ethics, its system of values and norms can be seen as an application of Christian ethics or even more generally Catholic-Christian theology. It is to be emphasized that although traditional medical ethics makes references to the Hippocratic tradition, it is rather 'baptized' than 'pure' Hippocratic thought (Bulger and Barbato 2000; Waddington 1975). Bioethics (in its dominant contemporary form) is a secular discipline which does not apply any given ethical theory to medical practice but appropriate separate concepts form different theories to create in this way its own coherent system (Beauchamp 2007). Obviously, bioethics is not as fully elaborated as the system of Catholic religious tradition. Not all comprehensive doctrines – as Rawls observes – are rich enough to be named fully comprehensive doctrine (Catholic tradition); many of them are rather partially comprehensive (mainstream of bioethics) (Kilan 2009). What can be said, however, about both of them is that they are reasonable, i.e., they accept (on the basis on their own believes) the idea of toleration and – as such – cannot serve as a rationale for the use of coercive political power (Wenar 2008). It seems enough to mention the *Declaration of Religious Freedom* of the Vatican Council II (1965) and intellectual ties of bioethics with the concept of human autonomy (Gillon 2003) to demonstrate that both doctrines are intrinsically open to the idea of toleration. If so, the reasonable pluralism (as defined by Rawls) between medical ethics and bioethics is not only possible but also desirable. Such a pluralism consists in overlapping consensus, i.e., in beliefs which can be held in common by adherents of both doctrines because it contains on what both approaches to medical ethics may arrive at an agreement (Kilan 2009). To be sure, medical ethics and bioethics have essentially different views on

issues related to the philosophy of medicine. For medical ethics, the ultimate aim of medicine is to save human life (the concept of the sanctity of human life) and for bioethics it is to provide and guarantee acceptable quality of life (the concept of the quality of human life) (Thiel 2011). These differences effect how moral norms are formulated and justified. Even such profound differences do not exclude the existence of what was called the overlapping consensus.

It is true that rapid development of bioethics is correlated with marginalization of the traditional medical ethics Surprisingly, however, as Snelling (2004), p. 352 observes, 'in health care ethics is at least one area where the moral and legal position is dominated by an absolute position, and that is euthanasia'. Using the term 'absolute position' he, generally speaking, describes the doctrine which is called here 'traditional medical ethics'.

This article aims at studying whether the concept of 'ordinary/extraordinary means' can be accepted with regard to the issues related to withholding/withdrawing treatment or (even) in regard to active euthanasia by both traditional medical ethics and bioethics on the ground of the idea of 'overlapping consensus' between them?

44.2 Methods

According to the Polish law, this investigation is not subject to Institutional Review Board evaluation. The PubMed database literature review was done in order to recognize historical sources (tradition of origin) and the context of the contemporary use of the concept of ordinary/extraordinary means. Taking into account the theory of general normative ethics proper to the concept under study here, and in particular the idea of human act (*actus humanus*), the distinction between extra/ordinary means was specified in a way which makes it possible to differentiate this concept from other commonly used ideas in the moral debate over withholding/withdrawing treatment and euthanasia. Retrieved interpretations of these concepts are evaluated in the light of an integrated model of moral justification.

44.3 Results and Discussion

Literature review unequivocally binds the concept of extra/ordinary means with the Catholic theology and Christian ethics. Gillon (1986) indicates Dominic Banez (1528–1604), the Spanish theologian, professor of the university at Salamanca and one of the greatest commentators of St. Thomas Aquinas' works (Deegan 2008), as the first who used the distinction between ordinary and extraordinary means. In fact, Banez wrote about extra/ordinary means distinction in his work entitled *Scholastica Commentaria in Partem Angelici Doctoris S. Thomae*, and just in the works of St. Thomas Aquinas – as Henke (2004) notices – such a distinction is used in regard to the ethical obligation to preserve human life, or more precisely when providing moral arguments against committing suicide and speaking about fearlessness. In *Super Epistolas S. Pauli* St. Thomas Aquinas wrote: 'A man has the obligation to sustain his body, otherwise he would be a killer of himself… by percept, therefore, he is bound to nourish his body and likewise, we are bound to all the other items without which the body cannot life' (cited by Henke 2004, p. 120). On the pages of *Summa Theologica* (II, II, q. 126, a. 1.) (1920) he observed, however, that 'every man has it instilled in him by nature to love his own life and whatever is directed thereto; and to do so in due measure'. The generations of commentators of St. Thomas' works, including Banez, aimed at developing, specifying and limiting obligation expressed by Doctor Angelicus. Particularly important seem to be the works of Francisco de la Vitoria, Dominic Soto and Juan Card. De Lugo limiting here to the sixteenth and seventeenth centuries theologians (Henke 2004). The history of origin and development of the concept of extra/ordinary means is the subject

matters of several articles indexed in PubMed (Henke 2005; O'Rourke 1988; Sullivan 2007), for purposes of this article it is important that this concept was created and developed in the context of Thomism. Literature review proves that nowadays there is mainly in use a definition of extra/ordinary means of treatment elaborated by G. Kelly just in the middle of the twentieth century. The definition states that: 'Ordinary means are all medicines, treatments, and operations, which offer a reasonable hope of benefit and which can be obtained and used without excessive expense, pain, or other inconvenience. Extraordinary means are all medicines, treatments and operations, which cannot be obtained or used without excessive expense, pain, or other inconvenience, or which, if used, would not offer a reasonable hope of benefit'. (Kelly 1951, p. 550).

Had this concept not been supported and used by the hierarchy of Catholic Church, and in particular by popes, probably the theological distinction between extra/ordinary means of treatment would not have influenced medical ethics so profoundly. However, just in 1957, pope Pius XII declared: 'But normally one is held to use only ordinary means – according to circumstances of persons, places, times and culture – that is to say, means that do not involve any grave burden for oneself or another. A stricter obligation would be too burdensome for most men and would render the attainment of the higher, more important good too difficult. Life, health, all temporal activities are in fact subordinated to spiritual ends. On the other hand, one is not forbidden to take more than the strictly necessary steps to preserve life and health, as long as he does not fail in some more serious duty' (Pius XII 1958, p. 395–396). Since then, the distinction between extra/ordinary means of treatment has been many times reaffirmed by the succeeding popes and the central institutions of the Holy See (e.g., The Congregation for the Doctrine of the Faith) (Henke 2004).

Despite a long history of using the distinction between extra/ordinary means of treatment and, moreover, despite the highest Catholic authorities' commitment to evaluate moral conduct on the basis of this distinction, bioethical literature review proves that there are still serious objections to this concept. They are rooted primarily in the conviction that the definitions of extra/ordinary means remain unclear due to the use of such words/terms as: 'reasonable (hope)', 'excessive (expanse/pain/inconvenience)' (Snelling 2004, Devlin 1982). Consequently, ethical discourse which uses this concept to resolve moral dilemma (e.g., related to the question of euthanasia) remains inconclusive (Kuhse 1985). To be sure, during the history there have been attempts made to interpret the meaning of extra/ordinary means in more unequivocal terms (Beauchamp and Childress 2009; Gillon 1986). For instance, the term 'extraordinary' was interpreted as 'unusual' or 'not belonging to the customary medical practice', 'exceptional', while ordinary means are those which are usual, mundane and/or customary. Even if in the light of such interpretations the use of the distinction would be easier, they are unacceptable from theoretical (taking into account moral theory of Thomism, but not limiting to this one philosophical school) point of view. As Gillon (1986, p. 260) rightly observes that one cannot derive an 'ought' from an 'is' (a morally neutral is, that is). In fact, such interpretations of the distinction between extra/ordinary means suggest that the rules of the normative ethics are (ought to be?) relative to the data obtained by the disciplines which are generally classified as non-normative, descriptive ethics (e.g., psychology or sociology of morality), which is obviously unacceptable form the point of view of Thomism.

Another approach to interpret and clarify ambiguity regarding 'ordinary' and 'extraordinary' means lists series of contradictory descriptors which are intended to work as a binary matrix: common/uncommon, simply/complicated, non-technological/technological, inexpensive/expensive, noninvasive/invasive, natural/artificial, routine/heroic, etc. The means of treatment which are common, simple, non-technological, inexpensive, noninvasive, natural and routine are obviously 'ordinary' ones, otherwise (i.e., uncommon/complicated/ technological…) they would be classified as 'extraordinary' (Beauchamp and Childress 2009; Gillon 1986). This interpretation creates rather than resolves problems. Should any given means fulfill all the condition to be named ordinary? What if a given means is common, natural but expensive? What is more, taking in mind that the list of descriptors is not closed (it seems reasonable to add for instance one more, i.e., painless/painful), it becomes practically impossible to classify any means as truly ordinary or extraordinary. The second problem connected with this

interpretation is related to the fact that every word used in the pairs of contradictory descriptors should be properly defined. Instead of reducing ambiguity of the distinction between extra/ordinary means of treatment, it seems rather to multiply them enormously.

Even more serious objection against the distinction between ordinary and extraordinary means of treatment arises from the practice of medicine. The case of Karen A. Quinlan can serve as a clear example (Niebroj 2008). In 1975, 21 years old Karen Quinlan had a cardiopulmonary arrest. Despite receiving treatment she was deprived of any cognitive function and her vegetative life was supported by mechanical ventilation. Her father, a zealous Roman Catholic, by the court decision, was placed in the role of a guardian and decided to disconnect his daughter from respirator (which was recognized as an extraordinary mean of treatment); however did not permit to stop artificially feeding her (artificial nutrition and hydration was considered an ordinary mean of treatment). During almost10 years after disconnection from the ventilator Karen Quinlan has never regained consciousness, has lost about 40% of her weight and has been treated for multiple infections. The question arises whether the use of the distinction between extra/ordinary means caused the ten year-long period of futile therapy? The therapy which put Karen Quinlan in an undignified position. Does the use of the studied concept lead to incoherent actions (disconnection from a respirator which supposedly can cause death and using artificial nutrition to avoid death which was previously supposed). No wonder that Beauchamp and Childress (2009, p. 159) in their landmark book *Principles of biomedical ethics* conclude: 'distinction between ordinary and extraordinary treatment is morally irrelevant'.

On the other hand, however, before definitely rejecting the concept of extra/ordinary means of treatment, the word of caution is needed. It is worth noting that despite the piercing criticism this concept is unexpectedly commonly used. The literature review indicates that the distinction between extra/ordinary means is used to resolve a broad spectrum of moral dilemmas such as e.g., related to euthanasia (active/passive/physician assisted suicide) (Gostin 1997; Hunka 1993), artificial nutrition and hydration (Clark 2006), pediatrics/neonatal intensive care (Carnevale et al. 2006; Kaveny 2002), the work of Hospital Ethics Committee(s) (Bole 1990). It is also worth noting that the US *President's Commission for the Study of Ethical Problem in Medicine and Behavioral Research* when was examining four distinctions (all originated in the Catholic theology) used in the bioethical discourse rejected three of them (i.e., distinction between: act/omission, withholding/withdrawing treatment and intended/unintended consequences) and upheld only the distinction between extra/ordinary means of treatment (Atkinson 1984).

In the light of what was said above, the question arises whether the distinction under study is really morally irrelevant or whether erroneous interpretation of this distinction makes that it is evaluated as irrelevant. Instead of proposing a novel idea on how to interpret the concept of extra/ordinary means, a (more) reasonable solution seems to be discovering the interpretation known from the tradition of its origin.

Undoubtedly, one of the most fundamental (in the both senses: central and foundational) concept of the Thomistic ethics is the idea of human act (*actus humanus*) and the three essential elements of its moral evaluation. 'An act can be said to be morally good only when it fulfills three condition: when the act itself is morally good or indifferent in kind, when it enacts a good intention, and when it is done in a way that is morally appropriate given the circumstances' (Pope 2002, p. 33).

The first element which should be taken into consideration during the evaluation of morality of the human act is its *finis operis/finis proximus,* i.e., the end of the moral act, the object chosen (*res volita*) by a given act or intrinsic finality of the object of the act. It is called (depending on the interpretation) a material object or material element of the human acts (Sousa-Lara 2008). Traditionally, this element of the human act is considered having the most essential significance for moral value of the given act. Medical treatment has its end in health. No matter which means are used (extra/ordinary), the moral object is still the same. The material object of the human act permits to differentiate the concept of extra/ordinary means from that of futile treatment. The latter, as a human act which does not end in health should not be misled with actions the material object of which is just health.

The formal object/element of human act, i.e., its *finis operantis/finis remotus* or the formal reason for the wanting, is commonly understood as the intention of an acting person. It expresses the *ratio* under which the material object of the human act is perceived as a suitable good. Thomas clearly states that the good as such (e.g., health as health) will not move the will of human person, only the good apprehended as suitable is capable of causing the movement of the will (Thomas Aquinas 2003). The concept of the formal object of human acts seems to be particularly suitable to differentiate the concept of extra/ordinary treatments from that of persistent/obstinate therapy. In the case of the latter, the health (material object of medical therapy as medical therapy), although is considered as the good, seemingly is not apprehend as a suitable good. Therefore, persistent/obstinate therapy has to have a reason under which it is provided as another good (not health) which is perceived as a suitable one. What could be perceived as such a suitable good? Intuitively, two responses (logically mutually dependent on one another) come to mind: to satisfy social expectancies (patients themselves, their family member, etc.), and to avoid probable accusation of negligence in medical malpractice. *Finis operis* is supposedly different form *finis operantis* in the case of persistent/obstinate, it is not supposed (though also not excluded) in the case of extra/ordinary treatment.

The distinction between ordinary and extraordinary means of treatment belongs to the issues related to the third element of human act: its circumstances. Traditionally, there are listed seven different circumstances which should be taken in consideration when evaluating the morality of a human act. For instance, the circumstance of mode or manner is to help define the idea of aggressive therapy, which should not be identified either with futile therapy or with extraordinary treatment. In fact, aggressive therapy can be provided with the use of ordinary means of treatment. Aggressiveness describes the mode of how the therapy is provided and not the 'tools' used to treat.

It seems something natural and obvious that the distinction between extra/ordinary means is to be considered within the context of the circumstance of tools (called also circumstance of helps) used in/to realize human act. Essentially, the reflection over this circumstance focuses on the question whether tools used are adequate for the realization of material and/or (if different) formal object of a human act. It is always possible, even if only theoretically, to use all available tools to realize a given end. Such an excessive use of tools would be considered unreasonable in the prospect of the future needs and acts to be done. An excessive or extraordinary tool is not by definition unusual, expensive, technological and so on, or ineffective or of limited effectiveness. It is rather the one which is to be preserved for (an)other use(s). Bearing in mind that Catholic theology indicates salvation as the ultimate goal of life, it seems clear that the use of certain tools, i.e., extraordinary treatments if they could interfere with the ultimate aim of a human person, are not considered as the obligatory means (which was said *expressis verbis* in the cited above quotation form Pius XII) . The distinction between extra/ordinary treatments ought to be done from the perspective of the prospective goods which can/should be realized in a given person's life. To understand this distinction it seems necessary to accept that human acts should not be morally valuated separately, one by one. Every human act has its past and future, belongs to the continuum of a given person's life.

Lantz (2000) calls such an approach to moral discourse 'deep ethics', which is one of the essential elements of a more complicated theoretical approach named 'holistic ethics'. Holistic ethics is not only a deep one but also wide (i.e., contextualized) and broad (i.e., is using complex concepts such as health, care, family, etc.). For him, Thomism is an evident example of holistic ethics, while utilitarianism, to the contrary, the best example of reductionist ethics. Bearing in mind, to what degree bioethics is influenced by utilitarianism, it should not wonder why bioethics finds difficulties in accepting the concepts elaborated within the theory of the holistic ethics. It is to be emphasized however, that – according to the Lantz's opinion – bioethical approaches based on the theory of reflective equilibrium (known form the philosophy of Rawls), including the mainstream of bioethics, i.e., principlism, are really close to or at least open to holistic ethics. An attempt to create a strictly bioethical, based on an integrated model of justification, approach to biomedical ethics, called 'life programs bioethics', which contemporaneously assumes the perspective of the holistic ethics has been presented elsewhere by (Niebroj 2010a, b) the so.

44.4 Conclusions

The concept of extra/ordinary means of treatment created within the context of Catholic theology and Christian philosophy (in particular in Thomism) need to be interpreted in the perspective proper to the holistic ethical theories. The objections raised against this concept by bioethicists seem to result from erroneous interpretations which assume a narrow, known from of reductionist ethics, e.g., from utilitarianism, as an approach to the morality. It is possible, however, for bioethics, on the ground of its own theory, to broaden the perspective of the moral evaluation of a human conduct. A properly understood distinction between extraordinary and ordinary means of treatment would belong to the overlapping consensus between traditional medical ethics and bioethics.

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Chapter 45
Psychological Attachment in Patients with Spondylosis of Cervical and Lumbar Spine

Henryk Pedziwiatr

Abstract Persons with spondylosis of the cervical spine have a low sense of security, difficulties in relationships with their mothers, difficulties in contact with their own body and in coping with dysphoric affect. The question arises: Are those problems the result of the current medical condition, or one of its causes? In order to find the answer one should look closer at the period of an individual's life when a sense of security and a pattern of emotional relationships are formed, and a sense of own body and defence attitudes are developed. The earliest period of life in which these processes occur is the initial relationship between the child and mother; the period of attachment and object relation. If the attachment style in the group studied does not deviate significantly from the control group, it ought to be assumed that the present problems are situational. The problems would then a result of a chronic difficult (stressful) situation which is spondylosis of cervical or lumbar spine. In an attempt to answer the above question, preliminary studies in a 90-person group were conducted. The group included 30 patients with spondylosis of the cervical spine, 30 patients with spondylosis of the lumbar spine, and 30 control persons without spondylosis.

Keywords Psychological attachment • Spondylosis • Psychosomatics • Dysphoric affect • Stress –Lumbar spine

45.1 Introduction

In the studies of the relationship between somatic diseases and changes in the psyche of patients a special attention is paid to groups of somatic diseases which are at high risk of mental disorders. These include the diseases, the treatment of which is connected with severe pain, body deformity or the occurrence of multiple symptoms (Engel 1967). Spondylosis is a disease with complex symptoms, including persistent pain, which can lead to distorted somatic posture. It is chronic and conservative therapy is used to delay its progress (Pedziwiatr and Czajkowska 2006).

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The etiology and pathogenesis of spondylosis have not yet been clearly defined. It is suggested that, in addition to genetic factors, static and dynamic overloads of the spine resulting from holding the body in one position for a long time while, e.g., working or studying, or lifting weights play an important role in its development (Pedziwiatr 2008).

According to Steciwko and Kassolik (2000) any changes in the curvature of the cervical spine cause an increase in muscle tension in the neck and shoulder girdle which can disturb circulation in vertebral arteries, the symptoms of which include pain, vertigo, or tinnitus. The most common changes in the setting of the cervical spine are shallowing or abolishing of lordosis and the formation of degenerative changes. The formation of pathological changes in this area is spread over time and affects osteo-articular, muscular, vascular, and nervous structures. It may become one of the causes of cervical spondylosis. The presence of vegetative, atrioventricular, and visual symptoms suggests there is a vasomotor factor associated with the irritation of sympathetic fibres of vertebro-basilar arterial system (Lucas et al. 1994).

According to Chapman (1974), the vasomotor factor and vegetative disorders are connected with the basic emotional attitude of the patient. Patients with such disorders show suppressed anger and hostility, the need to gain sympathy, depressed mood, anxiety, and sense of guilt. A study in women with cervical spondylosis (Pedziwiatr and Czajkowska 2006) has revealed disorders of their sense of security, one-sided attention in the emotional sphere, a strong sense of external pressure and insecurity, and introversion. The women show a significant lack of balanced contact between the somatic sphere and emotional spheres. The studies on the emotionality of patients with cervical spondylosis show similarities to the occurrence of risk factors for diseases known as Type A Behaviour Pattern (TABP) (Pedziwiatr 2008). Persons with TABP typically display negative affect in the form of: hostility, impatience, bad temper, strong defensive attitudes, a tendency to experience emotional tensions, emotion repression, increased neurotic trait (depression, hypochondria, or hysteria), and compulsiveness (Friedman and Rosenman 1957).

The question thus arises of whether these problems are a result or the underlying cause of the current medical condition. The answers should be sought for in the period of life when a sense of security is formed, a pattern of emotional relationships is set, and a sense of own body and defence attitudes are developed. The earliest period of life in which the discussed processes occur is during the initial relationship between the child and mother; the period of attachment and object relations. If the attachment style in the tested group does not deviate significantly from the results of healthy individuals, it would reasonable to assume that the present problems are situational, i.e., resulting from of a chronic difficult (stressful) situation to which spondylosis belongs.

The theories of relationships with an object, which describe and explain the course of the psychophysical development and development of an individual help recognize and understand the mechanisms of pathology formation. Bowlby (1999) has defined attachment as an instinctive, based on biological mechanisms, deep emotional bond between the child and the caretaker. This relationship develops in the first year of life and becomes a ‘matrix’ of subsequent emotional and social relationships of an individual. Attachment behaviours are a result of the child’s responses to internal and external signals. On the basis of repetitive experiences connected with the roles of the child and the parent in their mutual relations, fully internalized cognitive structures that underpin the development of personality are generated (Friedrich 1995). It can, therefore, be assumed that the pattern of the child’s attachment, stabilizes and consolidates when the child develops, and it becomes increasingly difficult to modify or affect it by recent experiences.

Ainsworth (1977), observing children, has identified three basic types of attachments:

- Anxiety-ambivalent attachment (Type A) – it is formed when the infant is uncertain as to the availability of the attachment figure. The infant demonstrates uncertainty and strong anxiety associated with separation from the mother. He has difficulty with exploring the environment, tends to hold to mother in anxiety, and often gets angry at her.

- Safe attachment (Type B) – it develops when an attachment figure is easily available for the child and his responsiveness. A child with this type of attachment is friendly toward strangers, but when he is separated from the mother, he responds with distress; when mother comes back, he seeks physical proximity.
- Avoidance attachment (Type C) – this type is formed as a result of physical and mental unavailability of a caretaker, his intrusive behavior toward the child, or emotional rejection of the child.

A similar model of attachment styles is suggested by Hazan and Shaver (1994). Individuals with Type A attachment tend to be aggressive and have more behavioral disorders. Types A & C are associated with a tendency for depression because of helplessness (Type A) or alienation (type C). These two attachment styles have a significant impact on the way the individual deals with stress situations, which can be both a cause of a somatic disease and its effect. They are also significantly correlated with certain personality traits such as neuroticism, emotional stability, secrecy, blaming and alertness (Plopa 2006).

In the present study I posed the following research questions.

- Are attachment styles in patients with cervical and lumbar spondylosis different from those present in healthy individuals? If any difficulties in the mental sphere of patients with spondylosis are the consequence of pathological somatic changes, the results of the different styles should match the range of those in healthy individuals for all the styles or high results for Type B and low for Types A & C styles (no bond pathology), which would suggest the emergence of a situational negative affect associated with somatic symptoms (pain, restriction of movement), rather than permanent trends.
- Do individual attachment styles depend on the type of spondylosis? If the attachment style is one of the factors leading to spondylosis, the results of patients with cervical spondylosis and lumbar spondylosis should differ from the results of healthy individuals to a significant degree, and people who are ill should have a certain style of attachment, other than the safe style, treated as a feature.

45.2 Methods

This research was in conformity with the Declaration of Helsinki for Human Research and was approved by a local ethics Committee. The study was conducted in patients who had degenerative changes of cervical or lumbar spine with abolished or shallowed lordosis (spondylosis) treated at the Psychosomatic Health Center in the city of Zielona Gora in western Poland from April 2009 to September 2010. The subjects in the control group were without spondylosis. There were three groups consisted of 30 subjects (29 females and 1 male) each. The occurrence of cervical or lumbar lordosis in X-ray images was accepted as a selection criterion which, to a large extent, determines the severity of degenerative changes. All patients complained of pain that limited the motion range of the neck and head, but did not limit their capacity for work and leisure. The exclusion criterion was other diseases or treatment that could affect the results. The subjects were aged between 33 and 70 and were not divided into age categories since there is no correlation between age and attachment type (Plopa 2006). To define the attachment style, the Attachment Styles Questionnaire of Plopa (2006) was used. The questionnaire distinguishes three attachment styles: safe, anxiety-ambivalent, and avoiding style. This classification is based on the concept of Hazan and Shaver (1994). The tables present the study results which are converted into stens, grouped into three categories: low – 1–4, average – 5–6, and high – 7–10 stens.

45.3 Results

The results for each attachment style differed significantly from each other in the groups studied, which reveals there are distinct patterns of attachment in subjects with cervical spondylosis (CS) and lumbar spondylosis (LS) in relation to the styles presented by the healthy control group (HC) (Table 45.1).

Analysis of the results of different attachment styles reveals significant differences in the group of patients with lumbar spondylosis and in the control group (Table 45.2). In the patients with cervical spondylosis, in relation to the results of the other groups, the differences between various styles tend to be less and insignificant. The control group presents the dominant safe (healthy) style (Table 45.3). In the group of patients with cervical spondylosis there is no dominant style (Table 45.4). Moreover, the intensity of the safe style lowers from the dominant to average level, and the intensity of the other attachment styles increases from low to high in comparison with the results of the control group (Table 45.3). This arrangement of styles in the group of patients with cervical spondylosis shows that there is an increase in unfavorable trends of the development of pathological reactions to stressful or difficult situations, and in the ways of differentiating the environment as safe or dangerous. This could increase the occurrence of situations subjectively perceived as difficult and trigger the somatisation of emotional difficulties.

A low level of the anxiety-ambivalent style among the patients with lumbar spondylosis (Table 45.5) differs significant from the similar style in both healthy subjects and patients with cervical spondylosis (Table 45.2). The arrangement of attachment styles in patients with lumbar spondylosis reveals a

Table 45.1 Differences in attachment styles between patients with cervical spondylosis (CS) and healthy control (HC), between patients with lumbar spondylosis (LS) and healthy controls (HC), and between patients with CS *vs.* LS (one-way ANOVA)

Attachment style	F	p
CS & HC safe	10.25	0.002
CS & HC anxiety-ambivalent	10.01	0.002
CS & HC avoiding	30.00	0.000
LS & HC safe	0.53	0.471
LS & HC anxiety-ambivalent	5.44	0.023
LS & HC avoiding	0.04	0.835
CS & LS safe	0.24	0.627
CS & LS anxiety-ambivalent	7.70	0.007
CS & LS avoiding	7.57	0.008

Table 45.2 Differences between attachment styles in patients with cervical spondylosis (CS), lumbar spondylosis (LS), and in healthy controls (HC) (means of raw scores)

Spondylosis	Attachment style	Mean ± SD	p
CS	Safe – Anxiety – ambivalent	–0.07 ± 0.69	0.601
	Safe – avoiding	0.00 ± 1.34	1.000
	Anxiety – ambivalent – avoiding	0.07 ± 1.20	0.763
LS	Safe – Anxiety – ambivalent	4.60 ± 2.59	0.001
	Safe – avoiding	5.80 ± 2.55	0.001
	Anxiety- ambivalent – avoiding	1.20 ± 1.67	0.001
HC	Safe – Anxiety – ambivalent	1.10 ± 1.06	0.001
	Safe – avoiding	1.57 ± 1.01	0.001
	Anxiety – ambivalent – avoiding	0.47 ± 0.73	0.002

Table 45.3 Attachment style in the healthy control group (HC)

Control group	Result level	Frequency	Valid percent
Safe attachment	Low	1	3.3
	Average	2	6.7
	High	27	90.0
Anxiety-ambivalent attachment	Low	14	46.7
	Average	9	30.0
	High	7	23.3
Avoiding attachment	Low	24	80.0
	Average	3	10.0
	High	3	10.0

Table 45.4 Attachment styles in patients with cervical spondylosis (CS)

Cervical spondylosis	Result level	Frequency	Valid percent
Safe attachment	Low	6	20.0
	Average	8	26.7
	High	16	53.3
Anxiety-ambivalent attachment	Low	4	13.3
	Average	10	33.3
	High	16	53.3
Avoiding attachment	Low	6	20.0
	Average	8	26.7
	High	16	53.3

Table 45.5 Attachment styles in patients with lumbar spondylosis (LS)

Lumbar spondylosis	Result level	Frequency	Valid percent
Safe attachment	Low	0	0
	Average	2	6.7
	High	28	93.3
Anxiety-ambivalent attachment	Low	22	73.3
	Average	6	20.0
	High	2	6.7
Avoiding attachment	Low	24	80.0
	Average	4	13.3
	High	2	6.7

distinct pattern of attachment; the safe style predominates and the anxiety-ambivalent style is at a very low level (Table 45.5). That suggests there is a tendency to suppress the anxiety occurring in relation with the attachment object and to shift it to the somatic level. Because attachment styles are formed in the first 3 years of life, and then they are stabilized and automated, it can be assumed that the previously reported mental difficulties are more features than states caused by somatic diseases.

45.4 Discussion

Studies into somatic diseases show that neuroticism plays an important role in the formation and treatment of these diseases. Neuroticism is defined as a tendency to express negative emotions (anxiety and tension), which exert a negative influence on the individual's behavior in relatively stressful conditions, manifested

by stimulation of the autonomic nervous system, especially its sympathetic part. A study conducted by Plopa (2006) showed a positive correlation of neuroticism with the anxiety-ambivalent and avoiding attachments, which, as shown in the present study, are characteristic of patients with cervical spondylosis, in contrast to patients with lumbar spondylosis.

Moreover, it is suggested that psychosomatic disorders may occur as a consequence of repeated stressful situations or lack of satisfaction in the lives of individuals, or as a result of non-adaptive strategies of coping with stress (Baradell and Klein 1993; Buss 2001; Krueger 2002). Plopa (2006) showed that persons with the anxiety-ambivalent attachment style and avoiding style often manifest an emotional avoiding style of coping with stress, which was also presented by the patients with cervical spondylosis in the present study.

The quality of attachment decides about the child's acquisition of self-regulatory skills, which are accompanied by the development of the nervous system networks responsible for the control of emotions, which include: the right brain hemisphere, the limbic system, and the autonomic nervous system (Schor 2001). Proper self-regulatory skills develop when the mother's attitude is adequate and leads to the formation of the safe attachment pattern in the child. The inadequate attitude of the mother leads to the formation of a non-safe (anxiety-ambivalent or avoiding) attachment pattern that disturbs the normal development of reflective self-consciousness of the child. The consequences of such disordered development for own emotional states are the experiencing and regulating them on the basis of a physical record, instead of a mental one. The child experiences the affect not as a psychological state, but only as a situational somatic experience (Fonagy et al. 1995).

An incorrect interpretation of arousal is connected with an unsatisfied physical need and the lack of correct connections between arousal and a way of reacting to it in order to restore the optimal level of internal stress (homoeostasis). As a consequence, persistent excessive excitation may lead to increased sensitivity to a certain group of stimuli or reduced sensitivity as an attempt to cope with an unrecognized tension. Similar reactions are described by the authors studying the consequences of trauma for the correct child development (Herman 1995). Dysfunctional reception of stimuli from the body (propioception) can also impair para-spinal muscles' tension balance and cause the interferences of motor stereotypes, resulting from the deflection of the neuromuscular control mechanisms (Janda 1987). Consequently, the active stability of the spine is impaired and the so-called passive stabilizers (ligament, joint capsules) are more engaged to keep the stability. This leads to spondylosis (Chmielewski 1999). Difficulties in the reception of stimuli may then lead to changes in the mental sphere (Self), as well as to a somatic disease (spondylosis). According to the literature, problems with the differentiation and interpretation of physical stimuli and a weaker sense of own borders, characteristic of patients with lumbar spondylosis, may be formed in early childhood and are the essential elements of personality development, which is important in the development of somatic diseases (Anzieu 1979; Orbach 2002).

Based on the theoretical background and the analysis of the present results, the following conclusions can be drawn:

- In patients with cervical spondylosis and lumbar spondylosis the attachment styles appreciably differ from those in healthy subjects.
- Patients with cervical spondylosis present low levels of the safe attachment style and increased levels of the anxiety-ambivalent and avoiding styles. However, the differences between various styles are statistically insignificant, which shows there is no dominant style of attachment.
- Attachment styles in patients with cervical spondylosis are appreciably connected with the personality trait – neuroticism which is known as a predicator of various somatic and mental diseases. These attachment styles also are connected with the parents' unfavorable educational attitudes and the emotional style of coping with stress.
- In patients with lumbar spondylosis the safe (healthy) attachment style dominates, but there also is the anxiety-ambivalent style at a low level. This may suggests a tendency to suppress anxiety. In these patients the differences between various attachment styles are statistically significant.

As a result of this study some questions arise which remain open. They refer to a cause and effect link between the attachment style and cervical and lumbar spondylosis, to potential therapy which could help alleviate somatic symptoms of muscular tension, as well as possible psychotherapeutic actions which could alter the attachment style pattern.

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Chapter 46
Fear and Anger Among Adolescents and the Behavior of Their Mothers

Anna Jarmolowska

Abstract The aim of the present study was to show differences between adolescents from complete and incomplete families concerning their perception of parents' behavior, their fear, and expressed and unexpressed anger. The research included 126 girls and boys. The methodology consisted of standard scientifically verified and validated psychometric tools to assess the feelings and behavior outlined above. The major finding was that in the adolescents from incomplete families the acceptant and inconsequent behavior significantly increased the level of fear they felt which was associated with the expression of anger. Both reactions – fear and anger seem to be strictly connected with the adolescents' gender.

Keywords Adolescent • Family • Gender • Anger • Fear • Behavior

46.1 Introduction

Parental behavior clearly influences the child's personality and functions at different steps of growth and eventually adult years. The issue concerns, in particular, mother's behavior and her absence in the child's educational process. (Ziemska 1973; Plopa 1983; Rostowska 2002). Parental behavior is often seen as a structure of three components: cognition, emotion, and behavior.

Plopa (1987) has created a scale which constitutes a base for empirical research of parents' psycho-educational demeanor as perceived by the child or adolescent and reflected in his/her behavior. There are six steps in this scale:

- Acceptance – The parent accepts the child as he is, there is an atmosphere inviting to free exchange of thoughts, views, and emotions.
- Rejection – The child does not feel any pleasure or warmth in being close with parents; he perceives the parents as cold persons who do not see to his needs or problems.
- Autonomy – The parent treats the child as a nearly adult person and the parent's demeanor is flexible, according to the adolescent's needs in progressing developmental aspects.
- Protective Demeanor – The parent treats the child as a person who constantly needs to be protected.

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- Demanding Demeanor – The parent treats the child in a demanding manner according to the parent's absolute educational model.
- Inconsequence – The parental attitude toward the child is unstable depending on the parent's temporary mood or on personal problems, not necessarily connected with the family life.

During adolescence, reactions of anger appear as a result of similar situations to those in the younger years, but are intensified. One of the reasons evoking anger is that an almost grown-up person is treated as a child. The issue mostly concerns the system of punishment and limitation. Heavy-handed criticism, mocking, excessive pointing to the child's lack of experience, or breaking his aspirations for adulthood all lead to psychological disturbances. The manner of anger manifestation differs from child-to-child and changes with age (Hurlock 1960; Oginska-Bulik 1998). Nevertheless, two types of reaction may be defined:

- Impulsive – directed strictly against the person or object evoking irritation;
- Held back – reactions are hidden by a child.

In the present study I posed the following research questions:

- Do adolescents from complete families differ from those from incomplete ones?
- Are there any differences in the level of fear between the adolescents from both groups?
- Is the level of expressed and unexpressed anger different in both groups?
- What are the relations between parents' demeanor and adolescents' fear or anger?

46.2 Methods

The study was performed in conformity with the Declaration of Helsinki for Human Experimentation and the protocol was approved by a local Ethics Committee.

A 126 adolescents of either sex were included into the study. The adolescents were students of high schools located in major cities of northern Poland. Two groups were created and the criterion for division was the structure of family; a group of adolescents coming from incomplete families, who were brought up by the mother only (61 persons) and another group coming from complete families, i.e., the adolescents having both parents (65 persons). The latter group was taken as reference.

The study was one of a self-reported survey. The following questionnaires were employed:

- The Scale of Parental Behavior by Plopa (1987);
- The Inventory of the State and Properties of Fear (ISCL) by C. Spielberger, J Strelau, M. Tysarczyk and K. Wrzesniewski, consisting of two separate scales, one is designated to measure the state of fear, while the other to measure the properties of fear, each consisting of 20 items. The questionnaire is a Polish adaptation of the State-Trait Anxiety Inventory by Spielberger et al. (1970);
- The Anger Expression Scale (SEG) by N. Oginska-Bulik & Z. Juczynski. The scale consists of 20 items, ten of which are designed to measure the anger directed to the outside and another ten directed to the inside. The scale assesses the level of anger-related behaviors unrelated to particular situation, but rather corresponding to general situations.

46.3 Results and Discussion

Mothers' demeanor toward the adolescents from complete and incomplete families, the level of fear perceived by the adolescents and the type of anger they express in their behavior are depicted in detail in Tables 46.1, 46.2 and 46.3.

Table 46.1 Mothers' demeanor toward adolescents from complete and incomplete families

Demeanor		Complete families	Incomplete families
Acceptance	Girls	62.0 ± 9.0*	60.0 ± 10.2*
	Boys	55.4 ± 10.5	53.2 ± 11.9
Autonomy	Girls	58.8 ± 11.1	58.4 ± 6.4
	Boys	57.8 ± 10.9	59.0 ± 7.4
Protection	Girls	53.9 ± 11.6	52.7 ± 8.4
	Boys	49.1 ± 9.8	48.9 ± 8.2
Demand	Girls	39.7 ± 14.6	34.9 ± 14.9**
	Boys	42.4 ± 12.9	46.6 ± 11.1***
Inconsequence	Girls	38.4 ± 14.3	34.8 ± 14.0*
	Boys	39.6 ± 13.0	42.7 ± 11.2

Values are means ± SD
*$p < 0.05$ and **$p < 0.001$ for inter-gender differences within a given group of demeanor
***$p < 0.05$ for differences between complete and incomplete families within a given gender

Table 46.2 The level of fear perceived by adolescents in complete and incomplete families

	Complete families	Incomplete families
Girls	47.3 ± 10.7*	46.2 ± 11.6
Boys	40.1 ± 8.1	43.1 ± 7.5

Values are means ± SD
*$p < 0.05$ for inter-gender differences within a given group

Table 46.3 The type of anger present in adolescents from and incomplete complete families

Anger		Complete families	Incomplete families
Expressed	Girls	26.7 ± 7.7	23.5 ± 6.6*
	Boys	26.1 ± 6.3	27.9 ± 6.0
Unexpressed	Girls	33.9 ± 5.5	33.9 ± 5.5
	Boys	31.7 ± 6.7	31.8 ± 6.6

Values are means ± SD
*$p < 0.05$ for inter-gender differences within a given group

The adolescents differed in the area of the perception of motherly manners toward them. These differences were the following. The boys from incomplete families perceived their mothers as more demanding and inconsequent than the boys from complete families. The girls always perceived their mothers as more acceptant than the boys did, regardless of whether the family was complete or broken. Concerning the expression of fear, the psychometric tool employed failed to demonstrate appreciable differences between the adolescents from complete and incomplete families. However, the girls from complete families expressed fear to a significantly greater extent than those from broken, fatherless families. Likewise, no significant differences were found between the adolescents from complete and incomplete families, either in expressed or hidden anger. However, the boys from fatherless families demonstrated an appreciably greater proneness for expressing anger than the girls from these families.

I also found a number of associations between the motherly demeanor and the level of fear and anger. These were the following. The more acceptant the mothers' behavior, the lower was the children's level of fear. The more inconsequent the mothers' behavior, the greater were both the children's level of fear and the expression of anger. A greater expression of anger also was associated with less acceptant mothers' behavior and less autonomy given by the mother to the adolescents.

In conclusion, children from broken, fatherless families apparently display some psychological problems likely being related to a lesser feeling of safety or acceptance. The acceptant and providing a degree of autonomy to the child mother's attitude seems to have a mitigating effect on the child's disturbance caused by the lack of father in the family.

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Chapter 47
Psychosomatic Disorders Among Adopted People

Alicja Kalus

Abstract Adoption is connected with a number of traumatic experiences, of which the experience of being abandoned by biological parents is of major significance. The fact of being abandoned usually involves a stay at a hospital and later on in various forms of family or institutionalized foster care, until the child is finally placed in an adoptive family. An important research question, both on theoretical and empirical grounds, concerns the psychosomatic dependencies between adoption and children's psycho-physical development. The article presents an attempted synthesis of the theoretical findings and the results of the conducted empirical research. Considerations, apart from its cognitive aim, also have a practical end, i.e. to indicate problems in adopted children's development which should be of special importance for adoptive parents.

Keywords Adoption • Children • Family • Psychosomatic disorders • Physical development

47.1 Introduction

Adoption constitutes an important and up-to-date issue for theoretical considerations and for empirical research. The reason for this is a high rate of orphaned children and of married couples deciding on adoption. A child which qualifies for adoption has a history of traumatic experiences, the more significant of which is the experience of rejection (at various stages of development) by biological parents, and the experience of staying at a hospital, in an institution, or in a foster family.

According to the theory of psychosomatics, especially in its classic form, we use the term 'psychosomatic disorders' to characterize illnesses the etiopathogenesis and course of which are strongly influenced by mental, most notably, emotional factors (Johnson 1998). Alexander (1987), a classic scholar in psychosomatics, highlights the significance of emotional factors for the emergence of psychosomatic disorders. Among such factors, we distinguish physical and emotional traumatic experiences in early childhood, the emotional climate within the family, and the loss of an intimate person (death, emotional rejection). These factors play an important role in the development of adopted children, especially in the pre-adoption period.

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Given the above findings, it seems reasonable to raise the following issue: *In what way do traumatic experiences connected with being an adopted child, particularly in the pre-adoption period, influence children's psycho-physical development?*

47.2 Adoption as a Source of Traumatic Experiences for Children

Reports from studies concerning the relationship between adoption and psychosomatic problems of adopted people seem to be divergent. Researchers (Haugaard 1998) have been trying to find a pattern of disorders, characteristic of adopted people. Such hypotheses are based on data, according to which adopted children more often participate in various forms of counseling during adolescence. Impulsiveness, aggression, antagonistic and antisocial attitudes, displayed by the adopted, are some of the crucial problems (Grotevant and McRoy 1990). Grotevant (1997) attempted to explain the reasons behind a significant number of adopted people among the sufferers from mental problems. The author states that adopted children are exposed to disorders during adolescence due to factors causing distress and distorting the child's development during the prenatal period (alcohol and drug-abuse by the biological mother, a series of stressful situations to which she is subjected, improper diet and insufficient medical care given to her, etc.). However, it needs to be highlighted that this does not concern the entire population of adopted children, and is also characteristic of children brought up in biological families. The author also states that adoptive parents may be more open to seeking psychological aid among specialists, because they were prepared for that during the adoption process. Despite a significant number of studies conducted in this area, researchers have not succeeded in isolating any coherent group of disorders or psychological problems, which could be recognized as typical of adopted people (Haugaard 1998).

47.3 Analysis of Psychosomatic Disorders Among Adopted Children in Light of Selected Empirical Research

The first theories which gave shape to studies on adoption, in the early 1940s, drew attention to the psychologically negative effects of childlessness, i.e., the inability to attain motherhood, and, as a result, on the later ability of the adoptive mother to fully show motherly love to a child (Deutsch 1945). This psychoanalytical approach reflects the historical and present view that motherhood is based on instinct and that the problems of adopted children derive from disordered (improper) subconscious desires of their mothers (Eyer 1992). Critics of this line of argumentation, on the other hand, argue that using the term 'bad mother – biological or adoptive', and imputing the responsibility for the child's problems to the mother is rooted in the North American culture in which there is a schema of burdening the mother with the consequences of problems with the child (Caplan 1989; Eyer 1996; Wegar 1997).

From the psychoanalytical perspective, problems of adopted children were often defined as the so called 'adopted child syndrome' (Kirschner and Nagel 1988; Kirschner 1992). This term was applied in relation to antisocial behavior and personality traits of adopted children, resulting from their inability to integrate two different – often characterized as 'good' or 'bad' – parental ideas (Simon and Senturia 1966). The negative traits of children's character are, with time, expanded to the emerging tendencies of the parents to project their own unaccepted impulses on the adopted child and his biological parents, ultimately leading to the creation of a 'denial and repression' schema in the family (Kirschner 1992). A tendency of psychoanalytically oriented scientists to disregard the social context of experiences connected with adoption may contribute to deforming the nature of many problems.

The basis for the attachment theory was the studies conducted in the 1940s and 1950s in the United States and in Europe. These studies concerned the negative influence of the loss of mother-care on the development of small children, resulting from such events as long placement in institutions, e.g., hospitals, frequent changes of the person fulfilling the role of the mother; being separated from the mother as a result of divorce, death, or other events, such as the mother's mental illness or the appearance of siblings. Bowlby (1997) mentions three phases which children go through: protest, despair, and detachment.

Adoption is always connected with the attachment-separation-loss chain. Adopted children often go through a series of experiences connected with loss. That is why the attachment theory was accepted by many theoreticians of adoption as potentially significant for an understanding of adjustment patterns of adopted children and their families, with special emphasis on children adopted after their first year of life, as well as those who experienced many guardian changes (Fahlberg 1979). 'Adopted children, having experienced bond loss, must go through this process, in order to build new relationships with others. However, without fully developed cognitive and emotional processes, they may display behaviors provoking rejection which, paradoxically, they are afraid of, as if stating *I will do it before you will*. This can also be expressed through aggressive behavior. A different type of behavior will consist in constant complaining and conciliation, expressed through dysphoria and withdrawal, as if the children were stating *If I act like that, then maybe you will abandon me.* From this perspective parental care over an adopted child takes on a joining in mourning dimension' (Levy and Orlans 2003).

Research conducted on the attachment of infants, taken from their biological parents after their sixth month of age, indicate that they suffer due to various social and emotional difficulties, and that after 10 years many of these children still displayed certain relationship disorders (Yarrow and Goodwin 1973; Yarrow et al. 1973). Ethological theories emphasize the role of the attachment-separation-loss process as fundamental for the occurrence of problems among many adopted children, especially those adopted after their period of infancy (Bowlby 1969; Yarrow and Goodwin 1973; Yarrow et al. 1973; Steinhauer 1983). Studies conducted by Tizard (1977) documented the long-term influence of adverse upbringing and development conditions in early childhood on the development of attachment in children who were later adopted. Researchers concluded that at the age of two, adopted children, who were initially brought up in institutions, displayed stronger attachment and to a greater number of people than children who were not adopted. Attachment theories were also used to study the stability *vs.* the breakability of adoptions among families with children, who were adopted at preschool or older age (Barth and Berry 1988). These studies indicated that children's positive behavior connected with attachment, which is also an indicator of increasing security in the family (e.g., parents could comfort their children, the children showed spontaneous emotions, and attributed significance to the parents' approval), increased with time among the children whose adoptions were successful. The opposite was true for those children who eventually had to leave the home of the adoptive family; they displayed lack of attachment behavior with time.

Stams et al. (2002) conducted research, based on the attachment theory, with special emphasis on the *internal working models* concept and on developmental hypotheses, the aim of which was to establish the character of the relationship between maternal sensitivity to children's reactions, children's attachment style and temperament, and their later adjustment in the scope of social, cognitive, and personality development as well as behavior problems. Their studies were based on reports of earlier analyses (Belsky 1981, 1984; Sroufe et al. 1993; Weinfield et al. 2000), conducted on the biologically tied mother-child dyads. The researchers concluded that maternal sensitivity to children's needs, their temperament and style of attachment are especially significant for predicting later social-emotional and cognitive adjustment. Stams et al. (2002) studied adopted children (a sample of 146 children, placed in adoptive families before their sixth month of life) who were not biologically tied with their adoptive parents (studies independent of genetic ties). The researchers set a hypothesis, based on assumptions stemming from Bowlby's attachment theory, that 'the type of parent–child relationship in the infancy

and early childhood period is an important factor, influencing coherence in the development of an individual over a time-span, and facilitating children's adjustment in mid-childhood, especially in favorable external conditions' (Bowlby 1988).

Studies by Brodzinsky et al. (1984); Stams et al. (2000) indicate that adopted children display many more behavioral disorders and go to mental health centers more often than their peers. Maternal sensitivity to children's needs and reactions during early and mid-childhood, the attachment style between the mother and infant, and temperament displayed during the first months of life enable, to a great extent, the prediction of later adjustment. Temperamental problems, revealed during early childhood, are connected with a lower level of adjustment at the age of 7 years, in the scope of social and cognitive development, and with behavior issues. The researchers stated that in case of adopted children there is a large probability of predicting their later adjustment on the basis of characteristics of their relationship with their parents in early childhood. High sensitivity of the mother to infant reactions and a secure attachment style constitute a basis for predicting a better social and cognitive development. What is more, there is a significant relationship between temperament and disordered attachment. Such a combination of two risk factors – disordered attachment and 'difficult temperament' – allows predicting, with a great degree of probability, a lower level of cognitive development. These studies indicate that an anxious and disordered attachment style (see Ainsworth and Bowlby 1954) does not necessarily mean maladjustment in the mid-childhood period. Disordered attachment was a predictor of later difficulties with adjustment only in situations when it was accompanied by early difficulties connected with the child's temperament. 'The combination of these two factors is connected with later less optimal ego-control and a lower level of cognitive development in the mid-childhood period' (Stams et al. 2002). Disordered attachment in early childhood is, on the other hand, connected with externalized behavioral problems. An important conclusion to be drawn from the studies above outlined is that disordered attachment in early childhood is not in itself a condition ensuring the development of adjustment problems. It is only the co-occurrence of two factors – difficult temperament and quality of mother-child relations – which can cause less optimal adjustment abilities such as worse ego-control and cognitive development. Among the limitations of these studies is the omission of the father-child relationship. 'The relationship between the type of attachment and the quality of the mother-child interaction, on the one hand, and the later adjustment of the child, on the other, could be treated as a specific indicator of an individual's development coherence. From the point of view of the attachment theory, the degree of individual development coherence is a combination of past and present influences of environmental and individual factors (Sroufe 1997).

47.4 Conclusions

Disorders of psychosomatic character are connected with difficult experiences of emotional nature. The above considerations indicate that adoption, though often described in the literature as a happy ending, is connected with numerous traumatic experiences in the life of children. It seems justified to state that adoption constitutes a significant source of psychosomatic disorders.

Bowlby's attachment theory and the results of studies conducted on the basis of its theoretical assumptions show that adopted children go through traumatic stages of experiencing loss (hospitalization syndrome), which consequently results in numerous difficulties in emotional and social development.

Regardless of differences in opinions as to the participation of adopted people in various forms of treatment or counseling, it is worth noticing that the repertoire of difficulties or even disorders among adopted people is wide. It seems important to put forward a question, which could constitute an interesting research issue – how do adopted people cope with traumatic experiences in adult life in marital or parental relations?

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Chapter 48
Market Surveillance of *In Vitro* Diagnostics by the BfArM Until End 2010: Safety of IVD for Therapeutic Drug Monitoring

R. Siekmeier and D. Wetzel

Abstract The European Directive 98/79/EC on *in vitro* diagnostic medical devices (IVD) regulates the marketing and post market surveillance of IVD in the European Economic Area. In cases of incidents and field corrective actions, the manufacturers have to inform the responsible Competent Authorities (CA). In Germany, the Federal Institute for Drugs and Medical Devices (BfArM) is the responsible CA for most IVD. In this study all notifications regarding IVD for therapeutic drug monitoring (TDM) between begin 1999 until end of 2010 were analysed. A total of 2,851 notifications were received, of which 65 were related to IVD for TDM included in this study (54 tests *vs*. 11 analysers). Reports were received from manufacturers (58), CAs (5 cases) and users (2 cases). Most frequently IVD used for TDM of toxicologically relevant substances, antibiotics, antiepileptics and immunosuppressives were affected. Investigations of the manufacturers were able to identify the underlying root causes of product failures in 50 cases (76.9%), 40 (74.1%) of which were tests and 10 (90.9%) analysers. In 11 cases (16.9%, all tests), the root cause remained unclear and in 4 cases (6.2%, 3 tests, 1 analyser) a product failure was excluded. Product failures in tests were most commonly material defects (12 cases), interferences (7 cases) and manufacturing errors (7 cases), whereas in the analyser group software errors (5 cases) were most common. Corrective actions were performed in 56 cases (86.2%); 46 (85.2%) in tests, and 10 (90.9%) in analysers. In the group of tests these were predominantly (multiple entries) customer information (46 cases, mandatory in case of a recall), recall (29 cases), modifications in production or quality management (29 cases) and modifications of the instructions for use (9 cases). However, in the analyser group corrective actions were typically customer information (10 cases), recall (5 cases) and software-update (4 cases). The obtained data demonstrate that there are differences in the type of product failures between analysers and tests, which are followed by different corrective actions depending on the root causes of product failure accordingly. The results and the experience since 1999 suggest that the system for post marketing surveillance of IVD is an established tool to enhance product safety even though further optimisation is possible.

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48.1 Introduction

The Directive 98/79/EC from 1998 regulates conformity assessment, marketing and the post-marketing surveillance of *in vitro* diagnostic medical devices (IVD) in Europe (Directive 98/79/EC of the European Parliament 1998). The substance of the European Directive has been implemented in Germany by means of the 2nd Amendment on the German Law on Medical Devices (MPG, Medizinproduktegesetz) on January 1st 2002 (Medizinproduktegesetz 2002) as amended in 2009. The law is supported by the Ordinance on the Medical Devices Vigilance System (MPSV) from June 24th 2002 (Verordnung über die Erfassung, Bewertung und Abwehr von Risiken bei Medizinprodukten 2002) which was also revised in 2010. In brief, the manufacturers are obliged to systematically review the experience gained from devices on the market, to implement corrective actions as necessary and to report incidents and recalls (notification) to the responsible Competent Authority (CA). According to the Ordinance on the Medical Devices Vigilance System, in Germany professional operators and users also have to report incidents to the CA that they observe when using the products (Verordnung über die Erfassung, Bewertung und Abwehr von Risiken bei Medizinprodukten 2002). The same obligation applies to pharmacies and other retail organisations if incidents related to OTC-products sold by them to lay people come to their knowledge. In Germany the Federal Institute for Drugs and Medical Devices (BfArM, Bundesinstitut für Arzneimittel und Medizinprodukte) and the Paul-Ehrlich-Institute (PEI) are responsible for registration and examination of issues related to IVD. The latter is responsible for only selected IVD for infection testing and immune hematological diagnostics as well as tissue-typing as specified in Annex II of Directive 98/79/EC (Directive 98/79/EC of the European Parliament 1998; Medizinproduktegesetz 2002; Verordnung über die Erfassung, Bewertung und Abwehr von Risiken bei Medizinprodukten 2002; Siekmeier et al. 2008; 2009; 2010).

In evaluating the reports and other relevant information regarding the remaining risk after implementation of corrective actions the task of the CA is to evaluate the risk (in terms of probability of occurrence of harm and severity of the harm) and to assess it for acceptability. In case of unacceptable risks the necessary corrective action is to be determined. If manufacturers have already taken measures under their own responsibility, the CA takes decision on whether or not these are adequate. Any field safety corrective action (FSCA) performed by the manufacturers must be properly communicated to the customers and users. In Germany this is typically done by contemporary sending of customer information letters; the letter must also be sent to the BfArM for information and publication on the homepage of this CA (Siekmeier et al. 2010; Guidelines on a Medical Devices Vigilance System 2007).

As CE-marked devices can be freely moved and marketed in the entire European Economic Area (EEA), there is a need for information to be exchanged between CAs, in particular when a FSCA becomes necessary. The Directive therefore requires that the European CAs inform each other and the European Commission of cases that lead to corrective actions. Having been informed through a vigilance report, all CAs can then monitor the corrective action in their area of responsibility and determine if similar products of other manufacturers may also be affected by the observed safety issue.

Up to now only few data regarding the experience with market surveillance of IVD have been published (Siekmeier et al. 2008, 2009, 2010; Halbauer et al. 2009; Siekmeier and Lütz 2007a, b; Spitzenberger et al. 2007). Furthermore, the group of IVD is very heterogeneous regarding the users of the products (professional users *vs*. lay users), the type of the products (e.g., tests, calibrators, control materials, culture media and analysers), the technology used (e.g., culture, biochemistry,

immunology and molecular biology) as well as the clinical field where the products are used (e.g., clinical chemistry, hematology, coagulation, microbiology and therapeutic drug monitoring). Aim of this study was to analyse all notifications related to IVD for therapeutic drug monitoring (TDM) received by the BfArM until end of 2010, as this type of IVD can play a key role in the diagnosis of life threatening diseases.

48.2 Methods

All notifications of IVD received by the BfArM between begin of 1999 and end of 2010 were included in the study. The number included a small subset of notifications received 1999–2002, i.e., in the transition period prior to implementation of Directive 98/79/EC into national regulations (MPG) and the MPSV (Medizinproduktegesetz 2002; Verordnung über die Erfassung, Bewertung und Abwehr von Risiken bei Medizinprodukten 2002). Detailed analysis was made for tests and reagents, including calibrators and controls (test group) as well as for laboratory analysers (analyser group) serving for therapeutic drug monitoring (TDM). In the latter group only notifications directly affecting tests for TDM were included. Analysis was made separately for tests and reagents on one hand and laboratory analysers on the other hand regarding the source of notification, failure mode, the underlying root cause of product failure and the corresponding corrective measures performed by the manufacturers.

48.3 Results

48.3.1 Number of Reports

The number of notifications received by the BfArM steadily increased since the beginning of the observation period in 1999. Until end 2010 BfArM had received a total of 2,851 notifications concerning IVD. Of these, about 44.3% were related to IVD for lay use (predominantly IVD for self measurement of blood glucose followed by IVD for pregnancy testing in urine and IVD for self monitoring of blood coagulation) (see Table 48.1). 65 notifications (2.3% of all notifications) were related to IVD for TDM. These included 54 issues related to tests or reagents and 11 issues related to laboratory analysers. The majority of notifications included one type of product only (e.g., one reagent or one test parameter on a laboratory analyser). However, a small subset included several products (1 notification in the group of tests and reagents, 2 notifications in the group of laboratory analysers). In consequence, the number of affected laboratory parameters is higher than the number of received notifications.

48.3.2 Sources of Reports

The majority of notifications (58 out of 65; 89.2%) were received from the manufacturers or their distributors. Minor numbers of notifications were received from other CAs; European CAs (3 notifications), national authorities (2 notifications), or users (2 notifications). There was obviously no difference between the group of tests and reagents on one hand and the group of laboratory analysers on the other hand (see Table 48.2).

Table 48.1 Number and type of notifications related to medical products in total and related to IVD received by the BfArM

Year	Total number of notifications to BfArM	Number of notifications to BfArM related to IVD	Proportion of lay use IVD related to all IVD notifications (%)	Proportion of notifications related to IVD to all notifications (%)
1999	1,818	13	0.7	15.4
2000	1,934	21	1.1	23.8
2001	2,019	33	1.6	24.2
2002	2,266	58	2.6	46.6
2003	2,535	121	4.8	32.2
2004	3,097	200	6.5	16.0
2005	3,387	207	6.1	24.2
2006	3,862	235	6.1	35.7
2007	4,646	583	12.5	68.1
2008	4,883	506	10.4	55.9
2009	4,894	392	8.0	41.3
2010	5,780	482	8.3	36.3

Table 48.2 Sources of IVD notifications for therapeutic drug monitoring (n = 65)

Source of report	Tests and reagents (n)	Analysers (n)	Total (n)
Manufacturers	47	11	58
Other competent authorities	5	0	5
Users	2	0	2
All[a]	54	11	65

[a]No notifications received from other sources: e.g. market competitors, media, lawyers

48.3.3 Types of Products

The analysis regarding the affected laboratory parameters reflects the clinical relevance of the different parameters of TDM. Due to the inclusion of more than one product in some notifications (especially notifications related to analyser failures) the number of affected parameters was higher than the number of notifications. Most affected compounds of TDM were toxicologically relevant compounds (e.g., drugs of abuse), antiepileptics, antibiotics and immunosuppressives. However, there were some minor differences of the parameters affected between test group and analyser group (see Table 48.3).

48.3.4 Frequency and Type of Product Failure

Analysis of product failures was conducted separately for the test group and the analyser group. In tests and reagents, the underlying root cause of product failure was identified in 40 out of the 54 cases (74.1%). A product failure was excluded by the investigations performed by the manufacturers in 3 cases (5.5%), while 11 cases (20.4%) remained unclear. However, the number of cases with unclear root causes included 8 cases in which the manufacturers confirmed a product failure but were not able to identify the underlying root cause and 3 cases of IVD not marketed in Germany, in which the root cause was not reported to the BfArM *via* vigilance report from the reporting foreign CA. In cases with proven product failure, the most frequent causes were material defects (12 cases, e.g., insufficient stability or contamination of enzymes or antibodies serving as raw material, variation of the proper-

Table 48.3 Notifications concerning the affected parameters of therapeutic drug monitoring (TDM)

Parameter	Tests and reagents (n)	Analysers (n)	All (n)
Antibiotics	11	4	15
Gentamycin	6	1	7
Tobramycin	1	1	2
Vancomycin	4	2	6
Antiepileptics	10	5	15
Carbamazepine	2	2	4
Phenobarbital	6	1	7
Phenytoin	2	0	2
Valproic acid	0	2	2
Antipsychotics	2	3	5
Benzodiazepines	2	1	3
Lithium	0	2	2
Tricyclic antidepressives	0	0	0
Cardiac drugs	5	2	7
Quinidine	1	0	1
Digoxin	2	1	3
Digitoxin	1	1	2
Lidocaine	1	0	1
Immunosuppressives	14	0	14
Cyclosporine	3	0	3
Everolimus	1	0	1
Methotrexate	2	0	2
Sirolimus	3	0	3
Tacrolimus	5	0	5
Others	14	4	18
Acetaminophen/paracetamol	2	1	3
Amanitin	1	0	1
Drugs of abuse	6	1	7
Ethanol	3	0	3
Salicylate	1	1	2
Theophylline	1	1	2

ties of the used raw materials within their specifications resulting in a reduced test performance), manufacturing errors (7 cases, e.g., improper printing of barcodes, overloading of the conjugate, erroneous antibody concentration due to a weighing error, incorrect assembly of the test strip), and interferences (7 cases, e.g., interferences with other drugs or metabolites as well as different proteins in the sample). The other causes were labelling error (4 cases, e.g., incorrect lot numbers, incorrect target value of the analyte in the control material, incorrect type of sample material, insufficient safety data), insufficient design (3 cases, e.g., lack of test robustness, impaired reagent stability due to a suboptimal formulation, systematic bias in comparison to other methods due to the reagent formulation), miss of specification (3 cases, e.g., analytical recovery lower than stated by the manufacturer, interference of ethanol evaporating from other reagents stored at the same time on the analyser), packaging error (2 cases, e.g., increased humidity in the sealed packages, erroneous position of reagent bottles in the kit), calibration error (1 case, e.g., incorrect ratio of calibrators in the kit), and faulty instructions for use (1 case, indefinite description of an interference). In the analyser group, the underlying root cause of product failure was identified in 10 out of 11 cases (90.9%), in the remaining case (9.1%) a product failure was excluded. The most common causes of product failure were software errors (5 cases, e.g., misidentification of test cartridges, incorrect reading of reagent shelf-life data, reagent carry-over and insufficient washing steps, stop of the workflow), and design faults

Table 48.4 Product failures in IVD for therapeutic drug monitoring (n = 65)

	Tests and reagents n (%)	Analysers n (%)	All n (%)
No. of cases (%)	54 (100.0)	11 (100.0)	65 (100.0)
No. product failure (%)	3 (5.5)	1 (9.1)	4 (6.2)
User error	0	0	0
Root cause not identified[a](%)	11 (20.4)	0 (0.0)	11 (16.9)
Product failure identified (%)	40 (74.1)	10 (90.9)	50 (76.9)
Material defect	12	0	12
Software error	0	5	5
Calibration error	1	0	1
Electrical error	0	0	0
Mechanical error	0	0	0
Miss of specification	3	0	3
Manufacturing error	7	1	8
Incorrect instruction for use	1	0	1
Non-microbial contamination	0	0	0
Packaging error	2	0	2
Microbial contamination	0	0	0
Interference by other substances	7	0	7
Design fault	3	3	6
Labeling error	4	1	5

[a]Includes a small number of root causes not reported to the BfArM for IVD not marketed in Germany

(3 cases, reagent carry-over). Other causes were a production error (1 case, chemical contamination of reagent buffer due to inappropriate tubes in the production process), and a labelling error (1 case, incorrect data sheets) (see Table 48.4).

48.3.5 Corrective Actions

Corrective actions are performed for reduction of risks caused by products which are already on the market (e.g., customer information and recall) or for future products to ensure their safety (e.g., changes of raw materials and changes in production). As the regulations covering medical devices do not distinguish between those actions and most corrections target the products in the market as well as future releases, we do not differentiate in our analysis. Usually corrective actions are performed in cases of proven product shortcomings. Nevertheless, sometimes in cases of unidentified product failures, user errors and excluded product failures, manufacturers do perform corrective measures to reduce potential risk for future failures without being able to identify a root cause, e.g., isolated incidents.

In our analysis of corrective actions we defined cases in which corrective actions were performed only outside of Germany (i.e., when the affected product is not marketed in Germany) as cases without corrective actions. Training of a single customer, e.g., after isolated user errors were not defined as corrective actions, whereas training of all customers was considered as a corrective action. In our study, 46 corrective actions (85.2%) were performed in the test group (further 3 corrective actions outside Germany only). In 1 case without confirmed product failure and in 7 cases with unclear root causes (further 3 cases outside of the German market) manufacturers performed corrective actions. Most frequently corrective actions were (multiple entries) customer information (46 cases, mandatory in case of recall), recalls (29 cases), and modifications to production and/or quality management (29 cases). Other frequent corrective actions were modifications of the instructions for use (9 cases) as well as changes of design (7 cases), labelling (7 cases), and a change of material (6 cases, including

changes of raw material batches), whereas termination of marketing (3 cases) and software-update (1 case) were less frequent (see Table 48.5). In the analyser group, corrective actions were performed in 10 cases (90.9%) and were typically (multiple entries) customer information (10 cases), recalls (5 cases), software-updates (4 cases), and modification to production and/or quality management (4 cases). Other corrective actions were modification of the instructions for use (2 cases) or labelling (1 case) (see Table 48.5).

48.4 Discussion

Until end of 2010 a total number of 2,851 vigilance notifications related to IVD were received by the BfArM and the annual number of reports strongly increased (Siekmeier et al. 2008, 2009; Siekmeier and Lütz 2007b). This suggests that the European system for market surveillance is well functioning, even though there is an unknown rate of underreporting (from manufacturers and their distributors and especially from users of the affected products) which should not be underestimated. However, further optimisation in the vigilance system details (e.g., improvement of frequency and quality of notifications from users to the CAs, establishing and maintaining the European database, uniform criteria and procedures for international information exchange between CAs and the public by vigilance reports and publication of field corrective actions performed by the manufacturers, such as recalls and customer information due to product failure on the homepages of the CAs) should be gained for.

The study evaluates 65 IVD for TDM, of which 54 were tests, reagents, calibrators and control materials and 11 laboratory analysers. In contrast to the number of entities in the first test group, the number of entities in the IVD analyser group is biased by the inclusion criteria for the study. Out of the large number of notifications related to laboratory analysers only those were included which had or might have had a specific effect on the result of a TDM test, whereas others, e.g., general software errors which might cause sample misidentifications or mix-ups, short circuits, leaks not affecting the results as well as general consumables, were excluded. In consequence, the number of notifications included in the analyser group is small but provides more detailed information regarding specific problems resulting in erroneous results of TDM. Based on our definition, only 65 out of the 2,851 notifications (2.3%) were related to IVD which are used for TDM. However, this proportion is much higher (4.1%) if the 1,263 notifications related to IVD for lay use (e.g., systems for self-monitoring of blood glucose or coagulation, pregnancy tests) were excluded.

In both groups (tests and reagents as well as analysers) most of the notifications were received from manufacturers with a few distributors, while only few notifications were received from users, thereby indicating an underreporting on the side of the users. This confirms prior observations with lower proportions of notifications from users of IVD for professional use than from lay users (Siekmeier et al. 2008, 2009, 2010; Halbauer et al. 2009; Siekmeier and Lütz 2007a, b; Spitzenberger et al. 2007).

The number of TDM parameters affected is higher than the number of notifications. This was due to a few notifications which affected several parameters, e.g., up to 6 TDM parameters influenced by a software error in the analyser group. However, the list of affected parameters reflects the major groups of parameters in TDM playing a role in toxicological diagnostics and medical treatment.

The underlying root causes of product failures were identified in 74.1% and 90.9% of the notifications related to tests and reagents as well as laboratory analysers, respectively. But root causes remained unclear in 20.4% of cases in the test group, whereas all causes of product failures were identified in the analyser group. The high proportion of confirmed product failures and identified root causes is very similar to prior reports of IVD for professional use and much higher than in IVD for lay use (Siekmeier et al. 2008, 2009, 2010; Siekmeier and Lütz 2007a, b). Comparison of the data obtained between test and analyser groups demonstrates differences in the outcomes of the vigilance system, thereby resulting in different safety levels. Firstly, there are relevant differences in the proportions of

Table 48.5 Corrective actions in IVD for therapeutic drug monitoring (n = 65)

	Tests and reagents n (%)	Analysers n (%)	All n (%)
No. of cases	54 (100.0)	11 (100.0)	65 (100.0)
No corrective actions	8 (14.8)	1 (9.1)	9 (13.8)
Corrective actions[a]	46 (85.2)	10 (90.9)	56 (86.2)
Product recall/batch recall	29	5	34
Cessation of marketing	3	0	3
Change of design	7	0	7
Modification of production and / or quality management	29	4	33
Customer information[b]	46	10	56
Modification of the instruction for use	9	2	11
Software-update	1	4	5
Modification of labelling	7	1	8
Modification of raw material	6	0	6
Customer education[c]	0	0	0

[a]Multiple entries for the different subgroups of corrective actions
[b]Alone or in combination with a recall (in case of a recall customer information is mandatory)
[c]Training of a single customer, e. g., after a user error was not defined to be a customer education

identified and unclear root causes of product failure. This indicates that it might be more difficult to identify product problems in the complex mixture of reagents and under the conditions of sample reagent interactions than to identify technical problems in laboratory analysers. Generally, identification of product failures requires the product for investigation by the manufacturers. One might assume that this is no problem for the manufacturers as they have retained samples of the test and reagent batches as well as the analysers storing detailed data on their technical equipment and software. In most cases the investigation of the original user reagent, the patient sample and the corresponding raw data stored on the analyser might provide important information (e.g., in cases of interferences). Unfortunately, original reagents, patient samples and raw data are often not available to manufacturers for further investigation. Provision of these materials would improve the results of root cause investigation by the manufacturers and reduce the number of cases remaining unclear. Secondly, there are differences regarding the type of the identified root causes of product failure. In detail, tests and reagents are typically prone to material errors, production errors and interferences whereas laboratory analysers bear the risk of software malfunction. However, even though the present study investigated IVD for TDM only, the obtained results confirm the outcomes of prior studies investigating IVD for use in haematology, coagulation testing and diagnostics of infective diseases (Siekmeier et al. 2008, 2009, 2010; Siekmeier and Lütz 2007b).

In our study corrective actions were performed in the test group in 85.2% and in the analyser group in 90.9% of cases. Compared with a lower proportion of identified root causes in the test group, this shows that in this group corrective actions were performed even in cases without product failure or cases with unclear root causes of product failure. This underlines the important role of the manufacturer investigations to ensure and to improve safety and quality of their IVD. Most frequent corrective actions in both groups were customer informations and recalls, both reducing the risk caused by IVD already in the market. However, there were relevant differences in the preventive corrective measures because these depend on the underlying identified or assumed root causes of product failure. Correspondingly, these were frequently modification of production and/or quality management, modification of the instructions for use as well as changes of design, labelling and the used raw materials in the group of tests and reagents whereas software-updates were frequently performed in the group of laboratory analysers.

In summary, the results of this study suggest that the European surveillance system for IVD is an established tool for ensuring the safety of these products, even though there is room for optimisation.

For example, the exchange of information between European CAs as well as between German CAs and local German surveillance authorities could be further optimised. Comparison of the data of this study with the results of prior studies of our CA again demonstrates the specific character of distinct groups of IVD. The important role of the manufacturer to identify root causes of product failures and to perform the timely adequate corrective actions has also been shown. However, a number of weak points affecting performance and safety of IVD were identified supporting manufacturers and users to further improve the safety of IVD for therapeutic drug monitoring.

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

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Chapter 49
Market Surveillance of *In Vitro* Diagnostics by the BfArM Until End 2010: How Safe Are Products for Tumor Diagnostics?

R. Siekmeier and D. Wetzel

Abstract The European Directive 98/79/EC on *in vitro* diagnostic medical devices (IVD) regulates the marketing and post market surveillance of IVD in the European Economic Area. In cases of incidents and field corrective actions the manufacturers have to inform the responsible Competent Authorities (CA). In Germany, the Federal Institute for Drugs and Medical Devices (BfArM) is the responsible CA for most IVD. In this study all notifications regarding IVD (tests, calibrators, kits, and control materials, except laboratory analyzers) for tumor diagnostics received by the BfArM between begin 1999 until end of 2010 were analyzed. All notifications were analyzed in respect to the type of product, the source of notification, the underlying product defects and the corrective actions performed. In the observation period, a total of 2,851 notifications were received of which 84 were related to IVD for tumor diagnostics included in this study (clinical chemistry – 63, histology – 6, molecular biology – 3, rapid tests – 12). Reports were received from manufacturers (68 cases), CA (8 cases), users (4 cases) and other sources (4 cases). In the group of IVD based on clinical chemistry means, the affected products were mostly those for the measurement of prostate specific antigen (PSA, 14 cases), human chorion gonadotropine (13 cases), carcino embryonic antigen (6 cases), CA 19–9 (6 cases), α_1-fetoprotein (6 cases) and CA 125 (5 cases), whereas in test strips 9 out of the 12 notifications were related to PSA. Investigations of the manufacturers were able to identify the underlying root causes of product failures in 66 cases (78.6%). In 10 cases (11.9%) the root cause remained unclear and in 6 cases and 2 cases (7.1% and 2.4%) a product failure was excluded or a user error was the underlying cause. Most common root causes of product failures were material defects (24 cases) and manufacturing errors (15 cases). Corrective actions were performed by the manufacturers in 64 cases (76.2%) and were predominantly (multiple entries possible) customer information (62 cases, mandatory in case of a recall), recalls (45 cases), modifications in production or quality management (45 cases) and design changes (14 cases). The obtained results suggest that the system for post marketing surveillance of IVD is an established tool to enhance product safety and provides valuable information on product specific problems serving for improvement of product safety.

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49.1 Introduction

The Directive 98/79/EC from 1998 regulates conformity assessment, marketing and the post market surveillance of *in vitro* diagnostic medical devices (IVD) in Europe (Directive 98/79/EC of the European Parliament 1998). The substance of the European Directive has been implemented in Germany by means of the 2nd Amendment on the German Law on Medical Devices (MPG, Medizinproduktegesetz) on January 1st 2002 (Medizinproduktegesetz 2002) which was subject of several revisions in the meantime. The latter has been flanked by the Ordinance on the Medical Devices Vigilance System (MPSV, Medizinproduktesicherheitsplanverordnung) from June 24th 2002 (Verordnung über die Erfassung, Bewertung und Abwehr von Risiken bei Medizinprodukten 2002) which was also revised later on. In brief, the manufacturers shall be obliged to systematically review the experience gained from devices on the market, to implement corrective actions, where necessary and to report incidents and recalls to the responsible Competent Authoritiy (CA). According to the Ordinance on the Medical Devices Vigilance System, in Germany also professional operators and users have to report incidents that they observe when using the products to the CA (Verordnung über die Erfassung, Bewertung und Abwehr von Risiken bei Medizinprodukten 2002; Bornhak et al. 2002; Guidelines on a Medical Devices Vigilance System 2007; Medical Devices Post Market Surveillance 2006). The same obligation applies to pharmacies and other retail traders if incidents related to OTC-products sold by them to lay people come to their attention. In Germany the Federal Institute for Drugs and Medical Devices (BfArM, Bundesinstitut für Arzneimittel und Medizinprodukte) and the Paul-Ehrlich-Institute (PEI) are responsible for the registration and examination of issues related to IVD. The latter is responsible for only few IVD for infection testing and immune hematological diagnostics as well as tissue-typing as specified in Annex II of Directive 98/79/EC (Directive 98/79/EC of the European Parliament 1998; Verordnung über die Erfassung, Bewertung und Abwehr von Risiken bei Medizinprodukten 2002; Siekmeier et al. 2008, 2009, 2010).

In evaluating reports or other relevant information regarding risks, the task of the CA is to characterize the risk (in terms of probability of occurrence and severity of the harm) and to assess it for acceptability. In case of unacceptable risks, the necessary corrective action is to be determined. If manufacturers have already taken measures in their own responsibility, the CA has to take a decision on whether or not these are adequate. Any necessary field corrective action performed by the manufacturers must be properly communicated to the customers and users. In Germany, this is typically done by contemporary provision of customer information letters; the letter must also be sent to the BfArM for information and publication on their web resource.

As CE-marked devices in principle enjoy free movement in the entire European Economic Area (EEA), there is a need for information to be exchanged between CAs, in particular, when a field corrective action is to be taken. The Directive therefore requires that the European CAs inform each other and the European Commission of cases that lead to corrective actions. Having been informed through a vigilance report, all CAs can then monitor the corrective action in their area of responsibility (if this is deemed to be necessary) and also consider whether similar products of other manufacturers may also be affected by the observed problem.

Up to now, only few data regarding the experience on market surveillance have been published (Siekmeier et al. 2008, 2009, 2010; Siekmeier and Lütz 2007a, b; Spitzenberger et al. 2007; Halbauer et al. 2009). Furthermore, the group of IVD is very heterogeneous regarding the users of the products

(professional users *vs.* lay users), the type of the products (e.g., tests, calibrators, control materials, culture media and analysers), the underlying analytical methods (e.g., culture, biochemistry, immunology and molecular biology) as well as the clinical field where the products are used (e.g., clinical chemistry, hematology, coagulation, microbiology and therapeutic drug monitoring). Therefore, aim of this study was to analyze all notifications related to tests, reagents, calibrators and control materials for tumor diagnostics in the fields of clinical chemistry, histology and molecular biology received by the BfArM until end of 2010.

49.2 Methods

All notifications on IVD received by the BfArM between begin of 1999 and end of 2010 were included in the study. The number included a small subset of notifications received 1999–2002, i.e., in the transition period prior to implementation of Directive 98/79/EC into national regulations by the 2nd Amendment of the German Law on Medical Devices (Medizinproduktegesetz, MPG) and the Ordinance on the Medical Devices Vigilance System (Medizinproduktesicherheitsplanverordnung, MPSV) (Medizinproduktegesetz 2002; Verordnung über die Erfassung, Bewertung und Abwehr von Risiken bei Medizinprodukten 2002). Detailed analysis was made for tests and reagents (including calibrators and controls) which serve for tumor diagnostics. Notifications regarding laboratory analyzers and their general consumables (e.g., buffers and solutions which are not test specific, cuvettes) were excluded. Tests for determination of human chorion gonadotropine/β human chorion gonadotropine (hCG/βhCG) in urine were also excluded as these tests exclusively serve for pregnancy testing but not for tumor diagnostics. However, IVD specified for measurement of hCG/βhCG in serum or plasma were included. Analysis was made for tests performed on laboratory analyzers and rapid tests (mostly test strips). The group of laboratory tests and reagents was split into the subgroups of clinical chemistry based IVD (mostly measurement of so called 'tumor markers' in plasma or serum by immunological means), IVD for histological tumor diagnostics (e.g., histological staining reagents and reagents for immunological detection of tumor specific antigens) and IVD for detection of tumor specific mutations by molecular biological means. Analyses were made regarding the source of notification, the underlying root causes of product failure and the corresponding corrective measures performed by the manufacturers.

49.3 Results

49.3.1 Number of Reports

The number of notifications obtained increased strongly within the observation period (from 13 in 1999 to 482 in 2010). At the end of the observation period, BfArM had received a total number of 2,851 notifications concerning IVD of which about 44.3% were related to IVD for lay use (predominantly IVD for self measurement of blood glucose followed by IVD for pregnancy testing in urine and IVD for self monitoring of blood coagulation). 84 notifications (2.9% of all notifications or 5.3% of all notifications regarding professional use IVD) were related to IVD for tumor diagnostics, 72 of which were IVD for laboratory use only and 12 were rapid tests which may also sometimes serve for lay use but were not included into the number of lay use products listed before.

Table 49.1 Sources of notification (n = 84)

	IVD based on clinical chemistry means[a]	IVD based on histological means[b]	IVD based on molecular biological means[c]	All IVD except rapid tests	Rapid tests[d]	All
	n	n	n	n	n	n
Manufacturers	51	6	3	60	8	68
Other Competent Authorities	7	0	0	7	1	8
Users	1	0	0	1	3	4
Other sources[e]	4	0	0	4	0	4
All	63	6	3	72	12	84

[a]IVD for measurement of proteins and metabolites in plasma, serum or urine (except IVD specified exclusively for pregnancy testing)
[b]IVD containing secondary antibodies and staining solutions or primary antibodies for detection of tumor proteins
[c]IVD for detection of tumor specific mutations
[d]Test strips and IVD for stool testing
[e]Notifications from press, competitors, television and lawyers

49.3.2 Sources of Reports

Most notifications for products analyzed in this study (n = 68, 81.0 %) were received from manufacturers. Only few notifications were received from other CAs (8 cases, 9.5%), users (4) or other sources (4 cases, e.g., press, competitors, television, and lawyers). However, there were some differences between the distinct groups and subgroups of IVD included in this study. In detail, within the distinct subgroups of IVD for laboratory tumor diagnostics (mostly clinical chemistry based IVD, IVD for histological and molecular biological diagnostics) the proportion of notifications by manufacturers or their distributors ranged between 81 and 100%. Corresponding proportions of notifications from other CAs ranged between 0% and 11% (see Table 49.1). In contrast, notifications from users tended to play a major role in a small group of rapid tests, where 3 out of the 12 (25%) were received directly from professional users (hospital and resident laboratories) or via the Drug Commission of the German Pharmaceutical Association (1 and 2 notifications, respectively) (see Table 49.1).

49.3.3 Types of Products

As expected, the largest group were IVD for laboratory diagnostics of tumor diseases mostly based on clinical chemistry means. We included two notifications in this group regarding IVD for tumor diagnostics based on proteomic means. The other groups of IVD were, in descending size order, rapid tests (tests and required reagents), IVD for histological tumor diagnostics and IVD for molecular biological tumor diagnostics. In the group of clinical chemistry based tests, prostate specific antigen (PSA, prostate cancer) was the parameter most frequently affected (14 notifications). Other parameters notified in relevant numbers were hCG/βhCG (13 cases, teratoma, trophoblast tumor, pregnancy test), carcino embryonic antigen (CEA, 6 cases, colon cancer, breast cancer, lung cancer), CA 19–9 (6 cases, pancreas cancer, cancer of the bile duct), α_1-fetoprotein (6 cases, liver cancer, teratoma), CA 125 (5 cases, ovarial cancer), CA 15–3 (3 cases, breast cancer) and thyreoglobulin (3 cases, thyroid cancer) whereas notifications related to IVD for measurement of other parameters played only minor roles (11 cases, e.g., β_2-microglobulin (lymphoma, plasmocytoma), light chains (plasmocytoma), CA 72–4 (ovarian cancer, gastric cancer), pyruvate kinase type tumor M2 (TUM2-PK, colon cancer), 5-hydroxy indole acetic acid (5-HIAA, adrenal gland cancer), metanephrines (adrenal gland cancer) and proteomic based tests (urine tests for prostate and bladder cancer)). However, the number of affected parameters

slightly exceeded the number of notifications as there were few reports regarding several IVD and parameters. In contrast to a large spectrum of parameters in the group of laboratory tests 9 out of the 12 notifications in the group of rapid tests were related to IVD for the determination of PSA (test strips only). The remaining 3 notifications were related to stool tests for diagnostics of colorectal cancer (tests and reagents). IVD for histological tumor diagnostics included secondary antibodies and staining solutions (3 notifications) as well as products for detection of tumor specific proteins (3 notifications, human epidermal growth factor receptor 2 (HER-2) and thyroid transcription factor-1 (TTF-1)), whereas IVD based on molecular biological means (3 notifications) served for diagnostics of K-RAS and EGFR (epithelial growth factor receptor) mutations.

49.3.4 Frequency and Type of Product Failure

Analysis of all received notifications regarding the underlying product failures demonstrated that the root causes of product failure were identified in 66 out of the 84 cases (78.6%), whereas a product failure was definitely excluded by the manufacturers in 6 cases (7.1%) only. In the remaining cases, the product failure was caused by user errors (2 cases, 2.4%) or the root cause remained unclear (10 cases, 11.9%). However, the latter group included cases in which a product failure has been confirmed by the investigation of the manufacturers but not reported to the BfArM because the product was not marketed in Germany or the distribution was stopped and cases in which the manufacturers confirmed a product failure but were not able to identify the underlying cause (see Table 49.2). In order to get more detailed information analysis for the types of product failure was made separately for different product groups. However, due to the small number of products in the groups of IVD based on histological means and IVD based on molecular biological means and the obvious lack of differences these products were analysed together with IVD based on clinical chemistry means. In the combined group, a product failure was confirmed in 57 out of the 72 cases (79.2%). The underlying causes of product failure were most frequently material defects (19 cases, lack of quality of raw materials purchased from other manufacturers, aggregation and/or interaction of different raw materials in the reagent, variation of the antigenicity or susceptibility for interferences of the raw materials) and manufacturing errors (15 cases, incorrect concentration of reagent components, e.g., due to human error or insufficient standard operating procedures, malfunction in the production process, e.g., resulting in non-microbial contamination or insufficient function of the reagent caps or incorrect coating of wells). Other relevant causes were calibration errors (5 cases, e.g., erroneous calibration of reference panel or master calibrator, incorrect ratio between free and complexed PSA, erroneous threshold level for the test signal) and miss of specification (4 cases, e.g., non-suitability of samples after freezing, non-fulfillment of linearity or sensitivity, positive reaction even in other than the specified tumors), whereas microbial contamination (3 cases, e.g., agglutination due to microbial contamination), interferences by other substances in the patient sample (3 cases, interferences of not identified compounds and analyte concentrations beyond the linearity range), design shortcomings (3 cases, lacking robustness for variations in sample handling, insufficient linearity at high analyte concentration), labeling error (2 cases, missing target values of the recovery, incorrect concentration provided in the barcode), packaging error (2 cases, wrong reagent flask, correct reagent flask in the wrong position of a reagent kit) and an incorrect instruction for use (1 case, translation error) seldom occurred. In 8 cases (11.1%) the root cause of product failure was not identified or not reported and in 2 cases (2.8%) a user error (incorrect sample dilution, use of tests from different manufacturers for determination of total PSA and free PSA not according to the instruction of the manufacturer) was the underlying cause. In the group of rapid tests the root cause of product failure was identified in 9 out of the 12 cases (75.0%). Typically material defects were the cause of product failure (5 cases, low performance of the nitrocellulose membrane, peroxide degrading compounds in the alcohol of the developer solution). Other identified causes

Table 49.2 Product failures in IVD for tumor diagnostics (n = 84)

	IVD based on clinical chemistry means[a]	IVD based on histological means[b]	IVD based on molecular biological means[c]	All IVD except rapid tests	Rapid tests[d]	All
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Number of cases	63 (100)	6 (100)	3 (100)	72 (100)	12 (100)	84 (100)
No product failure	5 (7.9)	0 (0)	0 (0)	5 (6.9)	1 (8.3)	6 (7.1)
User error	2 (3.2)	0 (0)	0 (0)	2 (2.8)	0 (0)	2 (2.4)
Root cause not identified[e]	7 (11.1)	1 (16.7)	0 (0)	8 (11.1)	2 (16.7)	10 (11.9)
Product failure identified	49 (77.8)	5 (83.3)	3 (100.0)	57 (79.2)	9 (75.0)	66 (78.6)
Material defect	17	1	1	19	5	24
Software error	0	0	0	0	0	0
Calibration error	4	0	1	5	1	6
Electrical error	0	0	0	0	0	0
Mechanical error	0	0	0	0	0	0
Miss of specification	3	1	0	4	0	4
Manufacturing error	11	3	1	15	0	15
Incorrect instruction for use	1	0	0	1	0	1
Non-microbial contamination	0	0	0	0	0	0
Packaging error	2	0	0	2	2	4
Microbial contamination	3	0	0	3	0	3
Interference by other substances	3	0	0	3	0	3
Constructional fault	3	0	0	3	0	3
Labeling error	2	0	0	2	1	3

[a]IVD for measurement of proteins and metabolites in plasma, serum or urine (except IVD specified exclusively for pregnancy testing)
[b]IVD containing secondary antibodies and staining solutions or primary antibodies for detection of tumor proteins
[c]IVD for detection of tumor specific mutations
[d]Test strips and IVD for stool testing
[e]Includes a small number of root causes not reported to the BfArM for IVD not marketed in Germany

were packaging errors (2 cases, boxing of an old version of the instruction for use, boxing of a conjugate not suitable for the test), labeling error (1 case, discrepant shelf-life times between outer and inner packages of the test) and calibration error (1 case, incorrect cut-off value due to not taking into account the change of the sample material from blood to serum). In the remaining cases the root causes were not reported to the BfArM (2 cases) or a product failure was excluded (1 case) (see Table 49.2).

49.3.5 Corrective Actions

Corrective actions are performed for reduction of risks of products which are already on the market (e.g., customer information and recall) or for future products to enhance safety (e.g., changes of raw materials and changes in production or quality management). Both types of corrective actions are closely linked (often termed corrective action and preventive action; CAPA) and therefore not differentiated for in our analysis. Usually corrective actions are performed in cases of proven product failures but even in cases of unidentified product failures, user errors and excluded product failures manufacturers can perform corrective measures to reduce potential risk for future failures.

In our analysis of corrective actions we defined cases in which corrective actions were performed only in other countries but not in Germany (e.g., in cases where the affected product is not marketed in Germany) as cases without corrective actions. Three cases without corrective actions but with information of German Laender Authorities regarding possible non-conformity of the marketed IVD were also categorized as no corrective action. Information of a single customer only, e.g., after user errors was not defined either as a corrective action, whereas training of all customers was considered a corrective action.

For all product groups taken together, corrective actions were performed in 64 cases (76.2%). The remaining 20 cases (23.8%) included 6 cases in which the German market was not affected because the product was distributed in other countries only and 3 cases in which the BfArM only informed the German Laender Authorities because of questionable product conformity. Analysis was differentiated further into the groups of laboratory tests (all IVD based on clinical chemistry means, histological means and molecular biological means), on the one hand, and rapid tests, on the other hand. In the first group, corrective actions were performed in 54 out of the 72 cases (75.0%) (see Table 49.3). Proportion of corrective actions was lower in IVD based on clinical chemistry means (71.4%) than in IVD based on histological and IVD based on molecular biological means (100.0% both). All except 3 corrective actions (2 more in case of a corrective action not affecting the German market as the product was not distributed there) were performed in cases of proven product failure. Most frequent corrective actions were (multiple entries) customer information (54 cases, mandatory in case of recall), modification of production and/or quality management (41 cases) and recall (37 cases). Less frequent corrective actions were change of design (9 cases), modification of the instruction for use (7 cases), modification of the raw material (5 cases), and stop of marketing (3 cases), software-update (2 cases) and modification of labelling (1 case). Due to a small number of cases in the groups of IVD based on histological means and IVD based on molecular biological means, analyses for differences between these subgroups should be made carefully as chance findings cannot be excluded. However, the proportions of recalls and changes of design trended to be higher in the groups of IVD based on histological or molecular biological means than in the group of IVD based on clinical chemistry means (8 recalls out of the 9 notifications *vs.* 29 recalls out of the 63 notifications and 3 changes of design out of the 9 notifications *vs.* 6 changes of design out of the 63 notifications). On the other hand, modification of raw material and stop of marketing were only observed in the group of IVD based on clinical chemistry means (see Table 49.3). In the rapid tests group, corrective actions were performed in 10 out of the 12 cases (1 more corrective action outside of the German market only). Corrective actions were most frequently (multiple entries) customer information (8 cases, mandatory in case of recall), recall (8 cases), cessation

Table 49.3 Corrective actions in IVD for tumor diagnostics (n=84)

	IVD based on clinical chemistry means[a]	IVD based on histological means[b]	IVD based on molecular biological means[c]	All IVD except rapid tests	Rapid tests[d]	All
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Number of cases	63 (100)	6 (100.0)	3 (100.0)	72 (100)	12 (100)	84 (100)
No corrective actions	18 (28.6)	0 (0)	0 (0)	18 (25.0)	2 (16.7)	20 (23.8)
Corrective actions[e]	45 (71.4)	6 (100)	3 (100)	54 (75.0)	10 (83.3)	64 (76.2)
Product recall/batch recall	29	5	3	37	8	45
Stop of marketing	3	0	0	3	5	8
Change of design	6	1	2	9	5	14
Modification of production and/or quality management	33	5	3	41	4	45
Customer information[f]	45	6	3	54	8	62
Modification of the instruction for use	6	1	0	7	1	8
Software-update	2	0	0	2	0	2
Modification of labeling	1	0	0	1	1	2
Modification of raw material	5	0	0	5	0	5
Customer education[g]	0	0	0	0	0	0

[a]IVD for measurement of proteins and metabolites in plasma, serum or urine (except IVD specified exclusively for pregnancy testing)
[b]IVD containing secondary antibodies and staining solutions or primary antibodies for detection of tumor proteins
[c]IVD for detection of tumor specific mutations
[d]Test strips and IVD for stool testing
[e]Multiple entries for the different subgroups of corrective actions
[f]Alone or in combination with a recall (in case of a recall customer information is mandatory)
[g]Education of a single customer, e. g. after a user error was not defined to be a customer education

of marketing (5 cases), change of design (5 cases) and modification of production and/or quality management (4 cases). Other, seldom corrective actions were modification of the instructions for use (1 case) and modification of labelling (1 case) (see Table 49.3).

49.4 Discussion

Until end of 2010 a total number of 2,851 notifications related to IVD were reported to the BfArM and the annual number of reports is still increasing (Siekmeier and Lütz 2007a; Siekmeier et al. 2008, 2009). This suggests that the European system for market surveillance is well functioning even though there is an unknown rate of underreporting (from manufacturers and their distributors and especially from users of the affected products) which cannot be estimated. However, there should be further optimization in some details (e.g., improvement of frequency and quality of notifications from users to the CAs, establishing the European database, uniform criteria and procedures for information of the other international CAs and the public by vigilance reports and publication of field corrective actions performed by the manufacturers (e.g., recalls and customer information due to product failure), e.g., on the homepages of the CAs).

Our study included 84 IVD for tumor diagnostics. These were about 2.9% of all notifications related to IVD and about 5.3% of notifications related to professional use IVD in the observation period (begin 1999 – end 2010) demonstrating the relevance of this product group. As expected, conventional IVD for tumor diagnostics in plasma or serum based by clinical chemistry means were the largest group of these IVD, even though we included a small number of IVD based on proteomics in this group. Another large group were rapid tests (mostly test strips) for tumor diagnostics. In our view, this reflects the increasing role of such tests in the last years for patient self-testing and the interest of industry to develop and to introduce tests to be performed and to be paid for by patients separately. The other minor groups of IVD included in our study were IVD based on histological means and IVD based on molecular biological means. Both groups of products have been introduced into the market in the last years and reflect the increasing role of individualized diagnostics and treatment in oncology by detection of tumor specific proteins and mutations, respectively (Ogino et al. 2011). Likely, the number and role of such IVD will further increase as new tumor specific proteins and mutations will be identified which will be targets of oncological treatment. Notifications regarding analyzers even though they may specifically effect the outcomes of tumor tests (e.g., due to software errors and carry over of sample or reagent) were not included in our study as the underlying causes of product failure were very different and their number were smaller than the number of test related notifications.

Analysis was made separately for different product groups in order to identify differences due to variant analytical principles of the IVD (e.g., IVD based on clinical chemistry means, histological means and molecular biological means *vs*. rapid tests) and the user group (e.g., exclusively professional users in IVD based on clinical chemistry means, histological means and molecular biological means *vs*. professional and/or lay users in rapid tests). However, rapid tests for use in oncological diagnostics were not subject of our definition of lay use IVD (IVD for self testing of blood glucose or coagulation, pregnancy tests) even though some of these IVD might be specified also for lay use.

In all groups of IVD included in our study, most of the notifications were received from manufacturers (in few cases also from their distributors). Only few notifications were received from users indicating an underreporting in the latter group. However, the proportion of notifications from users trended higher in the group of rapid tests indicating specific differences of these IVD. In detail, a prior study demonstrated a high proportion of notifications from users in lay use products (mainly systems for self testing of blood glucose) which was much higher than the proportion of notifications in professional use IVD (Siekmeier et al. 2008, 2009, 2010; Siekmeier and Lütz 2007a, b). In the group of

laboratory tests, there was a proportion of notifications from other sources (e.g., press, competitors, television, lawyers). Even though their number was small such notifications sometimes played an important role (e.g., after a television report).

Analysis regarding the frequency of different parameters affected by notifications to the BfArM was only made in the group of IVD based on clinical chemistry means and rapid tests, as the other groups were too different and too small. However, one should consider that these parameters even though often termed 'tumor marker' typically serve for monitoring of tumor disease but not for screening (except prostate specific antigen, PSA which is also subject of controversial discussion), even though these tests are also used in primary diagnostics of cancer patients. In addition, the parameters not only serve for tumor diagnostics but also play a role in diagnostics and monitoring of non-malignant disease (e.g., CEA in inflammation of the colon, α_1-fetoprotein in hepatitis and acute liver damage, hCG/βhCG in pregnancy). In case of hCG/βhCG, we included only laboratory tests for analysis of plasma or serum, whereas tests for analysis of urine (with or without use of laboratory analyzers) were excluded because the latter serve exclusively for pregnancy testing. The most affected diagnostic parameter in both groups was PSA. In the group of laboratory tests, there were also relevant numbers of other affected parameters (e.g., CEA, CA 19–9, α_1-fetoprotein, CA 125) demonstrating the large role of these parameters in clinical routine. However, one should consider that even this group does not include only well established parameters from which some are used in special diagnostics only but also few novel parameters (e.g., tests based on proteomics technology for diagnostics of bladder and prostate cancer). In contrast, in the group of rapid tests 9 out of the 12 notifications were related to PSA (the remaining 3 were stool tests) based on test strip technology, indicating that these tests might be used not only by professional laboratory personnel but also by other user groups (e.g., in pharmacies, self testing by lay users). However, notifications in this group might be biased by notifications obtained from OEM manufacturers (OEM, other equipment manufacturers) related to similar products distributed in the market with different brand names.

Analysis by the manufacturer, identified the root causes of product failures in 78.6% of the reported cases with minor differences between the product groups included in the study. The high proportion of confirmed product failures and identified root causes is very similar to prior reports in professional use IVD and much higher than in IVD for lay use (Siekmeier et al. 2008, 2009, 2010; Siekmeier and Lütz 2007a, b). In 10 out of the 84 cases (11.9%), the root cause of product failure remained unclear. These included cases with confirmed product failure (some of them later on followed by corrective measures) and cases in which the patient sample allowed no more investigations or the retained products and trending of the products revealed no product failure but the cause of the failure at the customer's site remained unclear. In a few cases user errors were responsible for product failure. The proportion of these cases stands in ample agreement to the results of other studies in professional use products even though there is some variability of its frequency depending on the type of the product (Siekmeier et al. 2008, 2009, 2010; Siekmeier and Lütz 2007a). The occurrence of user errors again demonstrates that this cause of product failure should be considered by the manufacturers to strengthen their efforts into the usability process to further improve product safety. The most frequent root causes of product failure were material defects (defect of one batch of raw materials used for production or inadequate type of raw material) as well as manufacturing errors demonstrating the critical role of these root causes for product performance and once more underlining the results of other studies investigating reagents and tests (Siekmeier et al. 2008, 2009, 2010; Siekmeier and Lütz 2007a).

In principle, there are two types of corrective actions. The first one has the goal to reduce the risk of IVD which are already on the market and are or even may be affected by the reported product failure. This group of corrective actions includes recall, customer information and distribution stop of the affected product. Another type of a corrective action is the preventive action by which the manufacturer tries to reduce the risk of products which will be delivered in the market in the future.

In our study, a total of 64 corrective actions were performed reflecting 76.2% of all notifications. Analysis of the type of corrective action revealed that most frequent corrective actions were customer information which is mandatory in cases of recalls, recall and modification of production and/or quality

management which are often combined. These data again confirm the results of other studies for professional use products published by the BfArM and are different to the results obtained in lay use products (Siekmeier et al. 2008, 2009, 2010; Siekmeier and Lütz 2007a, b). Other frequent corrective actions were design changes, cessation of marketing, modification of the instruction for use and modification of the raw material, also standing in agreement with results of different product groups published before. However, there are some specific aspects to consider. For example, there is a very low rate of software updates in the IVD analysed in the present study demonstrating the large difference of this product group, when compared to different types of laboratory analyzers which were subject of other studies (Siekmeier et al. 2009, 2010). Further, the low rate of modification of raw material stands in conflict with the high frequency of material defects identified as underlying root cause of product failure. This obvious contradiction can be explained by the underreporting of the manufacturer in their final reports sent to the BfArM (modification of the raw material not explicitly mentioned) and the complete consumption of the raw material for product production before observation of product failure and identification of the root cause. Considering the high number of material defects as identified root cause of product failure assumption of some cases of underreporting might have relevantly increased the number of modifications of raw materials as a corrective action performed by the manufacturers. Contributing is that most corrective actions of this type are modifications of the used raw materials only, whereas material replacements might be combined with design changes of the product. Finally, the relatively high number of cessation of marketing and design changes are caused by the high frequency of these corrective actions in the group of rapid tests. Likely, this group of IVD differs from the other IVD included in this study in respect to the type of product, group of users and the corrective actions performed by the manufacturers and however, the results obtained for this group of IVD might be biased by reports of OEM manufacturers.

In summary, the obtained data suggest that the European surveillance system for IVD is an established tool for ensuring the safety of these products. However, there should be some optimizations, e.g., further improvement of the exchange of information between European CAs by implementation of the EUDAMED database as well as between German CAs and local German CAs. As in other previous studies, the results of this study indicate that there are some differences between the different IVD even within the small group of IVD for oncological diagnostics which are likely caused by different technologies and user groups. Analyses of Competent Authorities like in this study may help to identify weak points of product performance and time dependent changes of product related risk pattern (e.g., in cases of recently developed products) and support manufacturers and users to improve product safety.

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