ISSN 1806-3713

JBP
Jornal Brasileiro de **Pneumologia**
www.jbp.org.br

Volume 42, Number 2
March | April
2016

Volume 42, Number 2 March | April 2016

HIGHLIGHT

Review Article: New Anticoagulants

Continuing Education: the Importance of Sample Size

Asthma and Smoking in Adolescents

A CIDADE MARAVILHOSA TE ESPERA DE BRAÇOS ABERTOS PARA NOSSO PRÓXIMO ENCONTRO

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XXXVIII Congresso Brasileiro de Pneumologia e Tisiologia
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XIV Congresso Brasileiro de Endoscopia Respiratória

11 a 15 de outubro de 2016 • Riocentro, Rio de Janeiro/RJ

ISSN 1806-3713

Jornal Brasileiro de Pneumologia

Published once every two months J Bras Pneumol. v.42, number 2, p. 81-162 March/April 2016

ISSN 1806-3713

Jornal Brasileiro de Pneumologia

Expediente

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ADMINISTRATIVE SECRETARIAT OF THE BRAZILIAN JOURNAL OF PULMONOLOGY
Address: SCS Quadra 01, Bloco K, Asa Sul, salas 203/204. Edifício Denasa, CEP 70398-900, Brasília, DF, Brazil. Tel. +55 61 3245-1030/+55 0800 616218.
Assistant Managing Editor: Luana Maria Bernardes Campos.
E-mail: jpneumo@jornaldepneumologia.com.br
Circulation: 3.500 copies
Distribution: Free to members of the BTS and libraries
Printed on acid-free paper

SUPPORT:
Ministério da Educação
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GOVERNO FEDERAL BRASIL PAÍS RICO É PAÍS SEM POBREZA

ISSN 1806-3713

Jornal Brasileiro de Pneumologia

Published once every two months J Bras Pneumol. v.42, number 2, p. 81-162 March/April 2016

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EDITORIAL

ORIGINAL ARTICLE

ISSN 1806-3713

Jornal Brasileiro de Pneumologia

Published once every two months J Bras Pneumol. v.42, number 2, p. 81-162 March/April 2016

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J Bras Pneumol. 2016;42(2):81-81
http://dx.doi.org/10.1590/S1806-37562016000200001

Asthma and smoking: still a prevailing topic

Ubiratan de Paula Santos[1]

In the last 20 years, there has been a significant, progressive decline in the prevalence of smoking in both genders, worldwide[1] and in Brazil,[2] where that decline has been more pronounced. From 1980 to 2012, the worldwide prevalence declined from 41.2% to 31.1% in men and from 10.6% to 6.6% in women.[1] From 1989 to 2013, the prevalence of smoking in Brazil declined from 43.3% to 18.3% in men and from 27.0% to 10.8% in women.[2,3]

Despite progress brought about by successful public policies,[2] a survey conducted by the *Instituto Brasileiro de Geografia e Estatística* (IBGE, Brazilian Institute of Geography and Statistics) showed that the prevalence of smoking experimentation, a known risk factor for smoking initiation, was 19.6% among schoolchildren in the capital cities of Brazil.[4] Faced with the progressive decline in the prevalence of smoking worldwide and in Brazil, the tobacco industry has attempted not only to attract new markets in countries that do not adopt the more effective policies set forth in the Framework Convention on Tobacco Control[5] but also to attract young people with new, more appealing packaging, novel forms of advertising, and the use of flavored additives that enhance the efficiency of the process of addition to smoking cigarettes with lower nicotine content, as well as, recently, the introduction of electronic cigarettes.[6,7]

In an article published in this issue of JBP, Fernandes et al.[8] assessed the prevalence of allergic rhinitis, asthma, and smoking in 3,235 adolescent students (13-14 years of age) attending public schools in the city of Belo Horizonte, capital of the Brazilian state of Minas Gerais, and found the prevalence of allergic rhinitis, asthma, and smoking experimentation to be 35.3%, 19.8%, and 9.6% respectively. In keeping with the progressive decline in the prevalence of smoking in general in the country, the prevalence of smoking experimentation observed by those authors was 50% lower than the 20.7% reported for adolescents in the general population of the city in a survey conducted by the IBGE in 2012.[4] The data presented by Fernandes et al.[8] differ from those obtained in previous studies of adults and adolescents conducted in Brazil[9] and other countries,[10,11,12] all of which showed that the prevalence of smoking among individuals with asthma is similar to or higher than that seen in the general population. However, despite the favorable findings, data from the Fernandes et al. study[8] demonstrate the need to persist in the development of interventions for adolescents with asthma, not only because of the general hazards of smoking but also because of its implications for the control, treatment, and evolution of asthma, for which smoking is an adverse factor.[10,13] One recent extensive review presented evidence, albeit still inconclusive, that smoking is a risk factor for the incidence and exacerbation of asthma in adolescents.[13]

Although Fernandes et al.[8] have addressed a known issue, their data make an important contribution to the understanding of the situation in Brazil, drawing distinctions with other countries. Their findings have implications for health professionals, as well as for the development and evaluation of public policies.

REFERENCES

1. Ng M, Freeman MK, Fleming TD, Robinson M, Dwyer-Lindgren L, Thomson B, et al. Smoking prevalence and cigarette consumption in 187 countries, 1980-2012. JAMA. 2014;311(2):183-92. http://dx.doi.org/10.1001/jama.2013.284692
2. Levy D, de Almeida LM, Szklo A. The Brazil SimSmoke policy simulation model: the effect of strong tobacco control policies on smoking prevalence and smoking-attributable deaths in a middle income nation. PLoS Med. 2012;9(11):e1001336. http://dx.doi.org/10.1371/journal.pmed.1001336
3. Szklo AS, de Souza MC, Szklo M, de Almeida LM. Smokers in Brazil: who are they? Tob Control. 2015. pii: tobaccocontrol-2015-052324.
4. Brasil. Ministério do Planejamento, Orçamento e Gestão. Instituto Brasileiro de Geografia e Estatística (IBGE). Pesquisa Nacional de Saúde do Escolar 2012. Brasília: IBGE; 2013.
5. WHO Framework Convention on Tobacco Control (FCTC) [homepage on the Internet]. Geneva: WHO; c2016 [cited 2016 Mar 28]. Framework Convention on Tobacco Control [about 3 screens]. Available from: http://www.who.int/fctc/text_download/en/index.html
6. Lovato C, Linn G, Stead LF, Best A. Impact of tobacco advertising and promotion on increasing adolescent smoking behaviours. Cochrane Database Syst Rev. 2003;(4):CD003439. http://dx.doi.org/10.1002/14651858.cd003439
7. Talhout R, van de Nobelen S, Kienhuis AS. An inventory of methods suitable to assess additive-induced characterising flavours of tobacco products. Drug Alcohol Depend. 2016;161:9-14. http://dx.doi.org/10.1016/j.drugalcdep.2015.12.019
8. Fernandes SSC, Andrade CR, Caminhas AP, Camargos PA, Ibiapina CC. Prevalence of tobacco experimentation in adolescents with asthma and allergic rhinitis. J Bras Pneumol. 2016;42(2):84-87.
9. Stelmach R, Fernandes FL, Carvalho-Pinto RM, Athanazio RA, Rached SZ, Prado GF, et al. Comparison between objective measures of smoking and self-reported smoking status in patients with asthma or COPD: are our patients telling us the truth? J Bras Pneumol. 2015;41(2):124-32. http://dx.doi.org/10.1590/S1806-37132015000004526
10. Lemiere C, Boulet LP. Cigarette smoking and asthma: a dangerous mix. Can Respiratory J. 2005;12(2):79-80. http://dx.doi.org/10.1155/2005/179032
11. Cui W, Zack MM, Zahran HS. Health-related quality of life and asthma among United States adolescents. J Pediatr. 2015;166(2):358-64. http://dx.doi.org/10.1016/j.jpeds.2014.10.005
12. Katebi R, Williams G, Bourke M, Harrison A, Verma A. What factors are associated with the prevalence of atopic symptoms amongst adolescents in Greater Manchester? Eur J Public Health. 2015. pii: ckv139. [Epub ahead of print]
13. National Center for Chronic Disease Prevention and Health Promotion (US) Office on Smoking and Health. The health consequences of smoking—50 years of progress: A report of the Surgeon General. Atlanta, GA: Centers for Disease Control and Prevention US; 2014.

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J Bras Pneumol. 2016;42(2):82-83
http://dx.doi.org/10.1590/S1806-37562016000200002

Respiratory muscles in interstitial lung disease: poorly explored and poorly understood

Bruno Guedes Baldi[1], João Marcos Salge[1]

Interstitial lung diseases (ILDs) are a heterogeneous group of parenchymal lung disorders characterized by permanent structural changes that result in mechanical modifications, notably a significant reduction in the elasticity of the lung parenchyma.[1] Among individuals with ILDs, dyspnea and lower exercise tolerance are quite common complaints, varying in severity and having psychosocial repercussions, as well as a negative impact on quality of life, affecting the patients and their families. [2] Many factors, alone or in combination, can contribute to those symptoms, including altered gas exchange, airflow limitation, pulmonary vascular involvement (usually by pulmonary capillary destruction and hypoxemia-induced vasoconstriction) and left ventricular dysfunction, as well as impairment of the respiratory musculature and accessory muscles,[1-8] together with possible mechanisms specifically related to the etiology of the ILD in question.

Due to the typical predominance of parenchymal changes in ILDs, the contribution of extrapulmonary factors to the pathophysiology of exercise intolerance is often overlooked. Despite its potential importance, the respiratory musculature has rarely been evaluated in studies addressing the mechanisms of dyspnea in ILDs in particular or in those investigating exercise intolerance in general.[9] In individuals with ILDs, the increased elastic recoil overloads the respiratory musculature, increasing its activity and the work of breathing.[4] Often, inspiratory pressure is preserved in the early stages of ILD,[10] largely due to the fact that ILD has a minimal impact on the position of the diaphragm—as compared with that of COPD, for example—the muscle fiber length-tension ratio therefore being maintained, with no mechanical disadvantage for generating inspiratory force. However, in the more advanced stages of the disease, with the progression of volume loss, there is a breakdown of this positioning, promoting the occurrence of neuromuscular dissociation (i.e., reduced ability to activate the respiratory musculature in response to increased demand from the respiratory center), which often exacerbates during exercise.[3,6,10]

In an article published in the current issue of the JBP, Santana et al.[11] show that a change in diaphragmatic mobility during deep breathing, as assessed by ultrasound, is quite prevalent (60%) in patients with ILDs of various etiologies and levels of functional severity. Theirs was the first study to assess diaphragm thickness during tidal breathing in patients with ILDs. The authors established a cut-off point derived from a simple spirometric measure (FVC < 60% of the predicted value) as a risk factor for reduced diaphragmatic mobility.[11]

There have been few studies evaluating the function of the respiratory muscles, including the diaphragm, by invasive or noninvasive measures, in patients with ILD, and those that have been conducted have produced discrepant results. He et al.[12] demonstrated that the mobility of the diaphragm during deep breathing, as assessed by ultrasound, was reduced only in patients with pulmonary fibrosis accompanied by emphysema and not in patients with idiopathic pulmonary fibrosis (IPF) alone. Therefore, the authors were unable to establish a correlation between ILD and a reduction in diaphragmatic mobility. However, in that study, a limiting factor in the interpretation of the results was the fact that patients with IPF had mild functional limitation.[12] In the study conducted by Elia et al.,[13] who evaluated the diaphragms of 16 patients with ILD, using catheters to measure pressures in the stomach and esophagus, there was no diaphragmatic fatigue at rest or after exercise. In the study conducted by Walterspacher et al.,[6] involving 25 patients with ILD, there was a reduction in diaphragmatic strength, as assessed with non-volitional measures.[6] In the study conducted by Faisal et al.,[10] diaphragmatic activity at rest and during exercise, as assessed by electromyography, was found to be greater in patients with ILD than in control and COPD patients.

As noted in the article published in this issue of the JBP,[11] ultrasound has several advantages for the evaluation of the diaphragm, especially because it is noninvasive, is easily performed and does not use ionizing radiation, as well as allowing the mobility and thickness of the diaphragm to be evaluated.[11] However, there is still a need for the development of reference values and the dissemination of clinical experience before ultrasound markers can be fully incorporated into medical practice for the clinical management of patients. In addition, this technique does not apply to the observation of the respiratory musculature during exercise, which would be a highly desirable attribute in the search for correlations between changes in the musculature and reduced exercise capacity.[13]

Although muscle involvement is common in patients with ILD, as evidenced in the study conducted by Santana et al.[11] and in previous studies, there are many aspects of the topic that have yet to be explored. From a patho-physiological point of view, the question is related to the significance of the observed changes in muscle function, whether they in fact attributable to a muscular mechanism primarily associated with the genesis of dyspnea or are only adaptive changes secondary to a reduction in lung volume, as observed during the progression of an ILD. In this context, it does not seem to be fully established whether the severity of the underlying disease acts as a

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ISSN 1806-3713

confounding factor in the interpretation of data from the assessment of the respiratory musculature. Regarding clinical implications, it is essential that future studies of the respiratory musculature evaluate specific subgroups of ILD separately, because the peculiarities of each disease could alter the results, as well as because the systemic inflammatory process associated with diseases such as inflammatory myopathies and sarcoidosis can have a direct effect on the respiratory musculature.[3,4,6,8] In addition, the true impact of the use of ultrasound in the longitudinal evaluation of patients, its prognostic implications, and its value in monitoring the progress of ILDs have yet to be explored, as has been done for other indicators, such as the degree of dyspnea, FVC, DLCO, and SpO_2.[1,14]

It is obvious that there are still many gaps in our knowledge of the role that the respiratory musculature plays in the pathophysiology of functional limitation and its monitoring in the clinical management of ILDs. We also emphasize that measures derived from ultrasound alone are not able to describe all aspects of respiratory muscle function. Ideally, functional assessments of the respiratory musculature would involve the use of ultrasound in combination with complementary methods, such as (invasive or noninvasive) measurements of force or electromyography. It is undeniable, however, that the study conducted by Santana et al.[11] represents a relevant and robust step in that direction, encouraging further research to supplement our knowledge in this area.

REFERENCES

1. Baldi BG, Pereira CA, Rubin AS, Santana AN, Costa AN, Carvalho CR, et al. Highlights of the Brazilian Thoracic Association guidelines for interstitial lung diseases. J Bras Pneumol. 2012;38(3):282-91. http://dx.doi.org/10.1590/S1806-37132012000300002
2. Collard HR, Pantilat SZ. Dyspnea in interstitial lung disease. Curr Opin Support Palliat Care. 2008;2(2):100-4. http://dx.doi.org/10.1097/SPC.0b013e3282ff6336
3. O'Donnell DE, Ora J, Webb KA, Laveneziana P, Jensen D. Mechanisms of activity-related dyspnea in pulmonary diseases. Respir Physiol Neurobiol. 2009;167(1):116-32. http://dx.doi.org/10.1016/j.resp.2009.01.010
4. Panagiotou M, Polychronopoulos V, Strange C. Respiratory and lower limb muscle function in interstitial lung disease. Chron Respir Dis. 2016 Jan 14. pii: 1479972315626014. [Epub ahead of print] http://dx.doi.org/10.1177/1479972315626014
5. Holland AE. Exercise limitation in interstitial lung disease - mechanisms, significance and therapeutic options. Chron Respir Dis. 2010;7(2):101-11. http://dx.doi.org/10.1177/1479972309354689
6. Walterspacher S, Schlager D, Walker DJ, Müller-Quernheim J, Windisch W, Kabitz HJ. Respiratory muscle function in interstitial lung disease. Eur Respir J. 2013;42(1):211-9. http://dx.doi.org/10.1183/09031936.00109512
7. Ryerson CJ, Collard HR, Pantilat SZ. Management of dyspnea in interstitial lung disease. Curr Opin Support Palliat Care. 2010;4(2):69-75. http://dx.doi.org/10.1097/SPC.0b013e3283392b51
8. Kabitz HJ, Lang F, Walterspacher S, Sorichter S, Müller-Quernheim J, Windisch W. Impact of impaired inspiratory muscle strength on dyspnea and walking capacity in sarcoidosis. Chest. 2006;130(5):1496-502. http://dx.doi.org/10.1378/chest.130.5.1496
9. Caruso P, Albuquerque ALP, Santana PV, Cardenas LZ, Ferreira JG, Prina E, et al. Diagnostic methods to assess inspiratory and expiratory muscle strength. J Bras Pneumol. 2015;41(2):110-23. http://dx.doi.org/10.1590/S1806-37132015000004474
10. Faisal A, Alghamdi BJ, Ciavaglia CE, Elbehairy AF, Webb KA, Ora J, et al. Common Mechanisms of Dyspnea in Chronic Interstitial and Obstructive Lung Disorders. Am J Respir Crit Care Med. 2016;193(3):299-309. http://dx.doi.org/10.1164/rccm.201504-0841OC
11. Santana PV, Prina E, Albuquerque AL, Carvalho CR, Caruso P. Identifying decreased diaphragmatic mobility and diaphragm thickening in interstitial lung disease: the utility of ultrasound imaging J Bras Pneumol. 2016;42(2):88-94.
12. He L, Zhang W, Zhang J, Cao L, Gong L, Ma J, et al. Diaphragmatic motion studied by M-mode ultrasonography in combined pulmonary fibrosis and emphysema. Lung. 2014;192(4):553-61. http://dx.doi.org/10.1007/s00408-014-9594-5
13. Elia D, Kelly JL, Martolini D, Renzoni EA, Boutou AK, Chetta A, et al. Respiratory muscle fatigue following exercise in patients with interstitial lung disease. Respiration. 2013;85(3):220-7. http://dx.doi.org/10.1159/000338787
14. Latsi PI, du Bois RM, Nicholson AG, Colby TV, Bisirtzoglou D, Nikolakopoulou A, et al. Fibrotic idiopathic interstitial pneumonia: the prognostic value of longitudinal functional trends. Am J Respir Crit Care Med. 2003;168(5):531-7. http://dx.doi.org/10.1164/rccm.200210-1245OC

J Bras Pneumol. 2016;42(2):84-87
http://dx.doi.org/10.1590/S1806-37562015000000296

Prevalence of self-reported smoking experimentation in adolescents with asthma or allergic rhinitis

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Submitted: 7 November 2015.
Accepted: 25 February 2016.

Study carried out in the Departamento de Pediatria e no Grupo de Pneumologia Pediátrica, Faculdade de Medicina, Universidade Federal de Minas Gerais, Belo Horizonte (MG) Brasil.

ABSTRACT

Objective: To determine the prevalence of smoking experimentation among adolescents with asthma or allergic rhinitis. **Methods:** This was a cross-sectional study involving adolescent students (13-14 years of age) in the city of Belo Horizonte, Brazil. The participants completed the Centers for Disease Control and Prevention and International Study of Asthma and Allergies in Childhood questionnaires, both of which have been validated for use in Brazil. We calculated the prevalence of smoking experimentation in the sample as a whole, among the students with asthma symptoms, and among the students with allergic rhinitis symptoms, as well as in subgroups according to gender and age at smoking experimentation. **Results:** The sample comprised 3,325 adolescent students. No statistically significant differences were found regarding gender or age. In the sample as a whole, the prevalence of smoking experimentation was 9.6%. The mean age for smoking experimentation for the first time was 11.1 years of age (range, 5-14 years). Among the adolescents with asthma symptoms and among those with allergic rhinitis symptoms, the prevalence of self-reported smoking experimentation was 13.5% and 10.6%, respectively. **Conclusions:** The proportion of adolescents with symptoms of asthma or allergic rhinitis who reported smoking experimentation is a cause for concern, because there is strong evidence that active smoking is a risk factor for the occurrence and increased severity of allergic diseases.

Keywords: Asthma/epidemiology; Rhinitis/epidemiology; Smoking/epidemiology.

INTRODUCTION

Tobacco is a legal drug that is widely used throughout the world. According to the World Health Organization, tobacco kills up to half of its users and will account for an estimated 8 million deaths annually by the year 2030; four out of five such deaths will occur in low- or middle-income countries. In addition, tobacco use is the major risk factor for noncommunicable diseases such as cancer, cardiovascular disease, diabetes, and chronic lung disease.[1]

The majority (70-80%) of smokers take up the habit before adulthood, setting up smoking as a pediatric disease that should therefore should be included in programs of care for children and adolescents worldwide.[1,2] This is particularly important, because the late consequences of smoking on health are directly related to the duration and intensity of the habit.[3,4]

According to one study conducted in Brazil, smoking experimentation in childhood or adolescence increases the chance of smoking in adulthood by 34 times, making it a predictor of that.[5] The National Student Health Study,[6] conducted in 2012, involved 109,104 9th-grade students (13-15 years of age) in various regions of Brazil, including all 26 state capitals and the Federal District of Brasília. The authors found that 19.6% of the students evaluated had already experimented with smoking

Passive and active smoking are both risk factors for asthma and allergic rhinitis in adolescents.[7-9] There are currently few data related to the long-term consequences of active smoking in childhood and adolescence, although there is some evidence suggesting that those consequences are substantial.[10,11] There have been few studies attempting to determine whether the prevalence of asthma symptoms is associated with smoking experimentation or active smoking in children and adolescents.[9]

Therefore, this study aimed to evaluate the prevalence of smoking experimentation in adolescents with symptoms of asthma or allergic rhinitis in the city of Belo Horizonte, Brazil.[12]

METHODS

In this cross-sectional study, involving adolescent students, the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire,[11] which assesses the prevalence and severity of symptoms of asthma and allergic rhinitis, was employed.

According to the ISAAC protocol, the study population should comprise at least 3,000 students between 13 and

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Financial support: None.

  ISSN 1806-3713

14 years of age, randomly selected from at least 14 schools. The Belo Horizonte Municipal Department of Education provided a list of public schools, including the number of students per school and the school year. The drawing was made by school from a list randomly generated in the program Epi Info, version 6.04.

Study criteria

We included students from 13 to 14 years of age who were enrolled at the schools selected for the study and completed the ISAAC questionnaire. The parents or legal guardians of all participating students gave written informed consent. All other students were excluded from the study.

Definitions

We evaluated 13- and 14-year-olds because adolescents of those ages are most likely to still be attending school, resulting in a larger pool of students and facilitating data collection. The ISAAC questionnaire is a widely used tool that has been validated for use in epidemiological studies of asthma and allergic rhinitis.

To assess the prevalence of symptoms of asthma and allergic rhinitis among adolescents, we used the version of the ISAAC questionnaire that was translated to Portuguese and validated for use in Brazil by Solé et al.[13] The questions used in order to determine the prevalence of the symptoms of asthma and allergic rhinitis were, respectively, "Have you had wheezing or whistling in the chest in the past 12 months?" and "In the past 12 months, have you had a problem with sneezing, or a runny, or blocked nose when you did not have a cold or the flu?"

Students who reported having smoked at least once were classified as experimenters.[14] To analyze the prevalence of smoking experimentation among the students, we used the questionnaire developed for the Centers for Disease Control and Prevention Global Youth Tobacco Survey.[15] The two questions employed were "Have you ever tried or experimented with cigarette smoking, even one or two puffs?" and "How old were you when you first tried a cigarette?"

In the selected schools, the combined questionnaire was administered to all 8th- and 9th-grade students who were 13 or 14 years old. To avoid losses due to school absenteeism, we visited each school at least twice.

The questionnaire was completed by the students themselves, in the classroom, under the supervision of one of the researchers, who had been trained and instructed not to interfere with the process.

Statistical analysis

Data analysis was performed using the Statistical Package for Social Sciences, version 14.0 for Windows (SPSS Inc., Chicago, IL, USA). We calculated ratios for the prevalence of asthma symptoms, allergic rhinitis symptoms, and smoking experimentation in the general population in relation to that observed in the students who reported symptoms of asthma and those who reported symptoms of allergic rhinitis. We also calculated the proportion of students with asthma symptoms and with allergic rhinitis symptoms in relation to gender and to age at smoking experimentation.

Ethical considerations

The study was approved by the Research Ethics Committee of the Federal University of Minas Gerais and by the Belo Horizonte Municipal Department of Education. After the school board had given its authorization, we obtained written informed consent from the parents or legal guardians of all participating students.

RESULTS

The sample comprised 3,325 students, of whom 1,825 (54.9%) were 13 years of age. Of the 3,325 students evaluated, 1,858 (56.1%) were female (Table 1). Gender distribution did not differ between the 13-year-old and 14-year-old age groups.

In our study sample, the prevalence of asthma symptoms was 19.8%. The prevalence of symptoms of allergic rhinitis was 35.3%.

Smoking experimentation was reported by 310 (9.6%) of the 3,325 students evaluated (Table 2). The mean age at smoking experimentation was 11.1 years (range, 5-14 years). In the sample as a whole, smoking experimentation was reported by 9.5% of the females and 9.8% of the males, a difference that was not statistically significant (p = 0.759).

Of the 635 adolescents with asthma symptoms, 86 (13.5%) reported smoking experimentation, compared with 118 (10.6%) of the 1,116 with allergic rhinitis (Table 2).

DISCUSSION

This study confirmed that smoking experimentation occurs in adolescents with symptoms of asthma and allergic rhinitis in Brazil.

It is known that approximately 80% of adolescent smokers develop nicotine dependence, and smoking experimentation can thus rapidly become addiction.[16] However, there have been few studies on smoking experimentation among adolescents. According to studies conducted in Brazil, the prevalence of smoking experimentation among adolescents in the country ranges from 14.6% to 47.5%.[6,17-20] In the present study, using the Portuguese-language version of the ISAAC questionnaire, supplemented with questions

Table 1. Demographic characteristics of the study sample.[a]

Characteristic	(N = 3,235)
Gender	
Female	1,858 (56.1)
Male	1,377 (43.9)
Age	
13 years	1,825 (54.9)
14 years	1,500 (45.1)

[a]Values expressed as n (%).

Table 2. Prevalence of smoking experimentation in the sample as a whole, as well as among adolescents with and without symptoms of asthma or allergic rhinitis.

Population	Total N	Experimenters n (%)	95% CI
Sample as a whole	3,235	310 (9.6)	(8.6-10.6)
Adolescents with asthma symptoms	635	86 (13.5)	(10.8-16.2)
Adolescents without asthma symptoms	2,560	224 (8.7)	(7.6-9.8)
Adolescents with allergic rhinitis symptoms	1,116	118 (10.6)	(8.8-12.4)
Adolescents without allergic rhinitis symptoms	2,028	187 (9.2)	(7.9-10.5)

focused on smoking experimentation selected from the Global Youth Tobacco Survey questionnaire,[15] which has also been validated for use in Brazil,[20] we found a lower rate (9.6%) in our sample as a whole.

A recent study conducted in Brazil showed that the overall prevalence of smoking experimentation among 9th-grade students (adolescents from 13 to 15 years of age) was 19.6%, being highest (28.6%) in the south of the country and lowest (14.9%) in the northeast.[6] That same study also showed that the proportion of 15-year-olds who had tried their first cigarette at ≤ 13 years of age was 15.4%.[6] The only previous study conducted in the city of Belo Horizonte was a home-based study focusing on smoking among adolescents and young adults (individuals 15 to 24 years of age), in which the overall prevalence of smoking and smoking experimentation was found to be 11.7% and 51.0%, respectively.[21] That represents the highest reported prevalence of smoking experimentation among all of the studies analyzed, although the age of the study sample differed from that of ours.

In the literature, there is considerable variation among the reported rates smoking experimentation, and the rates found in the present study were lower than those previously reported. There are several possible explanations for that discrepancy. Because our study was not population-based, it is possible that the number of adolescents who had tried smoking was underestimated. To minimize that bias (i.e., avoid losses due to school absenteeism), the questionnaire was applied in two visits. It is also possible that some of the adolescents evaluated denied having tried smoking for fear of exposure or due to shyness, characteristics typical of adolescents in relation to risk behavior, despite having been assured, at the time of completing the questionnaire, that the data would be kept confidential.

In general, there is great variability across studies in relation to smoking, because there are various definitions of smoking status: sporadic smoking, occasional smoking, habitual smoking, current smoking, and daily smoking. There have been few studies dealing with smoking experimentation. Therefore, there is need for more research in order to minimize these variations through the use of standardized methodology, which could facilitate the diagnosis and improve the monitoring of smoking among adolescents.

The focus of the present study was to analyze the prevalence of smoking experimentation among adolescents with asthma and allergic rhinitis. We found no studies were found on this subject in the literature, which is worrisome because there is strong evidence that active smoking is a risk factor for asthma, rhinoconjunctivitis, and atopic dermatitis, as well as for greater severity of their symptoms.[22]

The results of the present study could prove useful because, in addition to being in agreement with the literature regarding the early onset of smoking experimentation, they also show that the prevalence of such experimentation was higher among adolescents with symptoms of asthma or allergic rhinitis, especially those with asthma, than among adolescents in the general population.

The design of the present study did not allow us to identify the possible causes of the difference between adolescents with asthma or allergic rhinitis and adolescents in the general population in terms of the prevalence of smoking experimentation, especially between adolescents with and without asthma. However, although smoking by parents is a known risk factor for smoking and respiratory diseases in their offspring,[23,24] adolescence is a risk phase, mainly influencing the behavior of patients with chronic diseases, which can result in higher smoking prevalence, underscoring the need to maintain and intensify smoking control measures in this age group, especially in adolescents with allergic respiratory diseases.

In conclusion, reducing the prevalence of smoking is considered one of the greatest challenges for public health,[25] and public policies have been developed in order to reduce smoking and nicotine dependence, as well as passive smoking, among children and adolescents.[26] Despite the implementation of various educational, legislative, and economic interventions to combat smoking in Brazil, adolescents in the country are still vulnerable to smoking experimentation and smoking-related diseases. Health professionals should pay special attention to the possibility of smoking among adolescents, especially among those with asthma or allergic rhinitis.

REFERENCES

1. World Health Organization (WHO) [homepage on the Internet]. Geneva: WHO; c2016 [cited 2016 Mar 21]. Ban tobacco advertising to protect young people; [about 4 screens]. Available from: http://www.who.int/mediacentre/news/releases/2013/who_ban_tobacco/en
2. Farber HJ, Walley SC, Groner JA, Nelson KE; Section on Tobacco Control. Clinical Practice Policy to Protect Children From Tobacco, Nicotine, and Tobacco Smoke. Pediatrics. 2015;136(5):1008-17. http://dx.doi.org/10.1542/peds.2015-3108
3. World Health Organization (WHO) [homepage on the Internet]. Geneva: WHO; c2016 [cited 2016 Mar 21]. Inequalities in young

people's health. Health behaviour in school-aged children. International report from the 2005/2006 survey. [Adobe Acrobat document, 208p.]. Available from: http://www.euro.who.int/__data/assets/pdf_file/0005/53852/E91416.pdf?ua=1

4. Malcon MC, Menezes AM, Chatkin M. Prevalence and risk factors for smoking among adolescents [Article in Portuguese]. Rev Saude Publica. 2003;37(1):1-7. http://dx.doi.org/10.1590/S0034-89102003000100003
5. Silva MA, Rivera IR, Carvalho AC, Guerra Ade H Jr, Moreira TC. The prevalence of and variables associated with smoking in children and adolescents. J Pediatr (Rio J). 2006;82(5):365-70.
6. Instituto Brasileiro de Geografia e Estatística (IBGE) [homepage on the Internet].Brasília: IBGE [cited 2016 Mar 21]. Pesquisa Nacional de Saúde do Escolar 2012 [about 1 screen]. Available from: http://www.ibge.gov.br/home/estatistica/populacao/pense/2012/
7. Gómez M, Vollmer WM, Caceres ME, Jossen R, Baena-Cagnani CE. Adolescent smokers are at greater risk for current asthma and rhinitis. Int J Tuberc Lung Dis. 2009;13(8):1023-8.
8. Mak KK, Ho RC, Day JR. The associations of asthma symptoms with active and passive smoking in Hong Kong adolescents. Respir Care. 2012;57(9):1398-404. http://dx.doi.org/10.4187/respcare.01548
9. Yoo S, Kim HB, Lee SY, Kim BS, Kim JH, Yu J, et al. Effect of active smoking on asthma symptoms, pulmonary function, and BHR in adolescents. Pediatr Pulmonol. 2009;44(10):954-61. http://dx.doi.org/10.1002/ppul.21066
10. Barreto SM, Giatti L, Casado L, de Moura L, Crespo C, Malta D. Contextual factors associated with smoking among Brazilian adolescents. J Epidemiol Community Health. 2012;66(8):723-9. http://dx.doi.org/10.1136/jech.2010.122549
11. Henderson AJ. The effects of tobacco smoke exposure on respiratory health in school-aged children. Paediatr Respir Rev. 2008;9(1):21-7. http://dx.doi.org/10.1016/j.prrv.2007.11.005
12. Asher MI, Keil U, Anderson HR, Beasley R, Crane J, Martinez F, et al. International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. Eur Respir J. 1995;8(3):483-91. http://dx.doi.org/10.1183/09031936.95.08030483
13. Solé D, Vanna AT, Yamada E, Rizzo MC, Naspitz CK. International Study of Asthma and Allergies in Childhood (ISAAC) written questionnaire: validation of the asthma component among Brazilian children. J Investig Allergol Clin Immunol. 1998;8(6):376-82.
14. Centers for Disease Control and Prevention (CDC) [homepage on the Internet]. Atlanta: CDC; c2013 [cited 2013 Sep 23]. Global Youth Tobacco Survey (GYTS) – Overview. Available from: http://nccd.cdc.gov/gtssdata/Ancillary/Documentation.aspx?SUID=1&DOCT=1
15. Centers for Disease Control and Prevention (CDC). [homepage on the Internet]. Atlanta: CDC; c2013 [cited 2013 Sep 23]. National Youth Tobacco Survey (NYTS) [about 4 screens]. Available from: http://www.cdc.gov/tobacco/data_statistics/surveys/nyts/index.htm
16. Lenney W, Enderby B. "Blowing in the wind": a review of teenage smoking. Arch Dis Child. 2008;93(1):72-5. http://dx.doi.org/10.1136/adc.2006.109702
17. Bordin R, Nipper VB, Silva JO, Bortolomiol L. Smoking prevalence among students from a metropolitan area in the southern region of Brazil, 1991 [Article in Portuguese]. Cad Saude Publica 1993;9(2):185-9. http://dx.doi.org/10.1590/S0102-311X1993000200010
18. Machado Neto AS, Cruz AA. Smoking among school adolescents in Salvador (BA)[Article in Portuguese]. J Pneumol. 2003;29(5):264-72. http://dx.doi.org/10.1590/S0102-35862003000500004
19. Pasqualotto AC, Pasqualotto GC, Santos RP, Segat FM, Guillande S, Benvegnú LA. Relationship between adolescence and tobacco: a study of students sociodemographic factors in Santa Maria, RS, Brazil [Article in Portuguese]. Pediatria (São Paulo). 2002;24:11-6.
20. de Almeida LM, Cavalcante TM, Casado L, Fernandes EM, Warren CW, Peruga A, et al. Linking Global Youth Tobacco Survey (GYTS) data to the WHO Framework Convention on Tobacco Control (FCTC): the case for Brazil. Prev Med. 2008;47 Suppl 1:S4-10. http://dx.doi.org/10.1016/j.ypmed.2007.11.017
21. Abreu MN, Souza CF, Caiaffa WT. Smoking among adolescents and young adults in Belo Horizonte, Minas Gerais State, Brazil: the influence of family setting and social group. Cad Saude Publica. 2011;27(5):935-43. http://dx.doi.org/10.1590/S0102-311X2011000500011
22. Annesi-Maesano I, Oryszczyn MP, Raherison C, Kopferschmitt C, Pauli G, Taytard A, et al. Increased prevalence of asthma and allied diseases among active adolescent tobacco smokers after controlling for passive smoking exposure. A cause for concern? Clin Exp Allergy. 2004;34(7):1017-23. http://dx.doi.org/10.1111/j.1365-2222.2004.02002.x
23. Landau LI. Parental smoking: asthma and wheezing illnesses in infants and children. Paediatr Respir Rev. 2001;2(3):202-6. http://dx.doi.org/10.1053/prrv.2001.0141
24. Tanaka K, Miyake Y, Arakawa M, Sasaki S, Ohya Y. Prevalence of asthma and wheeze in relation to passive smoking in Japanese children. Ann Epidemiol. 2007;17(12):1004-10. http://dx.doi.org/10.1016/j.annepidem.2007.07.108
25. Doll R. Tobacco: an overview of health effects. In: Zaridze D, Peto R, editors. Tobacco: a major international health hazard. Lyon: International Agency for Research on Cancer; 1986. p. 11-22.
26. Farber HJ, Nelson KE, Groner JA, Walley SC; Section on Tobacco Control. Public Policy to Protect Children From Tobacco, Nicotine, and Tobacco Smoke. Pediatrics. 2015;136(5):998-1007. http://dx.doi.org/10.1542/peds.2015-3109

J Bras Pneumol. 2016;42(2):88-94
http://dx.doi.org/10.1590/S1806-37562015000000266

ORIGINAL ARTICLE

Identifying decreased diaphragmatic mobility and diaphragm thickening in interstitial lung disease: the utility of ultrasound imaging

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Submitted: 21 October 2015.
Accepted: 27 January 2016.

Financial support: This study received financial support from the Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP, São Paulo Research Foundation; Grant no. 2010/08947-9). The funding body played no part in the design, implementation, or analysis of the study.

ABSTRACT

Objective: To investigate the applicability of ultrasound imaging of the diaphragm in interstitial lung disease (ILD). **Methods:** Using ultrasound, we compared ILD patients and healthy volunteers (controls) in terms of diaphragmatic mobility during quiet and deep breathing; diaphragm thickness at functional residual capacity (FRC) and at total lung capacity (TLC); and the thickening fraction (TF, proportional diaphragm thickening from FRC to TLC). We also evaluated correlations between diaphragmatic dysfunction and lung function variables. **Results:** Between the ILD patients (n = 40) and the controls (n = 16), mean diaphragmatic mobility was comparable during quiet breathing, although it was significantly lower in the patients during deep breathing (4.5 ± 1.7 cm vs. 7.6 ± 1.4 cm; $p < 0.01$). The patients showed greater diaphragm thickness at FRC ($p = 0.05$), although, due to lower diaphragm thickness at TLC, they also showed a lower TF ($p < 0.01$). The FVC as a percentage of the predicted value (FVC%) correlated with diaphragmatic mobility ($r = 0.73$; $p < 0.01$), and an FVC% cut-off value of < 60% presented high sensitivity (92%) and specificity (81%) for indentifying decreased diaphragmatic mobility. **Conclusions:** Using ultrasound, we were able to show that diaphragmatic mobility and the TF were lower in ILD patients than in healthy controls, despite the greater diaphragm thickness at FRC in the former. Diaphragmatic mobility correlated with ILD functional severity, and an FVC% cut-off value of < 60% was found to be highly accurate for indentifying diaphragmatic dysfunction on ultrasound.

Keywords: Diaphragm/ultrasonography; Lung diseases, interstitial; Respiratory muscles; Respiratory function tests.

INTRODUCTION

Interstitial lung diseases (ILDs) are a heterogeneous group of pulmonary disorders characterized by breathlessness and decreases in lung volume, gas exchange, and exercise tolerance, as well as by poorer quality of life and lower survival.[1] Although those characteristics have been attributed to the parenchymal involvement, that concept was recently challenged because it has also been found that peripheral muscle function is impaired in patients with ILD.[2-4] In addition, diaphragm weakness and expiratory muscle fatigue after maximal exercise have been detected in ILD patients.[5-9] The main hypotheses for respiratory muscle dysfunction in ILD are related to systemic inflammation, disuse, hypoxia, malnutrition, corticosteroid use, and overload due to the increased elastic recoil of the lung.[6,7,10,11]

Ultrasound imaging of the diaphragm has been broadly applied in some chronic respiratory diseases, such as COPD, asthma, cystic fibrosis, and diaphragmatic paralysis, as well as during weaning from mechanical ventilation.[12-19] In comparison with other imaging methods, this technique has diverse advantages, such as the absence of radiation, portability, real-time imaging, and the fact that it is noninvasive. In addition, reduced diaphragmatic mobility and diaphragm thickness, as determined by ultrasound, has proven to be a good predictor of failure to wean from mechanical ventilation[18] and has been shown to correlate significantly with disease severity in COPD.[15]

We hypothesized that, on ultrasound, ILD patients would present diaphragm dysfunction, characterized by lower diaphragmatic mobility and less diaphragm thickening, when compared with healthy age- and gender-matched controls. We also hypothesized that such diaphragm dysfunction would correlate with the extent of the parenchymal involvement, as quantified by FVC, an index used in order to follow up and determine the prognosis in ILD patients.[20]

METHODS

Patients and controls

We recruited 40 consecutive patients from an ILD outpatient clinic at a tertiary care teaching hospital. The diagnosis of ILD was based on clinical features and pulmonary function test (PFT) results, as well as on the

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ISSN 1806-3713

findings of CT scans of the chest, bronchoalveolar lavage, and (in some cases) lung biopsy. Patients were excluded if they required home oxygen therapy, had an active infection, or had been diagnosed with a neuromuscular disease associated with ILD. We recruited a control group of 16 healthy volunteers who were matched to the patients for age, gender, body mass index, and smoking status. The study was approved by the Research Ethics Committee of the University of São Paulo School of Medicine Hospital das Clínicas (Protocol no. 0835/11), and all participants gave written informed consent.

Measurements

We recorded demographic data, as well as data related to comorbidities, corticosteroid use, immunosuppression therapy, smoking, and dyspnea, as quantified with the modified Medical Research Council (mMRC) scale.[21] Each of the patients and volunteers underwent PFTs and ultrasound imaging of the diaphragm on the same day.

PFTs

In all patients and control subjects, we used a calibrated pneumotachograph (Medical Graphics Corporation, St. Paul, MN, USA) to obtain the following variables: FVC, FEV_1, and inspiratory capacity. Using a body plethysmograph (Elite Dx; Medical Graphics Corporation), we also measured lung volumes: functional residual capacity (FRC) and total lung capacity (TLC). Predicted values were those derived for the Brazilian population.[22]

Ultrasound imaging of the diaphragm

In all patients and controls, we performed ultrasound imaging of the diaphragm using a portable ultrasound system (Nanomaxx; Sonosite, Bothell, WA, USA). During the procedure, patients were in a semi-recumbent position with a peripheral oxygen saturation ≥ 92%, receiving supplementary oxygen if necessary. For the evaluation of diaphragmatic mobility, we placed a 2-5 MHz convex transducer over the anterior subcostal region between the midclavicular and anterior axillary lines. The transducer was angled medially and anteriorly so that the ultrasound beam would reach the posterior third of the right hemidiaphragm. The ultrasound was used in B-mode to visualize the diaphragm and then in M-mode to measure the amplitude of the cranio-caudal diaphragmatic excursion during quiet breathing and deep breathing.[23,24] We recorded the averaged value of three consecutive measurements. We also assessed the mobility of the diaphragm during a sniff test in order to exclude the presence of paradoxical movement.

Diaphragm thickness was measured in B-mode with a 6-13 MHz linear transducer placed over the diaphragm apposition zone, near the costophrenic angle, between the right anterior and medial axillary lines. Diaphragm thickness was measured from the most superficial hyperechoic line (pleural line) to the deepest hyperechoic line (peritoneal line).[25-27] We measured the thickness of the diaphragm at FRC and then at TLC. Again, the averaged value of three consecutive measurements was recorded for each. We also calculated the thickening fraction (TF, proportional thickening of the diaphragm from FRC to TLC), as defined by the following equation:

$$TF = [(Tmin - Tmax)/Tmin] \times 100$$

where Tmin is the minimum thickness of the diaphragm (measured at FRC) and Tmax is the maximum thickness of the diaphragm (measured at TLC).

Statistical analysis

Categorical data are presented as absolute and relative frequency. Continuous data are presented as mean ± standard deviation or as median and 25-75% interquartile range, as appropriate. Categorical variables were compared using the chi-square test or Fisher's exact test. Continuous variables were compared using the Student's t-test or Mann-Whitney test, according to their distribution.

We used a linear model as well as an exponential model to correlate PFT variables with diaphragmatic mobility and diaphragm thickness. To identify the PFT variable that presented the strongest correlation with the diaphragmatic mobility or diaphragm thickness, we used a ROC curve, thus also identifying the best PFT cut-off value for identifying abnormalities in diaphragmatic mobility or diaphragm thickening. Diaphragmatic dysfunction was defined as showing values for diaphragmatic mobility or diaphragm thickness that were below the 95% confidence interval of the values obtained for the controls.

To adjust for possible confounders and to evaluate risk factors associated with the occurrence of diaphragmatic dysfunction, we performed a logistic regression analysis. To avoid overfitting of the logistic regression model, we did not use stepwise procedures and chose the predictor variables that yielded $p < 0.20$ in a univariate regression analysis and had clinical relevance. Four independent variables (age, body mass index, the percentage of the predicted FVC, and the percentage of the predicted FEV_1) were selected for the logistic regression model. Values of $p \leq 0.05$ were considered statistically significant. All statistical analyses were performed with the IBM SPSS Statistics software package, version 20.0 (IBM Corporation, Armonk, NY, USA).

RESULTS

The controls were well matched to the patients for age, gender, body mass index, and smoking status. As expected, lung volumes were lower in the ILD patients than in the controls (Table 1). The etiologies of the ILD were as follows: usual interstitial pneumonia (n = 6); nonspecific interstitial pneumonia (n = 7); fibrotic hypersensitivity pneumonitis (n = 5); giant mixed desquamative interstitial pneumonia (n = 1); associated connective tissue disease (n = 9); sarcoidosis (n = 2); pneumoconiosis (n = 2); and unknown (n = 8). Most of the patients had never used corticosteroids. However,

a significant proportion had breathlessness, more than 60% scoring ≥ 2 on the mMRC scale (Table 1).

Diaphragmatic mobility during quiet breathing did not differ significantly between the patients and the controls. However, during deep breathing, the degree of diaphragmatic mobility was lower in the patients (Table 2). None of the patients presented paradoxical movement of the diaphragm during the sniff test.

The diaphragm thickness at FRC was significantly higher in the patients than in the controls. However, the diaphragm thickness at TLC was significantly lower in the patients, resulting in a lower TF (Table 2).

None of the PFT variables correlated with diaphragm thickness at FRC, diaphragm thickness at TLC, the TF, or diaphragmatic mobility during quiet breathing (Table 3). However, diaphragmatic mobility during deep breathing correlated with all of the PFT variables (Table 3). The correlations were slightly stronger when we used exponential fitting than when we used linear fitting (Figure 1), and the strongest correlation was for FVC as a percentage of the predicted value; patients with lower FVC had lower diaphragmatic mobility during deep breathing. After we adjusted for confounders (age, body mass index, and the percentage of the predicted FEV_1), the percentage of the predicted FVC was the only factor associated with decreased diaphragmatic mobility during deep breathing (p = 0.01), as shown in Table 4.

Table 1. Characteristics of healthy volunteers (controls) and interstitial lung disease patients.[a]

Characteristic	Controls (n = 16)	Patients (n = 40)	p
Age, years	55 ± 11	55 ± 15	0.81
Male gender, n (%)	8 (50)	23 (57)	0.61
BMI, kg/m^2	26.8 ± 3.6	25.6 ± 4.5	0.32
Smoking status, n (%)			0.99
Never smoker	12 (75)	30 (75)	
Former smoker	4 (25)	10 (25)	
Current smoker	0	0	
FVC, L	3.26 ± 0.73	1.96 ± 0.71	< 0.01
FVC, % of predicted	88 ± 9	57 ± 16	< 0.01
FEV_1, L	2.68 ± 0.63	1.67 ± 0.58	< 0.01
FEV_1, % of predicted	90 ± 10	62 ± 19	< 0.01
FEV_1/FVC ratio	0.82 ± 0.05	0.85 ± 0.06	0.04
TLC, % of predicted		61 ± 12	
Corticosteroid use, n (%)			
Never	-	24 (60)	
Current	-	16 (40)	
Prednisone, < 20 mg/day	-	10 (62.5)	
Prednisone, ≥ 20 mg/day	-	6 (37.5)	
mMRC scale score, n (%)			
0 (no dyspnea)	-	0 (0)	
1 (mild dyspnea)	-	12 (30)	
2 (moderate dyspnea)	-	16 (40)	
3 (severe dyspnea)	-	10 (25)	
4 (very severe dyspnea)	-	2 (5)	

[a]Values expressed as mean ± SD, except where otherwise indicated. BMI: body mass index; TLC: total lung capacity; and mMRC: modified Medical Research Council.

Table 2. Diaphragmatic mobility, diaphragm thickness, and the thickening fraction (proportional diaphragm thickening from functional residual capacity to total lung capacity) in interstitial lung disease patients and healthy volunteers (controls).[a]

Variable	Controls (n = 16)	Patients (n = 40)	p
Diaphragmatic mobility			
During quiet breathing (cm)	1.78 ± 0.58	1.80 ± 0.67	0.91
During deep breathing (cm)	7.62 ± 1.44	4.46 ± 1.73	< 0.01
Diaphragm thickness			
At functional residual capacity (cm)	0.17 ± 0.04	0.19 ± 0.03	0.05
At total lung capacity (cm)	0.40 ± 0.10	0.32 ± 0.08	< 0.01
Thickening fraction (%)	131 ± 55	62 ± 32	< 0.01

[a]Values expressed as mean ± SD.

The 95% confidence interval for diaphragmatic mobility during deep breathing was 4.80-10.44 cm, and values below 4.80 cm during deep breathing were therefore considered indicative of decreased diaphragmatic mobility. A cut-off value of 60% of the predicted FVC had the highest accuracy for identifying decreased diaphragmatic mobility, with a sensitivity of 92%, a specificity of 81%, a positive predictive value of 88%, and a negative predictive value of 87% (Figure 2).

DISCUSSION

In the present study, we showed that patients with ILD presented decreased diaphragmatic mobility during deep breathing and a lower TF, in comparison with the control subjects. We also showed that diaphragmatic dysfunction is associated with the percentage of the predicted FVC and that a cut-off value of 60% of the predicted FVC has high accuracy for the diagnosis of diaphragm dysfunction.

The standardization of techniques has made the measurement of diaphragmatic mobility and diaphragm thickness feasible and reproducible, promoting the use of ultrasound imaging of the diaphragm in many respiratory diseases, such as asthma, cystic fibrosis, COPD, diaphragmatic paralysis, acute respiratory failure, and mechanical ventilation weaning.[12-14,17,28] To our knowledge, there has been only one previous study using ultrasound to evaluate the diaphragms of ILD patients and showing that diaphragmatic mobility was similar between ILD patients and healthy controls.[23] However, the sample in that study was small (18 patients) and was composed exclusively of patients with idiopathic pulmonary fibrosis. In addition, the authors did not evaluate diaphragm thickness.[29]

There are several possible causes of diaphragm atrophy in ILD patients, such causes including systemic inflammation, disuse, hypoxia, malnutrition, and respiratory myopathy secondary to the use of corticosteroids.[6,7,10,11] In contrast, the diaphragm overload resulting from the increased elastic recoil of the lung can, due to a training effect, increase diaphragm muscle mass.[30] The effects of those opposing forces depend on the extent of the parenchymal involvement, disease duration, use of drugs, hypoxemia level, physical activity level, and individual susceptibility. Previous studies using volitional tests reported unaltered respiratory muscle function in ILD patients.[31,32] However, two recent studies using non-volitional tests, although not employing ultrasound, demonstrated respiratory muscle dysfunction in ILD patients.[5,9] These discrepant results regarding the impact of the ILD on inspiratory muscle strength might be due to differences in the severity of ILD among the studies.

In patients with COPD, it has been shown that lung hyperinflation shifts the diaphragm caudally, imposing a mechanical disadvantage upon it.[33] In contrast, the decreased lung volume in ILD patients dislodges the diaphragm cranially, imposing an equivalent mechanical disadvantage, although it does so by shortening the radius of the diaphragm. In addition, the increased elastic recoil of the lung impairs diaphragmatic mobility during inspiration. Therefore, it should not

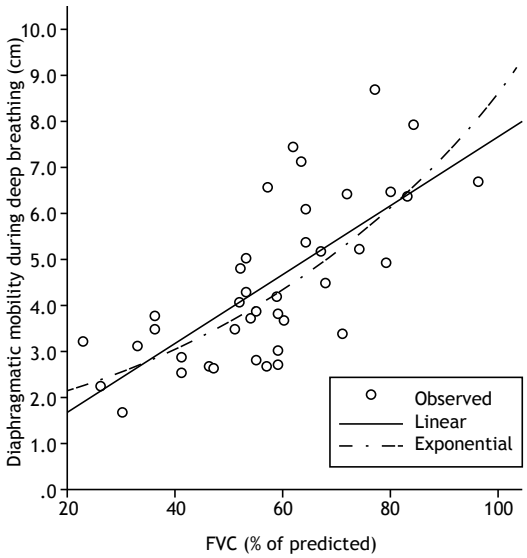

Figure 1. Linear and exponential correlations between diaphragmatic mobility during deep breathing and FVC as a percentage of the predicted value.

Table 3. Pulmonary function test variables in correlation with diaphragmatic mobility during deep breathing and with the thickening fraction (proportional diaphragm thickening from functional residual capacity to total lung capacity).

Variable	Diaphragmatic mobility during deep breathing		Thickening fraction		Diaphragmatic mobility during deep breathing		Thickening fraction	
	Linear fitting		Exponential fitting					
	r	p	r	p	r	p	r	p
FVC (% of predicted)[a]	0.72	< 0.01	0.22	0.17	0.73	< 0.01	0.24	0.14
FEV_1 (% of predicted)[a]	0.68	< 0.01	0.23	0.14	0.70	< 0.01	0.22	0.18
IC (% of predicted)[b]	0.38	0.05	0.17	0.41	0.42	0.03	0.09	0.69
TLC (% of predicted)[c]	0.50	< 0.01	0.20	0.27	0.53	< 0.01	0.27	0.14

IC: inspiratory capacity; and TLC: total lung capacity. [a]n = 40. [b]n = 25. [c]n = 31.

Table 4. Comparison between interstitial lung disease patients with and without diaphragmatic dysfunction.

Variable	Diaphragmatic dysfunction	p	Diaphragmatic dysfunction	p	
	No (n = 16)	Yes (n = 24)		OR (95% CI)	
Age, years	61 ± 10	52 ± 17	0.04	−0.003 (−0.01 to 0.006)	0.82
Male gender, n (%)	11 (48)	12 (52)	0.32		
Body mass index, kg/m^2	27.4 ± 3.4	24.5 ± 4.9	0.04	−0.01 (−0.04 to 0.01)	0.30
FVC, % of predicted	70 ± 12	49 ± 13	< 0.01	−0.03 (−0.06 to −0.01)	0.04
FEV_1, % of predicted	76 ± 14	53 ± 16	< 0.01	0.12 (−0.01 to 0.37)	0.34
Corticosteroid use, n (%)	6 (37)	11 (46)	0.75		

[a]Values expressed as mean ± SD, except where otherwise indicated.

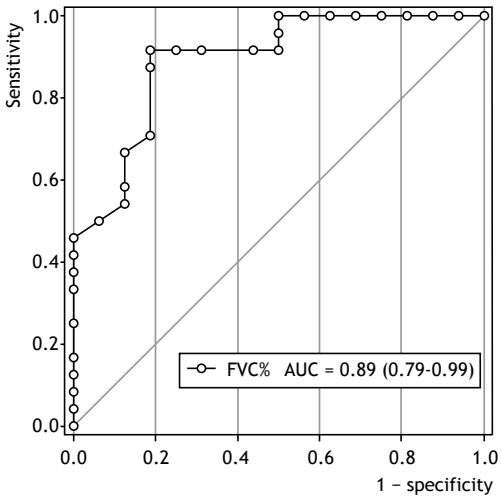

Figure 2. ROC curve of FVC as a percentage of the predicted value (FVC%) and the occurrence of decreased diaphragmatic mobility, showing the area under the curve (AUC).

be surprising that diaphragmatic mobility is reduced under these conditions of reduced lung volumes. However, the relationship between pulmonary volume and diaphragm excursion is debated and controversial in the literature. Cohen et al.,[34] studying ten normal subjects, recorded simultaneously the diaphragmatic excursion (using ultrasound in M-mode) and the tidal volume at different inspiratory volumes. The authors found that, at 15-87% of inspiratory capacity, there was a linear relationship between diaphragmatic excursion and tidal volume.[34] Houston et al.,[35] assessing hemidiaphragmatic movement, also found a linear relationship between inspiratory lung volume and diaphragmatic excursion. Another study, designed to validate ultrasound imaging of the diaphragm as an alternative to whole-body plethysmography, showed that the mean diaphragmatic excursion (during quiet breathing and at maximal sniff) correlated poorly with all of the lung volumes measured, although the authors did not investigate excursion during deep breathing.[36] Fedullo et al.,[37] investigating diaphragmatic motion after coronary artery bypass surgery, found no relationship between diaphragmatic mobility and vital capacity.

Similar to other studies that evaluated diaphragm thickness using ultrasound in other respiratory diseases, the present study showed that ILD patients presented a thicker diaphragm at FRC than did healthy controls, supporting the hypothesis of diaphragm thickening in response to respiratory muscle overload.[13,16] However, the greater diaphragm thickness at FRC resulted in a lower TF, probably indicating dysfunctional muscular hypertrophy or "pseudohypertrophy", as has previously been demonstrated in the diaphragms of young patients with Duchenne muscular dystrophy.[38] In ILD, the diaphragm appears to thicken over time but is unable to increase during maximal inspiration, unlike the physiological pattern seen in healthy controls.

The results of the present study demonstrate that ultrasound imaging of the diaphragm is a feasible method to evaluate diaphragmatic function. Diaphragmatic mobility is correlated with lung volume, a correlation that has been described in other lung diseases, such as COPD.[39] In clinical practice, ultrasound imaging of the diaphragm has high sensitivity and specificity to identify reduced diaphragmatic mobility in ILD patients with an FVC < 60% of the predicted value.

We showed that ultrasound imaging of the diaphragm is associated with PFT variables and that PFT trends constitute a major prognostic determinant of ILD. Therefore, we believe that ultrasound can be added to the arsenal of methods to follow up patients with ILD.[20] In addition to the chronic course of ILD, the identification of diaphragm dysfunction could alert physicians to the need to avoid or change the use of drugs that induce myopathy, such as corticosteroids.

The main limitation of our study was that we did not measure diaphragm force. However, Ueki et al.[27] found that a higher thickening ratio was strongly correlated with inspiratory strength in healthy subjects. Another study also showed a strong correlation between maximal inspiratory pressure and the TF in patients recovering from diaphragmatic paralysis.[40] In addition, because our results show not only reduced diaphragmatic mobility but also a reduced TF, we can conclude that diaphragmatic dysfunction is common in ILD patients. Another limitation is that, although our study has a power of 100% to estimate the coefficient of correlation between PFT and diaphragmatic mobility, it has a power of only approximately 40% to estimate that between PFT and diaphragm thickening.

In comparison with healthy controls, patients with ILD show reduced diaphragmatic mobility and a lower TF.

In addition, the cut-off point of an FVC < 60% of the predicted value showed high accuracy and sensitivity to identify decreased diaphragmatic mobility, as well being significantly associated with impaired lung function. The use of the results of ultrasound imaging of the diaphragm as a follow-up parameter and its relationship to respiratory muscle strength remain to be investigated.

REFERENCES

1. American Thoracic S, European Respiratory S. American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. This joint statement of the American Thoracic Society (ATS), and the European Respiratory Society (ERS) was adopted by the ATS board of directors, June 2001 and by the ERS Executive Committee, June 2001. Am J Respir Crit Care Med. 2002;165(2):277-304. Erratum in: Am J Respir Crit Care Med. 2002;166(3):426. http://dx.doi.org/10.1164/ajrccm.165.2.ats01
2. Mendoza L, Gogali A, Shrikrishna D, Cavada G, Kemp SV, Natanek SA, et al. Quadriceps strength and endurance in fibrotic idiopathic interstitial pneumonia. Respirology. 2014;19(1):138-43. http://dx.doi.org/10.1111/resp.12181
3. Spruit MA, Thomeer MJ, Gosselink R, Troosters T, Kasran A, Debrock AJ, et al. Skeletal muscle weakness in patients with sarcoidosis and its relationship with exercise intolerance and reduced health status. Thorax. 2005;60(1):32-8. http://dx.doi.org/10.1136/thx.2004.022244
4. Watanabe F, Taniguchi H, Sakamoto K, Kondoh Y, Kimura T, Kataoka K, et al. Quadriceps weakness contributes to exercise capacity in nonspecific interstitial pneumonia. Respir Med. 2013;107(4):622-8. http://dx.doi.org/10.1016/j.rmed.2012.12.013
5. Elia D, Kelly JL, Martolini D, Renzoni EA, Boutou AK, Chetta A, et al. Respiratory muscle fatigue following exercise in patients with interstitial lung disease. Respiration. 2013;85(3):220-7. http://dx.doi.org/10.1159/000338787
6. Hansen JE, Wasserman K. Pathophysiology of activity limitation in patients with interstitial lung disease. Chest. 1996;109(6):1566-76. http://dx.doi.org/10.1378/chest.109.6.1566
7. Holland AE. Exercise limitation in interstitial lung disease - mechanisms, significance and therapeutic options. Chron Respir Dis. 2010;7(2):101-11. http://dx.doi.org/10.1177/1479972309354689
8. O'Donnell DE, Chau LK, Webb KA. Qualitative aspects of exertional dyspnea in patients with interstitial lung disease. J Appl Physiol (1985). 1998;84(6):2000-9.
9. Walterspacher S, Schlager D, Walker DJ, Müller-Quernheim J, Windisch W, Kabitz HJ. Respiratory muscle function in interstitial lung disease. Eur Respir J. 2013;42(1):211-9. http://dx.doi.org/10.1183/09031936.00109512
10. Dekhuijzen PN, Decramer M. Steroid-induced myopathy and its significance to respiratory disease: a known disease rediscovered. Eur Respir J. 1992;5(8):997-1003.
11. Prasse A, Müller-Quernheim J. Non-invasive biomarkers in pulmonary fibrosis. Respirology. 2009;14(6):788-95. http://dx.doi.org/10.1111/j.1440-1843.2009.01600.x
12. Baria MR, Shahgholi L, Sorenson EJ, Harper CJ, Lim KG, Strommen JA, et al. B-mode ultrasound assessment of diaphragm structure and function in patients with COPD. Chest. 2014;146(3):680-5. http://dx.doi.org/10.1378/chest.13-2306
13. de Bruin PF, Ueki J, Watson A, Pride NB. Size and strength of the respiratory and quadriceps muscles in patients with chronic asthma. Eur Respir J. 1997;10(1):59-64. http://dx.doi.org/10.1183/09031936.97.10010059
14. DiNino E, Gartman EJ, Sethi JM, McCool FD. Diaphragm ultrasound as a predictor of successful extubation from mechanical ventilation. Thorax. 2014;69(5):423-7. http://dx.doi.org/10.1136/thoraxjnl-2013-204111
15. Dos Santos Yamaguti WP, Paulin E, Shibao S, Chammas MC, Salge JM, Ribeiro M, et al. Air trapping: The major factor limiting diaphragm mobility in chronic obstructive pulmonary disease patients. Respirology. 2008;13(1):138-44. http://dx.doi.org/10.1111/j.1440-1843.2007.01194.x
16. Dufresne V, Knoop C, Van Muylem A, Malfroot A, Lamotte M, Opdekamp C, et al. Effect of systemic inflammation on inspiratory and limb muscle strength and bulk in cystic fibrosis. Am J Respir Crit Care Med. 2009;180(2):153-8. http://dx.doi.org/10.1164/rccm.200802-232OC
17. Gottesman E, McCool FD. Ultrasound evaluation of the paralyzed diaphragm. Am J Respir Crit Care Med. 1997;155(5):1570-4. http://dx.doi.org/10.1164/ajrccm.155.5.9154859
18. Kim WY, Suh HJ, Hong SB, Koh Y, Lim CM. Diaphragm dysfunction assessed by ultrasonography: influence on weaning from mechanical ventilation. Crit Care Med. 2011;39(12):2627-30. http://dx.doi.org/10.1097/ccm.0b013e3182266408
19. Caruso P, Albuquerque AL, Santana PV, Cardenas LZ, Ferreira JG, Prina E, et al. Diagnostic methods to assess inspiratory and expiratory muscle strength. J Bras Pneumol. 2015;41(2):110-23. http://dx.doi.org/10.1590/S1806-37132015000004474
20. Latsi PI, du Bois RM, Nicholson AG, Colby TV, Bisirtzoglou D, Nikolakopoulou A, et al. Fibrotic idiopathic interstitial pneumonia: the prognostic value of longitudinal functional trends. Am J Respir Crit Care Med. 2003;168(5):531-7. http://dx.doi.org/10.1164/rccm.200210-1245OC
21. Mahler DA, Weinberg DH, Wells CK, Feinstein AR. The measurement of dyspnea. Contents, interobserver agreement, and physiologic correlates of two new clinical indexes. Chest. 1984;85(6):751-8. http://dx.doi.org/10.1378/chest.85.6.751
22. Pereira CA, Sato T, Rodrigues SC. New reference values for forced spirometry in white adults in Brazil. J Bras Pneumol. 2007;33(4):397-406. http://dx.doi.org/10.1590/S1806-37132007000400008
23. Boussuges A, Gole Y, Blanc P. Diaphragmatic motion studied by m-mode ultrasonography: methods, reproducibility, and normal values. Chest. 2009;135(2):391-400. http://dx.doi.org/10.1378/chest.08-1541
24. Testa A, Soldati G, Giannuzzi R, Berardi S, Portale G, Gentiloni Silveri N. Ultrasound M-mode assessment of diaphragmatic kinetics by anterior transverse scanning in healthy subjects. Ultrasound Med Biol. 2011;37(1):44-52. http://dx.doi.org/10.1016/j.ultrasmedbio.2010.10.004
25. Boon AJ, Harper CJ, Ghahfarokhi LS, Strommen JA, Watson JC, Sorenson EJ. Two-dimensional ultrasound imaging of the diaphragm: quantitative values in normal subjects. Muscle Nerve. 2013;47(6):884-9. http://dx.doi.org/10.1002/mus.23702
26. Cohn D, Benditt JO, Eveloff S, McCool FD. Diaphragm thickening during inspiration. J Appl Physiol (1985). 1997;83(1):291-6.
27. Ueki J, De Bruin PF, Pride NB. In vivo assessment of diaphragm contraction by ultrasound in normal subjects. Thorax. 1995;50(11):1157-61. http://dx.doi.org/10.1136/thx.50.11.1157
28. Pinet C, Cassart M, Scillia P, Lamotte M, Knoop C, Casimir G, et al. Function and bulk of respiratory and limb muscles in patients with cystic fibrosis. Am J Respir Crit Care Med. 2003;168(8):989-94. http://dx.doi.org/10.1164/rccm.200303-398OC
29. He L, Zhang W, Zhang J, Cao L, Gong L, Ma J, et al. Diaphragmatic motion studied by M-mode ultrasonography in combined pulmonary fibrosis and emphysema. Lung. 2014;192(4):553-61. http://dx.doi.org/10.1007/s00408-014-9594-5
30. de Troyer A, Yernault JC. Inspiratory muscle force in normal subjects and patients with interstitial lung disease. Thorax. 1980;35(2):92-100. http://dx.doi.org/10.1136/thx.35.2.92
31. Garcia-Rio F, Pino JM, Ruiz A, Diaz S, Prados C, Villamor J. Accuracy of noninvasive estimates of respiratory muscle effort during spontaneous breathing in restrictive diseases. J Appl Physiol (1985). 2003;95(4):1542-9. http://dx.doi.org/10.1152/japplphysiol.01010.2002
32. Nishimura Y, Hida W, Taguchi O, Sakurai M, Ichinose M, Inoue H, et al. Respiratory muscle strength and gas exchange in neuromuscular diseases: comparison with chronic pulmonary emphysema and idiopathic pulmonary fibrosis. Tohoku J Exp Med. 1989;159(1):57-68. http://dx.doi.org/10.1620/tjem.159.57
33. De Troyer A. Effect of hyperinflation on the diaphragm. Eur Respir J. 1997;10(3):708-13.
34. Cohen E, Mier A, Heywood P, Murphy K, Boultbee J, Guz A. Excursion-volume relation of the right hemidiaphragm measured by ultrasonography and respiratory airflow measurements. Thorax. 1994;49(9):885-9. http://dx.doi.org/10.1136/thx.49.9.885

35. Houston JG, Angus RM, Cowan MD, McMillan NC, Thomson NC. Ultrasound assessment of normal hemidiaphragmatic movement: relation to inspiratory volume. Thorax. 1994;49(5):500-3. http://dx.doi.org/10.1136/thx.49.5.500
36. Scott S, Fuld JP, Carter R, McEntegart M, MacFarlane NG. Diaphragm ultrasonography as an alternative to whole-body plethysmography in pulmonary function testing. J Ultrasound Med. 2006;25(2):225-32.
37. Fedullo AJ, Lerner RM, Gibson J, Shayne DS. Sonographic measurement of diaphragmatic motion after coronary artery bypass surgery. Chest. 1992;102(6):1683-6. http://dx.doi.org/10.1378/chest.102.6.1683
38. De Bruin PF, Ueki J, Bush A, Khan Y, Watson A, Pride NB. Diaphragm thickness and inspiratory strength in patients with Duchenne muscular dystrophy. Thorax. 1997;52(5):472-5. http://dx.doi.org/10.1136/thx.52.5.472
39. Levine S, Nguyen T, Kaiser LR, Rubinstein NA, Maislin G, Gregory C, et al. Human diaphragm remodeling associated with chronic obstructive pulmonary disease: clinical implications. Am J Respir Crit Care Med. 2003;168(6):706-13. http://dx.doi.org/10.1164/rccm.200209-1070OC
40. Summerhill EM, El-Sameed YA, Glidden TJ, McCool FD. Monitoring recovery from diaphragm paralysis with ultrasound. Chest. 2008;133(3):737-43. http://dx.doi.org/10.1378/chest.07-2200

J Bras Pneumol. 2016;42(2):95-98
http://dx.doi.org/10.1590/S1806-37562015000000099

Ex vivo lung perfusion in Brazil

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Submitted: 29 April 2015.
Accepted: 4 August 2015.

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ABSTRACT

Objective: To evaluate the use of ex vivo lung perfusion (EVLP) clinically to prepare donor lungs for transplantation. **Methods:** A prospective study involving EVLP for the reconditioning of extended-criteria donor lungs, the criteria for which include aspects such as a PaO_2/FiO_2 ratio < 300 mmHg. Between February of 2013 and February of 2014, the lungs of five donors were submitted to EVLP for up to 4 h each. During EVLP, respiratory mechanics were continuously evaluated. Once every hour during the procedure, samples of the perfusate were collected and the function of the lungs was evaluated. **Results:** The mean PaO_2 of the recovered lungs was 262.9 ± 119.7 mmHg at baseline, compared with 357.0 ± 108.5 mmHg after 3 h of EVLP. The mean oxygenation capacity of the lungs improved slightly over the first 3 h of EVLP—246.1 ± 35.1, 257.9 ± 48.9, and 288.8 ± 120.5 mmHg after 1, 2, and 3 h, respectively—without significant differences among the time points (p = 0.508). The mean static compliance was 63.0 ± 18.7 mmHg, 75.6 ± 25.4 mmHg, and 70.4 ± 28.0 mmHg after 1, 2, and 3 h, respectively, with a significant improvement from hour 1 to hour 2 (p = 0.029) but not from hour 2 to hour 3 (p = 0.059). Pulmonary vascular resistance remained stable during EVLP, with no differences among time points (p = 0.284). **Conclusions:** Although the lungs evaluated remained under physiological conditions, the EVLP protocol did not effectively improve lung function, thus precluding transplantation.

Keywords: Lung transplantation; Organ preservation; Brain death; Donor selection.

INTRODUCTION

Ex vivo lung perfusion (EVLP) is a novel strategy for reconditioning lungs, with a view to increasing the number of viable organs for transplantation and to reducing the mortality of patients awaiting a transplant.[1-3] The principle of the technique is to replicate the physiological environment that provides the substrates needed to maintain cell metabolism.

Initially, EVLP was described by Steen et al.[3] for the evaluation of non-heart-beating donor lungs, and, subsequently, it was modified for application to the reconditioning of extended-criteria donor lungs by the Toronto Lung Transplant Group, in Canada.[4] Lung reconditioning with subsequent transplantation has been employed by various transplant groups, with positive outcomes. Cypel et al.[2] reported on a series of 20 reconditioned extended-criteria donor lungs in which the PaO_2/FiO_2 ratio increased significantly at the end of the reconditioning process (2-4 h). Those authors found that the rate of primary graft dysfunction 72 h after transplantation was comparable for both recipients of EVLP lungs and recipients of conventionally selected lungs, and that no adverse events were directly attributable to EVLP. In other centers, such as those in Vienna (Austria), Paris (France), and Turin (Italy), the outcomes were similar to those obtained by the Toronto group.[5] Despite the positive outcomes, in the United Kingdom, a study showed that, of 13 reconditioned lungs, only 6 were transplanted, which represents a utilization rate of 46%.[6]

The present article reports on the use of EVLP clinically to prepare donor lungs for transplantation in Brazil.

METHODS

The study was approved by the Brazilian National Health Council–*Comissão Nacional de Ética em Pesquisa* (CONEP, Brazilian National Research Ethics Committee; Registration No. 16026; Process No. 25000.113350/2010-46). We used human brain-dead donor lungs that were rejected for conventional transplantation because their PaO_2/FiO_2 ratio was < 300 mmHg. Between February of 2013 and February of 2014, there were five lung recoveries for the lung reconditioning protocol. Immediately before recovery, bronchoscopic inspection with BAL was performed. The BAL procedure involved instillation of 40 mL of sterile saline (0.9% sodium chloride) into the segments of the basal pyramid of the right lower lobe, followed by aspiration until approximately 50% of the instilled amount was recovered and stored in a collection vial. Lung recovery was performed as usual for conventional transplantation. The lungs were perfused with Perfadex® (Vitrolife, Göteborg, Sweden) as the preservation solution, stored at 4°C in a special bag, and sent to the Heart Institute Surgery Center of the University of São Paulo School of Medicine *Hospital das Clínicas*, in the city of São Paulo, Brazil, to undergo the procedure.

The pulmonary artery and pulmonary veins were sutured onto special plastic cannulas, and the lung block was placed in a perfusion chamber (XVIVO Perfusion, Göteborg,

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Sweden). The perfusion system consists of cannulas, a membrane deoxygenator, a heat exchanger, a leukocyte filter, and a centrifugal pump (Maquet, Toronto, Canada). The system is primed with 1.5 L of Steen Solution® (Vitrolife), 500 mg methylprednisolone, 500 mg/500 mg imipenem/cilastatin sodium, and heparin (3,000 IU). The established flow corresponded to 40% of the cardiac output during ventilation at physiological levels: a tidal volume (V_T) of 6 mL/kg; a respiratory rate of 7 breaths/min; a positive end-expiratory pressure of 5 cmH_2O; and an FiO_2 of 21%. For flow increase, as well as for reheating and ventilation, we followed the protocol described by Cypel et al.[7]

Perfusion time was set at 4 h, and ventilatory and pulmonary gas exchange parameters were evaluated at the end of each hour. At the end of hour 3, perfusion was interrupted in the lungs with no prospects of improvement in lung function or respiratory mechanics with a view to transplantation. At evaluation, the ventilator was set at a V_T of 10 mL/kg of body weight, a respiratory rate of 10 breaths/min, a positive end-expiratory pressure of 5 cm cmH_2O, and an FiO_2 of 100%. A sample of the perfusate was collected from the outlet of the pulmonary artery and pulmonary vein for blood gas analysis, which measured $PaCO_2$, mixed venous carbon dioxide tension, PaO_2, mixed venous oxygen tension, lactate levels, and glucose levels. Ventilatory parameters measured included peak pressure, plateau pressure, mean airway pressure, static compliance, and V_T. Mean pulmonary artery pressure and perfusion flow were also measured.

The left lower lobe was sampled before and immediately after EVLP. The samples were fixed in 10% formalin for 24 h, embedded in paraffin, sectioned on a microtome into 5 µm thick slice, and stained with H&E. The presence/absence of pathological changes was investigated under light microscopy by a pathologist.

Descriptive statistics

Quantitative data are expressed as means and standard deviations. For each variable, the assumption of normal distribution was tested with the Shapiro-Wilk test. Categorical variables are expressed as frequencies.

Inferential statistics

For comparison of means, we used repeated measures ANOVA and the paired Student's t-test. The probability of a type I (α) error was set at 0.05 for all inferential analyses.

Descriptive and inferential statistics were calculated using the SPSS Statistics software package, version 21 (IBM Corporation, Armonk, NY, USA).

RESULTS

The lungs of five donors were submitted to EVLP at the Heart Institute Surgery Center. However, no transplants were performed, because none of the lungs met the functional criteria for transplantation.

Four male donors and one female donor were used, and the mean length intubation was 5.6 days. All lungs were obtained from brain-dead donors, because the current legislation in Brazil does not allow the use of non-heart-beating donors. The most common cause of death was traumatic brain injury, followed by subarachnoid hemorrhage. The reason the donor lungs were rejected for conventional transplantation was poor blood gas values (PaO_2/FiO_2 ratio = 100%). In three cases, discard was associated with radiological changes, and in two cases in which the PaO_2/FiO_2 ratio was satisfactory, the lungs were discarded either because of indefinite histology for brain neoplasm (this being the cause of brain death) or because the poor clinical condition of the recipient precluded transplantation (Table 1).

The mean oxygenation capacity (ΔPO_2) measured during EVLP showed little variation, with no statistically significant differences (Figure 1). After 1, 2, and 3 h of EVLP, respectively, ΔPO_2 values were 246.1 ± 35.7 mmHg, 257.9 ± 48.9 mmHg, and 288.8 ± 120.5 mmHg (Figure 1). A comparison of the ΔPO_2 values measured at recovery with those observed at the end of EVLP showed that, although the final mean ΔPO_2 was higher, there were no statistically significant differences (Figure 1). The mean PaO_2 of the recovered lungs was 262.9 ± 119.7 mmHg at baseline, compared with 357.0 ± 108.5 mmHg after 3 h of EVLP.

The mean static compliance after 1, 2, and 3 h, respectively, was 63.0 ± 18.7 mmHg, 75.6 ± 25.4 mmHg, and 70.4 ± 28.0 mmHg, with a significant difference in results between hour 1 and hour 2 ($p = 0.029$).In most of the EVLP procedures, the perfusion time was 180 minutes; in only one case was the perfusion time 240 minutes.

A comparative evaluation of the lung biopsy samples collected before and after EVLP showed that, in three cases, there was worsening of edema and formation of visible thrombi. The results of BAL examination revealed colonization by virulent bacteria with a high potential to cause pulmonary infection in three cases.

DISCUSSION

The EVLP technique has been disseminated worldwide, with positive outcomes at various centers. In 2013, research groups from Toronto, Vienna, and Paris presented their clinical results with EVLP at the International Society of Heart and Lung Transplantation Meeting.[5] The results showed that the reconditioned lung utilization rate was high and that the rates of primary graft dysfunction within the first 72 h were low. In the USA, the technique has been validated in a multicenter clinical trial and approved by the Food and Drug Administration.[8]

Despite the clearly demonstrated advances, we found discrepancies among the centers regarding the EVLP lung utilization rate for transplantation. In the present study, we report the use of EVLP at our center. We performed five lung perfusions; however, EVLP was

Table 1. Characteristics of the selected donors.

Gender	Age, years	Cause of death	MV, days	PaO_2, mmHg[a]	Donor
M	18	TBI	3	264,0	1
F	50	SAH	7	283,0	2
M	19	TBI	3	62,5	3
M	41	TBI	6	334,6	4
M	29	SAH	9	370,6	5

MV: mechanical ventilation; M: male; F: female; TBI: traumatic brain injury; and SAH: subarachnoid hemorrhage. [a]Arterial blood gas sampling with a positive end-expiratory pressure of 5 cmH_20 and an FiO_2 of 100%.

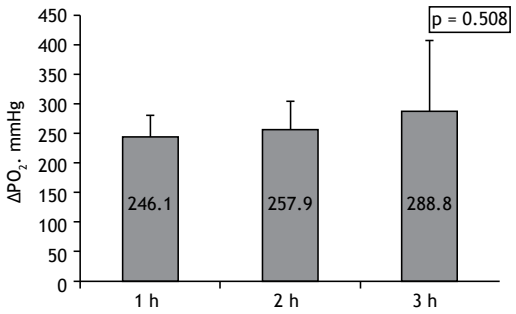

Figure 1. Evolution of ΔPO_2 (PaO_2 – PvO_2) throughout ex vivo perfusion. There were no statistically significant differences among the three time points evaluated (1 h, 2 h, and 3 h after the initiation of ex vivo perfusion).

unable to improve lung function because, in general, the recovered lungs showed pronounced physiological changes upon arrival at our surgery center.

Several factors may be related to the limited number of lung recoveries for EVLP in Brazil. In our country, organs are obtained only from brain-dead donors. This limitation leads to there being a small supply of lungs for EVLP, in comparison with the mean rates of other centers where lungs from non-heart-beating donors are used. Cypel et al. reported that 44% of 50 non-heart-beating donor lungs subjected to EVLP were used for transplantation in Toronto.[1]

The use of lungs from non-heart-beating donors is well established in the literature, and related data have been compiled into the International Society of Heart and Lung Transplantation registry, showing that the use of such lungs results in an increase in the number of transplants. In addition, a multicenter study reported that the outcomes of transplantation of lungs from non-heart-beating donors were similar to those of transplantation of lungs from brain-dead donors, suggesting that transplant teams should make continuous efforts to increase the number of transplants using non-heart-beating donors.[9]

In our sample, poor blood gas values alone were not the primary cause of donor rejection. The most common reason for donor rejection in 2013 was infection (in 35%), followed by morbidity history (in 16.7%), including smoking and use of inhaled drugs, and blood gas changes (in 15.6%).

The EVLP lung utilization rate for transplantation varies among the transplant centers that use the EVLP technique. The research groups in Lund (Sweden) and in Toronto are the most successful, with utilization rates of 67% and 87%, respectively. However, the Newcastle group, in the United Kingdom, reported a utilization rate of 46% and attributed it to complications related to the quality of the recovered lungs. Like the Newcastle group, we extended the criteria for donor lung recovery, including those with blood gas changes associated with edema and contusion.[6] Certainly the limited number of perfusions performed by our group and the inclusion of donor lungs with poor blood gas values associated with other changes had a significant impact on our utilization rate. The use of extended-criteria donor lungs resulted in a greater likelihood of dysfunctions, such as infection, alveolar infiltrate, excess secretions, and pulmonary embolism, compromising the EVLP reconditioning process. The main radiological findings were pulmonary infiltrate (contusion or congestion) and infection, confirmed by H&E histology and BAL culture at the end of EVLP. The comorbidities detected in three lungs by radiological imaging and histopathological analysis before EVLP may have negatively impacted reconditioning, given that the functional activity of those lungs did not progress satisfactorily. In addition, histological analysis of the lung tissue at the end of perfusion showed increased edema, thrombus formation, and other vascular changes in these cases. In the fourth case, in which there were mild radiological and histopathological changes, EVLP occurred satisfactorily, increasing lung functional indices up to values close to the acceptable threshold for transplantation. Regarding growth in BAL cultures, we detected colonization by virulent bacteria, with a high potential to cause pneumonia in recipients with suppurative disease, in three donors. At our center, previous studies reported high rates of BAL culture positivity in lung donors. A retrospective study reported that, of 49 lungs recovered for conventional transplantation, 31 had positive cultures, mainly for *Staphylococcus aureus* and *Pseudomonas aeruginosa*.[10] Our database provides evidence that the current situation remains unchanged, given that, in 2013, 26 of the 27 lungs recovered for conventional transplantation had positive cultures. This underscores the importance of investigation of the specific characteristics of the donors at each center so that possible remedial action can be taken before the use of EVLP. Postoperative complications related to the development of pneumonia can be prevented by combining EVLP and specific prophylactic antibiotic regimens. In one of the cases reported here, we found, on the basis of histopathological

results, that the donor had bronchiectasis. In another case, a relevant finding on microscopic examination was the presence of microthrombi. Both bronchiectasis and microthrombi had been missed on imaging. In the two cases, although EVLP was not satisfactory enough for the reconditioning process, it was important in the diagnosis of the comorbidities. We deem it necessary to use additional imaging modalities, such as CT, as well as early fiberoptic bronchoscopy to minimize the number of pathologically compromised donor lungs.

In a case report, Machuca et al. reported the use of EVLP for the treatment of lungs from a donor with pulmonary thromboembolism, with the addition of a thrombolytic agent to the perfusate, which resulted in improvement in the lungs and subsequent transplantation.[11] In an experimental study conducted by our team, we found a significant improvement in arterial blood gas values after 1 h of EVLP.[12,13] However, we highlight some methodological differences relative to the present study, such as the use of an FiO_2 of 100% throughout perfusion and the use of an open left atrium.

In recent years, EVLP has proven to be very important in the rehabilitation of extended-criteria donor lungs, increasing the number of transplants performed. Often, the severity of the comorbidities inherent in the donor lung has a major impact on the achievement of positive outcomes from the use of the EVLP technique. Among the various organ procurement centers, there are differences with regard to donor care protocols, that is, there is no consensus regarding thyroid hormone replacement, use of desmopressin (an antidiuretic hormone analog that has mild vasopressor activity), or use of a feeding tube.

During the development of our protocol, we found that donor lungs in Brazil have a higher rate of complications after brain death than do those available for reconditioning at other centers. The here reported non-utilization of EVLP donor lungs for transplantation suggests the need for investigation of the specific characteristics of the donors at our center. Such information may be highly relevant to making adjustments to the reconditioning technique so as to meet specific needs more fully, thus increasing the likelihood of success with EVLP.

Therefore, we conclude that, although the EVLP technique used at our center contributed to maintaining the lungs under physiological conditions, it did not effectively improve lung function, thus precluding the use of the lungs for transplantation.

REFERENCES

1. Cypel M, Yeung JC, Machuca T, Chen M, Singer LG, Yasufuku K, et al. Experience with the first 50 ex vivo lung perfusions in clinical transplantation. J Thorac Cardiovasc Surg. 2012;144(5):1200-6. http://dx.doi.org/10.1016/j.jtcvs.2012.08.009
2. Cypel M, Yeung JC, Liu M, Anraku M, Chen F, Karolak W, et al. Normothermic ex vivo lung perfusion in clinical lung transplantation. N Engl J Med. 2011;364(15):1431-40. http://dx.doi.org/10.1056/NEJMoa1014597
3. Steen S, Sjöberg T, Pierre L, Liao Q, Eriksson L, Algotsson L. Transplantation of lungs from a non-heart-beating donor. Lancet. 2001;357(9259):825-9. http://dx.doi.org/10.1016/S0140-6736(00)04195-7
4. Cypel M, Rubacha M, Yeung J, Hirayama S, Torbicki K, Madonik M, et al. Normothermic ex vivo perfusion prevents lung injury compared to extended cold preservation for transplantation. Am J Transplant. 2009;9(10):2262-9. http://dx.doi.org/10.1111/j.1600-6143.2009.02775.x
5. Machuca TN, Cypel M. Ex vivo lung perfusion. J Thorac Dis. 2014;6(8):1054-62.
6. Zych B, Popov AF, Stavri G, et al. Early outcomes of bilateral sequential single lung transplantation after ex-vivo lung evaluation and reconditioning. J Heart Lung Transplant. 2012;31(3):274-81. http://dx.doi.org/10.1016/j.healun.2011.10.008
7. Cypel M, Yeung JC, Hirayama S, Rubacha M, Fischer S, Anraku M, et al. Technique for prolonged normothermic ex vivo lung perfusion. J Heart Lung Transplant. 2008;27(12):1319-25. http://dx.doi.org/10.1016/j.healun.2008.09.003
8. Sanchez PG, Davis RD, D'Ovidio F, Cantu E, Weyant M, Camp P, et al. The NOVEL lung trial one-year outcomes. J Heart Lung Transplant. 2014;33(4):S71-S72. http://dx.doi.org/10.1016/j.healun.2014.01.226
9. Cypel M, Levvey B, Van Raemdonck D, Erasmus M, Love R, Mason D, et al. Favorable outcomes of donation after cardiac death in lung transplantation: a multicenter study. J Heart Lung Transplant. 2013;32(4):S15. http://dx.doi.org/10.1016/j.healun.2013.01.017
10. Campos S, Caramori M, Teixeira R, Afonso J Jr, Carraro R, Strabelli T, et al. Bacterial and fungal pneumonias after lung transplantation. Transplant Proc. 2008;40(3):822-4. http://dx.doi.org/10.1016/j.transproceed.2008.02.049
11. Machuca TN, Hsin MK, Ott HC, Chen M, Hwang DM, Cypel M, et al. Injury-specific ex vivo treatment of the donor lung: pulmonary thrombolysis followed by successful lung transplantation. Am J Respir Crit Care Med. 2013;188(7):878-80. http://dx.doi.org/10.1164/rccm.201302-0368LE
12. Pêgo-Fernandes PM, Mariani AW, Medeiros IL, Pereira AE, Fernandes FG, Valle Unterpertinger Fd, et al. Ex vivo lung evaluation and reconditioning. Rev Bras Cir Cardiovasc. 2010;25(4):441-6. http://dx.doi.org/10.1590/S0102-76382010000400006
13. Medeiros IL, Pêgo-Fernandes PM, Mariani AW, Fernandes FG, do Vale Unterpertinger F, Canzian M, et al. Histologic and functional evaluation of lungs reconditioned by ex vivo lung perfusion. J Heart Lung Transplant. 2012;31(3):305-9. http://dx.doi.org/10.1016/j.healun.2011.10.005

J Bras Pneumol. 2016;42(2):99-105
http://dx.doi.org/10.1590/S1806-37562015000000063

Administering the Sarcoidosis Health Questionnaire to sarcoidosis patients in Serbia

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Submitted: 7 April 2015.
Accepted: 25 August 2015.

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ABSTRACT

Objective: The aim of this study was to use a Serbian-language version of the disease-specific, self-report Sarcoidosis Health Questionnaire (SHQ), which was designed and originally validated in the United States, to assess health status in sarcoidosis patients in Serbia, as well as validating the instrument for use in the country. **Methods:** This was a cross-sectional study of 346 patients with biopsy-confirmed sarcoidosis. To evaluate the health status of the patients, we used the SHQ, which was translated into Serbian for the purposes of this study. We compared SHQ scores by patient gender and age, as well as by disease duration and treatment. Lower SHQ scores indicate poorer health status. **Results:** The SHQ scores demonstrated differences in health status among subgroups of the sarcoidosis patients evaluated. Health status was found to be significantly poorer among female patients and older patients, as well as among those with chronic sarcoidosis or extrapulmonary manifestations of the disease. Monotherapy with methotrexate was found to be associated with better health status than was monotherapy with prednisone or combination therapy with prednisone and methotrexate. **Conclusions:** The SHQ is a reliable, disease-specific, self-report instrument. Although originally designed for use in the United States, the SHQ could be a useful tool for the assessment of health status in various non-English-speaking populations of sarcoidosis patients.

Keywords: Sarcoidosis; Health status; Validation studies; Questionnaires; Self report; Serbia.

INTRODUCTION

Sarcoidosis is a multisystem, multiorgan disease of unknown etiology and unpredictable course. It is characterized by noncaseating granulomas that can involve any organ system and can affect persons of all races and ages.[1]

Albeit a disease with a low mortality rate, sarcoidosis can become a chronic malady in which patients develop various physical and mental disabilities.[1-3] The majority of sarcoidosis patients experience spontaneous disease remission within 2-5 years of diagnosis.[4] However, 10-30% of sarcoidosis patients develop chronic symptoms or progressive disease that can affect physical functioning and emotional well-being.[4-7]

Previous studies in sarcoidosis have focused on the pulmonary manifestations of the disease, as assessed by chest imaging and pulmonary function testing during the evolution of the disease.[8-10] These clinical variables do not always predict long-term outcomes. For the individual patient, chest X-rays and spirometry correlate poorly with perceived quality of life.[11] Reports describing health status and quality of life in sarcoidosis are limited to a few cross-sectional studies conducted in northern Europe or in the United States,[2,5,12-17] in which a variety of generic and respiratory-specific questionnaires have been used.[2,5,18-23] Our group previously reported results from the use of generic and respiratory-specific instruments for quantifying health status and quality of life in a cross-sectional study of sarcoidosis patients in Serbia.[24,25]

Five large-scale studies conducted in Europe reported impaired health status and quality of life in patients with sarcoidosis, in whom physical, emotional, and even social functioning were found to be limited, as they have been in other studies.[2,12-19] In the largest study of its kind conducted in the United States,[26] health status was assessed in 120 sarcoidosis patients with a variety of instruments, including the Medical Outcomes Study 36-item Short-Form Health Survey, the Saint George's Respiratory Questionnaire, the Center for Epidemiologic Studies Depression Scale, and the Perceived Stress Scale.[20,26-28]

To our knowledge, there have been no studies specifically evaluating health status in sarcoidosis patients in Central or Eastern Europe. Therefore, the primary aim of this study was to evaluate the health status of sarcoidosis patients with the first disease-specific sarcoidosis questionnaire—the self-report Sarcoidosis

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Financial support: This study received financial support from the Serbian Ministry of Education and Science (Grant nos. 175046 and 175081; 2011-2014).

Health Questionnaire (SHQ)—published in 2003 by a group of authors working in the United States.[29] Additional objectives were to assess the health status of sarcoidosis patients according to the treatment regimen and to assess the feasibility of using the SHQ in non-English-speaking sarcoidosis patients.

METHODS

Study design and patient sample

This was a cross-sectional study. The majority of patients recruited to participate in this study were registered with the Serbian Association of Sarcoidosis, which includes 1,562 patients with various clinical forms of sarcoidosis. We enrolled 346 patients with biopsy-confirmed sarcoidosis, diagnosed at the Clinic for Pulmonology of the Clinical Center of Serbia, in the city of Belgrade, Serbia. The patients were examined at regularly scheduled clinical visits, during which they voluntarily completed the SHQ and underwent spirometry. The study was approved by the local research ethics committee, and all of the patients gave written informed consent.

Health status instrument

The SHQ[29] is a 29-item, self-report questionnaire with responses ranging from "all of the time" (score of 1) to "none of the time" (score of 7). Higher scores indicate better health status. It takes approximately 10 min to complete the SHQ. This instrument measures three health status domains: daily functioning, physical functioning, and emotional functioning.

The original version of the SHQ was kindly provided to the Serbian Association of Sarcoidosis by Dr. Christopher Cox, of Duke University Medical Center. The instrument was officially translated into Serbian and adapted for use in Serbia with the assistance of two native-speaking language experts—one native speaker of Serbian and one native speaker of English—who worked independently on the translation from English to Serbian and the back-translation from Serbian to English, respectively.

Procedures

Patients completed the SHQ during their regularly scheduled clinical visits, undergoing pulmonary function testing on a spirometer (MasterLab; Jaeger, Würtzburg, Germany), in accordance with the American Thoracic Society/European Respiratory Society guidelines,[30] on the same day. We used the European Respiratory Society criteria for lung function impairment.[31] We measured DLCO using the single-breath method.[32]

Using the organ index devised for the "A Case Control Etiology of Sarcoidosis Study",[33,34] we assessed the current extent of organ involvement in our sarcoidosis patients. The diagnosis of sarcoidosis in any organ system was classified as definite, probable, or possible. Positive organ involvement encompassed the criteria for a definite or probable diagnosis, in accordance with the index cited above.

Treatment

Based on the clinical outcome, the patients were stratified into two groups: acute sarcoidosis (disease duration < 2 years), comprising 137 patients (39.6% of the sample); and chronic sarcoidosis (disease duration ≥ 2 years), comprising 209 patients (60.4% of the sample). Among the 346 patients, the recommended treatment regimen was monotherapy with prednisone in 246 (71.1%) and monotherapy with methotrexate in 67 (19.5%). In the chronic sarcoidosis patients, methotrexate was used as monotherapy or as a corticosteroid sparing agent (in combination with 5-10 mg/day of prednisone as maintenance therapy). No treatment was required in 33 patients (9.5%), 21 (63.6%) of whom were acute sarcoidosis patients, the remaining 12 (36.4%) having chronic, asymptomatic sarcoidosis.

Statistical analysis

To compare SHQ scores with the clinical characteristics of patients, we used two-sample t-tests for variables with two categories and one-way ANOVA for variables with more than two categories. Correlations were calculated by either the Pearson or Spearman method. Independent variables were considered significant at the $p < 0.05$ level in the univariate analyses and were assessed as a single block in multivariate regression models. Because SHQ scores are continuous data, we used multiple linear regression analysis in order to evaluate the contribution of risk factors to the total SHQ score or the score for each of its three domains. We used a stepwise model (backward elimination of variables) in which values of $p < 0.05$ indicated statistical significance. The variables evaluated in the multiple linear regression analysis included age (decade of life), gender, parenchymal lung disease on chest X-ray, the course of the disease (acute vs. chronic), extrapulmonary disease, specific system involvement (cutaneous, neurological, or cardiac disease), FVC, DLCO, carbon monoxide transfer coefficient, and the treatment regimen (prednisone alone, methotrexate alone, or a combination of the two). Statistical analyses were performed with the Statistical Package for the Social Sciences, version 10.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Table 1 summarizes the characteristics of the study patients. At the time of the administration of the SHQ, 33 (9.5%) of the 346 patients were asymptomatic. The remainder reported a variety of health problems, including low energy, fatigue, an undefined feeling of bodily pain, chest tightness, joint pain, and muscle discomfort.

Most—337 (97.4%)—of the patients had pulmonary involvement, whereas 122 (35.3%) also had extrapulmonary involvement. Among the 122 patients with extrapulmonary disease, the sarcoidosis affected one organ in 73 (59.8%), two organs in 30 (24.6%), and three or more organs in 19 (15.6%).

Patients with chronic sarcoidosis had significantly lower scores, indicating poorer health status, for all domains of the SHQ (Table 2). Erythema nodosum was seen in 21 (15.3%) of 137 patients with acute sarcoidosis. Although those patients were expected to show impaired physical functioning, due to polyarthralgia and (in some cases) fever, that was not found to be the case.

Patients were evaluated by decade of life, stratified into seven groups (Table 3). The SHQ scores differed significantly among the age groups for the daily functioning domain (ANOVA F = 3.85; p < 0.001) and for the physical functioning domain (ANOVA F = 4.49; p < 0.001), as did the total SHQ score (ANOVA F = 4.59; p < 0.001), although no such difference was found for the emotional functioning domain. The 114 patients in the 41- to 50-year age group had the lowest total SHQ scores, as well as the lowest scores for the daily functioning and physical functioning domains, whereas the 122 patients between 51 and 70 years of age had the lowest scores for the emotional functioning domain. There were only 3 patients over 70 years of age (Table 3).

Table 1. Demographic and clinical characteristics of the patients.[a]

Characteristic	N = 346
Age (years), mean ± SD	46.03 ± 10.8
Gender	
Female	257 (74.3)
Male	89 (25.7)
Ethnicity	
White	346 (100.0)
Symptomatic patients	313 (90.5)
Stage of the lung disease	
0 or 1 (no parenchymal lesions)	233 (67.3)
2-4 (with parenchymal lesions)	113 (32.7)
Pulmonary sarcoidosis	337 (97.4)
Extrapulmonary sarcoidosis	122 (35.3)
Number of organ systems involved, mean (range)	3 (1-5)
Extrapulmonary organ systems involved	
Eye	68 (19.7)
Skin	50 (14.5)
Heart	23 (6.7)
Nervous system (neurosarcoidosis)	22 (6.4)
Liver	16 (4.6)
Spleen	12 (3.5)
Bone	11 (3.6)
Bone marrow	1 (0.3)
Course of the sarcoidosis	
Acute	137 (39.6)
Chronic	209 (60.4)
Lung function	
Restrictive lung disease (FVC < 80%)	244 (70.5)
Obstructive lung disease (FEV_1/FVC ratio < 70%)	10 (2.9)
Normal	92 (26.6)
Treatment	
None	33 (9.5)
Prednisone only	246 (71.1)
Methotrexate only	21 (6.1)
Methotrexate plus prednisone	46 (13.3)

[a]Values expressed as n (%), except where otherwise indicated.

Significant differences were found between the patients with parenchymal lung disease (i.e., those in sarcoidosis stages 2-4) and those without (those in stage 0 or 1), in terms of the scores for the SHQ domains daily functioning and physical functioning, as well as total SHQ scores, all of which were lower in the former group (Table 2). Patients in whom the sarcoidosis affected three or more organs had the lowest mean total SHQ score (3.82 ± 0.94), as well as the lowest mean scores for the domains daily functioning (3.72 ± 0.91), physical functioning (4.00 ± 0.98), and emotional functioning (3.74 ± 0.95). Only the total SHQ score differed significantly between the groups stratified by location/organ involvement. The 50 patients with chronic cutaneous sarcoidosis had significantly lower scores for the daily functioning domain (ANOVA F = 1.353, p = 0.05). Likewise, the 23 patients with cardiac sarcoidosis had significantly lower scores for the physical functioning domain (ANOVA F = 1.523, p = 0.041), and the 23 patients with neurosarcoidosis had significantly lower total SHQ scores (ANOVA F = 1.912, p = 0.05). However, we found no significant differences among those groups in terms of the scores for the emotional functioning domain.

The scores for the SHQ domains daily functioning and physical functioning were significantly lower among the 122 patients with extrapulmonary sarcoidosis than among those with pulmonary involvement only, as were the total SHQ scores (p < 0.05 for all). We also found significant differences between the patients with normal lung function and those with restrictive lung disease (FVC < 80%), in terms of the scores for the daily functioning domain (ANOVA F = 1.42; p = 0.019) and the physical functioning domain (ANOVA F = 1.47; p = 0.012), as well as the total SHQ score (ANOVA F = 1.41; p = 0.023), although we found no such difference in terms of the scores for the emotional functioning domain.

At evaluation, 246 (71.1%) of the 346 patients were under treatment with prednisone only; 21 (6.1%) were under treatment with methotrexate only; 46 (13.3%) were under treatment with the combination of methotrexate and low-dose prednisone; and 33 (9.5%) were not receiving any pharmacological treatment. The patients receiving monotherapy with prednisone had significantly higher SHQ scores for all domains than did those receiving monotherapy with methotrexate or combination therapy with methotrexate plus prednisone (p < 0.05 for all). The 33 untreated patients had higher SHQ scores than did those receiving pharmacological treatment, the differences being statistically significant for all SHQ domains (Table 4). The patients treated with prednisone

Table 2. Clinical characteristics of sarcoidosis and Sarcoidosis Health Questionnaire scores.[a]

Characteristic of sarcoidosis	n	Sarcoidosis Health Questionnaire scores			
		Domains			Total
		Daily functioning	Physical functioning	Emotional functioning	
Course					
Acute	137	4.80 (0.87)	5.00 (0.95)	4.35 (0.76)	4.72 (0.72)
Chronic	209	4.16 (0.86)	4.43 (1.07)	4.13 (0.72)	4.24 (0.75)
p*		< 0.001	< 0.001	< 0.05	< 0.001
Location					
Extrapulmonary	122	4.14 (0.89)	4.45 (1.09)	4.12 (0.77)	4.24 (0.77)
Exclusively pulmonary	244	4.58 (0.90)	4.77 (1.02)	4.26 (0.79)	4.53 (0.76)
p*		< 0.001	< 0.05	> 0.05	< 0.001
Stage of the lung disease					
0 or 1 (no parenchymal lesions)	233	4.52 (0.93)	4.78 (1.03)	4.25 (0.81)	4.52 (0.78)
2-4 (with parenchymal lesions)	113	4.19 (0.85)	4.40 (1.08)	4.14 (0.75)	4.24 (0.74)
p*		< 0.05	< 0.05	> 0.05	< 0.05

[a]Values expressed as mean ± SD. *t-test.

Table 3. Age of sarcoidosis patients (by decade of life) and Sarcoidosis Health Questionnaire scores.[a]

SHQ scores	Decade of life (years)						
	11-20 (n = 2)	21-30 (n = 24)	31-40 (n = 81)	41-50 (n = 114)	51-60 (n = 95)	61-70 (n = 27)	71-80 (n = 3)
DF domain	4.69 (1.09)	4.84 (0.84)	4.73 (1.04)	4.20 (0.84)	4.32 (0.90)	4.30 (0.69)	4.41 (0.31)
PF domain	5.66 (0.47)	5.11 (0.69)	5.02 (1.04)	4.42 (1.10)	4.49 (1.05)	4.61 (0.92)	5.44 (0.42)
EF domain	4.95 (1.48)	4.54 (0.75)	4.34 (0.92)	4.14 (0.73)	4.12 (0.77)	4.12 (0.65)	4.36 (0.21)
Total	5.10 (1.01)	4.83 (0.60)	4.70 (0.85)	4.25 (0.76)	4.31(0.75)	4.34 (0.59)	4.74 (0.17)

SHQ: Sarcoidosis Health Questionnaire; DF: daily functioning; PF: physical functioning; and EF: emotional functioning. [a]Values expressed as mean ± SD.

only were divided into those with acute sarcoidosis (n = 104) and those with chronic sarcoidosis (n = 142). The prescribed doses of prednisone were higher for those with acute disease than for those with chronic disease (20-30 mg/day vs. 5-10 mg/day). The mean daily functioning domain score, physical functioning domain score, and total SHQ score were significantly lower among the patients with chronic sarcoidosis than among those with acute sarcoidosis ($p < 0.05$), although the mean emotional functioning domain score was not. Among the patients treated with prednisone, the mean emotional functioning domain score was higher in the acute sarcoidosis group (higher daily doses) than in the chronic sarcoidosis group (lower daily doses), as can be seen in Table 5.

In the multivariate analysis, chronic disease and cardiac disease were both found to be independent predictors of lower scores for the SHQ domain daily functioning. Chronic disease, combination therapy (prednisone plus methotrexate), and neurosarcoidosis were found to be independent predictors of lower physical functioning domain scores, whereas female gender and prednisone monotherapy were found to be independent predictors of lower emotional functioning domain scores. As shown in Table 6, female gender, chronic disease, combination therapy, and neurosarcoidosis were significantly associated with lower total SHQ scores.

DISCUSSION

In the present study, we have assessed the health status of sarcoidosis patients using the first sarcoidosis-specific health status questionnaire (the SHQ). We found that, among the 346 sarcoidosis patients evaluated, health status was significantly impaired in all three SHQ domains (daily functioning, physical functioning, and emotional functioning).

The overall health status (total SHQ score) was significantly lower in the female patients in our sample. In addition, we noted that the proportion of patients with chronic disease was significantly higher among the female patients (77.5%) than among the male patients (68.8%), which could explain the significantly lower SHQ scores among the female patients. In the largest sarcoidosis health status study conducted in the United States, 87 (78.4%) of the 111 sarcoidosis patients evaluated were female, although the authors did not report poorer health status for the female patients.[26] In the original SHQ validation study, involving 111 sarcoidosis patients, those same authors found no significant difference between the genders in terms of health status.[29] Another recent study conducted in the United States showed significant gender differences for the SHQ physical functioning domain.[35] In the present study, patients in the 41- to 50-year age group had the lowest SHQ scores. Unfortunately, those are often the most economically productive years and overall

poor health status creates a burden for such patients. Although the mean age of the patients in the original SHQ validation study was approximately 45 years,[29] the authors found no significant age-related difference in SHQ scores in their subsequent sarcoidosis health status study.[26]

The significantly lower SHQ scores in our patients with chronic sarcoidosis underscore the importance of patient perception of the burden of chronic sarcoidosis, predominantly in the daily functioning and emotional functioning domains. In the original SHQ validation study,[29] the proportion of patients who characterized their health status as fair—48 (43.2%)—did not differ significantly from that of those who characterized it as poor—16 (14.4%). However, in the subsequent study conducted by the same authors, there was a statistically significant difference between the symptomatic patients and asymptomatic patients, in terms of the mean total SHQ score.[26] In the present study, we found significant differences in the SHQ scores between the patients with acute sarcoidosis and those with chronic sarcoidosis, the former having significantly higher scores for all SHQ domains.

We also found that the scores for the daily functioning, physical functioning, and emotional functioning domains of the SHQ were inversely associated with the number of organ systems affected by sarcoidosis. Likewise, in the sarcoidosis health status study conducted in the United States, a higher the number of affected organs translated to lower SHQ scores.[26]

Because studies conducted in Europe have not utilized the SHQ, the results of those studies cannot be compared with those of the present study. However, comparing our results with those of the sarcoidosis health status study conducted in the United States, in which the SHQ was also employed, we noticed differences between the two patient samples. In the sample evaluated in the latter study, 80% of the patients were African American,[26] which often correlates with clinical phenotypes that are associated with more severe disease, a more aggressive course, and a worse prognosis.[36]

One limitation of our study is that we evaluated health status only with a disease-specific instrument (the SHQ) and did not compare those findings with those that might have been obtained with instruments that are more generic or with respiratory-specific questionnaires. However, in a recent study involving a predominantly European population of sarcoidosis patients, the SHQ was shown to correlate well with measures of health-related quality of life and fatigue.[19]

In the original SHQ validation study conducted in the United States,[29] the authors found that prednisone therapy was associated with lower SHQ scores and therefore with poorer health status. However, they were unable to determine the degree of influence that prednisone treatment had on the disease course. The patients enrolled in the present study were diagnosed and treated at a facility where prednisone is the first-line therapy for sarcoidosis. After two or three relapses, prednisone is usually withdrawn and methotrexate is prescribed, either as monotherapy or in combination with low doses of prednisone. The multiple linear regression analysis revealed that the chronic sarcoidosis patients treated with the methotrexate-prednisone combination had significantly lower scores for the SHQ domains physical functioning and emotional functioning, as well as lower total SHQ scores, in comparison with the

Table 4. Comparison of Sarcoidosis Health Questionnaire scores, by treatment regimen.[a]

Treatment	n	Sarcoidosis Health Questionnaire scores			
		Domains			Total
		Daily functioning	Physical functioning	Emotional functioning	
None	33	4.71 (0.94)	4.98 (1.11)	4.33 (0.88)	4.67 (0.82)
Prednisone only	246	4.51 (0.93)	4.78 (1.01)	4.28 (0.79)	4.52 (0.76)
Methotrexate only	21	4.15 (0.64)	4.05 (0.96)	3.93 (0.74)	4.05 (0.58)
Methotrexate plus prednisone	46	3.86 (0.68)	4.06 (1.04)	3.93 (0.66)	3.95 (0.67)
F*		5.49	6.11	3.27	6.68
p*		< 0.0001	< 0.0001	< 0.05	< 0.0001

[a]Values expressed as mean ± SD. *ANOVA.

Table 5. Comparison of Sarcoidosis Health Questionnaire scores among prednisone-treated patients, by sarcoidosis course.[a]

Course of sarcoidosis	n	Sarcoidosis Health Questionnaire scores			
		Domains			Total
		Daily functioning	Physical functioning	Emotional functioning	
Acute[b]	104	4.79 (0.87)	5.00 (0.94)	4.37 (0.81)	4.71 (0.71)
Chronic[c]	142	4.27 (0.92)	4.59 (1.04)	4.21 (0.77)	4.36 (0.77)
p*		< 0.001	0.001	> 0.01	< 0.001

[a]Values expressed as mean ± SD. [b]Receiving higher daily doses of prednisone. [c]Receiving lower daily doses of prednisone. *t-test.

Table 6. Multiple linear regression analyses of various risk factors for lower Sarcoidosis Health Questionnaire scores.[a]

Variable	Multiple linear regression analyses			
	SHQ domain scores			Total SHQ score
	Daily functioning	Physical functioning	Emotional functioning	
Gender (male vs. female)	ns	ns	−0.165 (0.003)	−0.138 (0.010)
Course (acute vs. chronic)	−0.449 (0.004)	−0.202 (0.000)	ns	−0.216 (0.000)
Therapy (P vs. MTX vs. P+MTX)	ns	−0.153 (0.008)	0.120 (0.041)	0.143 (0.013)
Neurosarcoidosis	ns	0.116 (0.036)	ns	0.109 (0.046)
Cardiac disease	0.345 (0.024)	ns	ns	ns

SHQ: Sarcoidosis Health Questionnaire; P: prednisone; MTX: methotrexate; and ns: not significant. [a]Statistics shown as β (p).

chronic sarcoidosis patients treated with prednisone alone. In addition, compared with the patients receiving the combination therapy, those receiving monotherapy with methotrexate had significantly better SHQ scores for all domains. That is the outstanding finding of this study. Decisions regarding treatment were based on physician perceptions of the severity of the disease. It is possible, in fact, that the patients treated with methotrexate alone exhibited less severe illness than did those treated with the methotrexate-prednisone combination.

We found the SHQ to be a useful instrument for assessing the health status of sarcoidosis patients in Serbia. The questionnaire was successfully translated into Serbian, and the results obtained were similar to those reported for a population of sarcoidosis patients in the United States. In addition, we have demonstrated significant differences in health status for the sarcoidosis patients who were female, as well as for those with the chronic form of the disease and for those in whom the sarcoidosis affected multiple organ systems. Furthermore, we found that monotherapy with methotrexate was associated with better SHQ scores than was monotherapy with prednisone or combination therapy with methotrexate plus prednisone. The SHQ can be a useful tool for comparing health status in sarcoidosis patient populations of various ethnic and geographic origins.

ACKNOWLEDGMENTS

We are thankful to Dr. Christopher Cox, of Duke University Medical Center, for providing us with the original SHQ and calculator, as well as granting us permission for its use. We are also grateful to Dr. Elyse Lower, of the University of Cincinnati Department of Internal Medicine, for her assistance and suggestions, both scientific and linguistic, in writing this manuscript.

REFERENCES

1. Statement on sarcoidosis. Joint Statement of the American Thoracic Society (ATS), the European Respiratory Society (ERS) and the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) adopted by the ATS Board of Directors and by the ERS Executive Committee, February 1999. Am J Respir Crit Care Med. 1999;160(2):736-55.
2. Wirnsberger RM, de Vries J, Breteler MH, van Heck GL, Wouters EF, Drent M. Evaluation of quality of life in sarcoidosis patients. Respir Med. 1998;92(5):750-6. http://dx.doi.org/10.1016/S0954-6111(98)90007-5
3. Chang B, Steimel J, Moller D, Baughman RP, Judson MA, Yeager H Jr, et al. Depression in Sarcoidosis. Am J Respir Crit Care Med. 2001;163(2):329-34. http://dx.doi.org/10.1164/ajrccm.163.2.2004177
4. Judson MA. Sarcoidosis: clinical presentation, diagnosis, and approach to treatment. Am J Med Sci. 2008;335(1):26-33. http://dx.doi.org/10.1097/MAJ.0b013e31815d8276
5. Judson MA. An approach to the treatment of pulmonary sarcoidosis with corticosteroids: the six phases of treatment. Chest. 1999;115(4):1158-65. http://dx.doi.org/10.1378/chest.115.4.1158
6. Chang JA, Curtis JR, Patrick DL, Raghu G. Assessment of health-related quality of life in patients with interstitial lung disease. Chest. 1999;116(5):1175-82. http://dx.doi.org/10.1378/chest.116.5.1175
7. De Vries J, Wirnsberger R. Fatigue, quality of life and health status in sarcoidosis. In: Drent M, Costabel U, editors. Sarcoidosis. European Respiratory Monograph 32. Lausanne: European Respiratory Society; 2005. p. 92-104. http://dx.doi.org/10.1183/1025448x.00032007
8. Loddenkemper R, Kloppenborg A, Schoenfeld N, Grosser H, Costabel U, Clinical findings in 715 patients with newly detected pulmonary sarcoidosis--results of a cooperative study in former West Germany and Switzerland. WATL Study Group. Wissenschaftliche Arbeitsgemeinschaft für die Therapie von Lungenkrankheitan. Sarcoidosis Vasc Diffuse Lung Dis. 1998;15(2):178-82.
9. Hunninghake GW, Gilbert S, Pueringer R, Dayton C, Floerchinger C, Helmers R, et al. Outcome of the treatment for sarcoidosis. Am J Respir Crit Care Med. 1994;149(4 Pt 1):893-8. http://dx.doi.org/10.1164/ajrccm.149.4.8143052
10. Gibson GJ, Prescott RJ, Muers MF, Middleton WG, Mitchell DN, Connolly CK, et al. British Thoracic Society sarcoidosis study: effects of long term corticosteroid treatment. Thorax. 1996;51(3):238-47. http://dx.doi.org/10.1136/thx.51.3.238
11. Pietinalho A, Tukiainen P, Jaahtela T, Persson T, Selroos O; Finnish Pulmonary Sarcoidosis Study Group. Early treatment of stage II sarcoidosis improves 5-year pulmonary function. Chest. 2002;121(1):24-31. http://dx.doi.org/10.1378/chest.121.1.24
12. De Vries J, Drent M, Van Heck GL, Wouters EF. Quality of life in sarcoidosis: a comparison between members of a patient organisation and a random sample. Sarcoidosis Vasc Diffuse Lung Dis. 1998;15:183-188.
13. Drent M, Wimsberger RM, Breteler MH, Kock LM, de Vries J, Wouters EF. Quality of life and depressive symptoms in patients suffering from sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis. 1998;15(2):59-66.
14. De Vries J, Michielsen H, Van Heck G, Drent M. Measuring fatigue in sarcoidosis: The Fatigue Assessment Scale (FAS). Br J Health Psychol. 2004;9(Pt 3):279-91. http://dx.doi.org/10.1348/1359107041557048
15. Wirnsberger RM, Drent M, Hekelaar N, Breteler MH, Drent S, Wouters EF, et al. Relationship between respiratory muscle function and quality of life in sarcoidosis. Eur Respir J. 1997;10(7):1450-5. http://dx.doi.org/10.1183/09031936.97.10071450
16. De Vries J, Rothkrantz-Kos S, van Dieijen-Visser MP, Drent M. The relationship between fatigue and clinical parameters in pulmonary sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis. 2004;21(2):127-36.
17. Drent M, Wirnsberger R, de Vries J, van Dieijen-Visser MP, Wouters EF, Schols AM. Association of fatigue with an acute phase response in sarcoidosis. Eur Respir J. 1999;13(4):718-22. http://dx.doi.org/10.1034/j.1399-3003.1999.13d03.x

18. Guyatt GJ, Feeny DJ, Patrick DL. Measuring health-related quality of life. Ann Intern Med. 1993;118(8):622-9. http://dx.doi.org/10.7326/0003-4819-118-8-199304150-00009
19. De Boer S, Wilsher ML. Validation of the Sarcoidosis Health Questionnaire in a non-US population. Respirology. 2012;17(3):519–24. http://dx.doi.org/10.1111/j.1440-1843.2012.02134.x
20. Antoniou K, Tzanakis N, Tzouvelekis A, Samiou M, Symvoulakis EK, Siafakas NM, et al. Quality of life in patients with active sarcoidosis in Greece. Eur J Intern Med. 2006;17(6):421-6. http://dx.doi.org/10.1016/j.ejim.2006.02.024
21. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992;30(6):473-83. http://dx.doi.org/10.1097/00005650-199206000-00002
22. Bowling A. Measuring Disease: A Review of Disease-specific Quality of Life Measurement Scales. Buckingham: Open University Press; 1995.
23. Bergner M, Bobbit RA, Kressel S, Pollard WE, Gilson BS, Morris JR. The sickness impact profile: conceptual foundation and methodology for the development of health status measure. Int J Health Serv. 1976;6(3):393-415. http://dx.doi.org/10.2190/RHE0-GGH4-410W-LA17
24. Gvozdenovic BS, Mihailovic-Vucinic V, Ilic-Dudvarski A, Zugic V, Judson MA. Differences in symptom severity and health status impairment between patients with pulmonary and pulmonary plus extrapulmonary sarcoidosis. Respir Med. 2008;102(11):1636-42. http://dx.doi.org/10.1016/j.rmed.2008.05.001
25. Gvozdenovic BS, Mihailovic-Vucinic V, Videnovic J, Zugic V, Ilic-Dudvarski A, Filipovic S. Quality of life and health status in sarcoidosis patients. In: Hoffmann EC, editor. Health-related quality of life. New York: Nova Science Publishers; 2009. p. 119-32.
26. Cox CE, Donohue JF, Brown CD, Kataria YP, Judson MA. Health-related quality of life of persons with sarcoidosis. Chest. 2004;125(3):997-1004. http://dx.doi.org/10.1378/chest.125.3.997
27. Jones PW, Quirk FH, Baveystock CM, Littlejohns P. A self-complete measure of health status for chronic airflow limitation. The St. George's Respiratory Questionnaire. Am Rev Respir Dis. 1992;145(6):1321-7. http://dx.doi.org/10.1164/ajrccm/145.6.1321
28. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. J Health Soc Behav. 1983;24(4):385-96. http://dx.doi.org/10.2307/2136404
29. Cox CE, Donohue JF, Brown CD, Kataria YP, Judson MA. The Sarcoidosis Health Questionnaire: a new measure of health-related quality of life. Am J Respir Crit Care Med. 2003;168(3):323-9. http://dx.doi.org/10.1164/rccm.200211-1343OC
30. MacIntyre N, Crapo RO, Viegi G, Johnson DC, van der Grinten CP, Brusasco V, et al. Standardisation of the single-breath determination of carbon monoxide uptake in the lung. Eur Respir J. 2005;26(4):720-35. http://dx.doi.org/10.1183/09031936.05.00034905
31. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced expiratory flows. Official statement of European Respiratory Society. Eur Respir J. 1993;6 Suppl 16:5-40. http://dx.doi.org/10.1183/09041950.005s1693
32. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J. 2005;26(2):319-38. http://dx.doi.org/10.1183/09031936.05.00034805
33. Judson MA, Baughman RP, Thompson BW, Teirstein AS, Terrin ML, Rossman MD, et al. Two year prognosis of sarcoidosis: the ACCESS experience. Sarcoidosis Vasc Diffuse Lung Dis. 2003;20(3):204-11.
34. Baughman RP, Teirstein AS, Judson MA, Rossman MD, Yeager H Jr, Bresnitz EA, et al. Clinical characteristics of patients in a case control study of sarcoidosis. Am J Respir Crit Care Med. 2001;164(10 Pt 1):1885-9. http://dx.doi.org/10.1164/ajrccm.164.10.2104046
35. Bourbonnais JM, Samavati L. Effect of gender on health related quality of life in Sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis. 2010;27(2):96-102.
36. Iannuzzi MC, Rybicki BA, Teirstein AS. Sarcoidosis. N Engl J Med. 2007;357(21):2153-65. http://dx.doi.org/10.1056/NEJMra071714

J Bras Pneumol. 2016;42(2):106-113
http://dx.doi.org/10.1590/S1806-37562015000000082

Pleural tuberculosis in the state of Roraima, Brazil, between 2005 and 2013: quality of diagnosis

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Submitted: 16 April 2015.
Accepted: 25 August 2015.

Study carried out at the Centro de Ciências da Saúde, Faculdade de Medicina. Universidade Federal de Roraima, Boa Vista (RR) Brasil.

ABSTRACT

Objective: To evaluate the quality of diagnosis and the epidemiological profile of patients with pleural tuberculosis in the state of Roraima, Brazil, in order to provide technical support for the development and implementation of public policies to combat the disease. **Methods:** This was a cross-sectional study designed to determine the prevalence of pleural forms of tuberculosis in Roraima between 2005 and 2013 and to evaluate the diagnostic criteria used, as well as their determinants. This study was based on secondary data from the Brazilian Case Registry Database, including all reported cases of pleural tuberculosis in the state during the study period. Diagnoses based on bacteriological or histopathological confirmation were defined as high-quality diagnoses. **Results:** Among the 1,395 cases of tuberculosis reported during the study period, 116 (8.3%) were cases of pleural tuberculosis, accounting for 38.9% of all cases of extrapulmonary tuberculosis in the sample. The incidence rate of pleural tuberculosis did not follow the downward trend observed for the pulmonary form of the disease during the same period. The prevalence of cases with a high-quality diagnosis was 28.5% (95% CI: 20.4-37.6%). In a univariate analysis, none of the demographic or clinical characteristics collected from the database were found to have a significant impact on the outcome (as explanatory variables). **Conclusions:** The quality of the diagnoses in our study sample was considered unsatisfactory. Limited access to specific diagnostic methods might have contributed to these results.

Keywords: Tuberculosis/diagnosis; Tuberculosis/epidemiology; Tuberculosis, pleural.

INTRODUCTION

Tuberculosis is a major public health problem worldwide. It is estimated that two billion people, approximately one third of the world population, are infected with *Mycobacterium tuberculosis*. In 2012, 8.6 million people developed tuberculosis and 1.4 million died from the disease worldwide; in Brazil, 82,755 new cases were reported.[1] Despite specific public policy efforts, Brazil is one of the 22 countries that collectively account for 80% of all cases of tuberculosis worldwide.[2] In 2008, tuberculosis was the fourth leading cause of death from infectious diseases and the leading cause of death in AIDS patients in Brazil.[2]

Among the extrapulmonary forms of tuberculosis, pleural tuberculosis is the most common in HIV-seronegative adults.[3] The diagnosis of pleural tuberculosis is primarily based on the detection of *M. tuberculosis* by direct examination or culture of pleural fluid or a pleural tissue specimen, as well as on the specific histopathological finding of granulomas.[3-5] A combination of histological examination and culture of a pleural tissue specimen leads to diagnosis in up to 90% of cases.[3-7]

The state of Roraima, which has great environmental and sociocultural diversity, is located in northern Brazil, within the boundaries of the "Legal Amazon", and shares an extensive border with Guyana and Venezuela. Roraima is characterized by the size of its indigenous population, which (at approximately 15%) is proportionally larger than is that of any other state in Brazil.[8,9] These individuals are considered to be more vulnerable to developing tuberculosis, some studies showing that the incidence of the disease is up to ten times higher in indigenous peoples than that in the general population.[10]

Within the state of Roraima, the Brazilian National Tuberculosis Control Program has been fully implemented in all 15 cities and in the two Special Indigenous Health Districts. In 2013, 170 new cases of tuberculosis were reported in the state, among which there were 12 cases of pleural tuberculosis.[11] However, pleural tuberculosis represents an additional challenge, given that the assessment required for a reliable diagnosis of the pleural form of tuberculosis is available only at the single tertiary referral center in Roraima, which opened relatively recently.

Despite documented advances in the provision of diagnostic services in the state of Roraima, the system of referral and counter-referral among the primary, secondary, and tertiary levels of health care is rudimentary.[12] There have been no studies investigating the epidemiological profile of patients with pleural tuberculosis in the state.

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Financial support: None.

ISSN 1806-3713

In addition, the quality of diagnosis among reported cases of pleural tuberculosis is unknown, as is the impact that the availability of a facility specializing in thoracic diseases has on that quality.

The objective of the present study was to evaluate the epidemiological profile of patients with, as well as the quality of diagnosis of, pleural tuberculosis in the state of Roraima. We also aimed to define the impact that the recent availability of sample collection techniques and methods used for specific diagnosis of tuberculosis within the public health care system in the state capital, Boa Vista, has had on the quality of diagnosis.

METHODS

Study design

This was a cross-sectional study designed to assess the prevalence of reported cases of pleural tuberculosis with a high-quality diagnosis in the state of Roraima, Brazil, between January of 2005 and December of 2013. The study was based on secondary data for the state, retrieved from the *Sistema de Informação de Agravos de Notificação* (SINAN, Brazilian Case Registry Database). For each reported case, the quality of diagnosis was assessed in accordance with the recommendations of the Brazilian National Ministry of Health National Tuberculosis Control Program, as described on its official reporting form.

A diagnosis of pleural tuberculosis was considered to be of high quality if the case reported met the following criteria: a positive smear microscopy or culture result in a pleural fluid sample or a positive culture result in a specimen of the parietal pleura; and histopathological positivity for AFB or histopathological results suggestive of tuberculosis, in a pleural specimen.[3] Individual, socioeconomic, and clinical patient data contained in the aforementioned instrument and potentially related to the diagnosis and progression of the disease were also analyzed.

In addition, data from the 2010 census[13] were used in order to estimate socioeconomic indicators and other risk factors that could be determinants of the dynamics of the diagnosis of the disease in question in the sample under consideration.

Sample and sampling

All cases of tuberculosis reported between 2005 and 2013 were analyzed consecutively and without selection. Of those, we included all cases of pleural tuberculosis (with or without pulmonary tuberculosis).[11] The sample was divided into two groups: cases reported between 2005 and 2009 (2005-2009 group); and cases reported between 2010 and 2013 (2010-2013 group). During the latter period, sample collection techniques and methods used for appropriate diagnosis of tuberculosis were available within the public health care system in the state of Roraima. The thoracic diseases department was accessible to patients in the latter group, as were diagnostic methods such as thoracentesis, percutaneous pleural biopsy, thoracoscopy, and video-assisted thoracoscopy. Such resources were not available within the referral network during the former period.

Data analysis

Categorical variables were expressed as absolute and relative frequencies, whereas quantitative variables were expressed as mean and standard deviation. The variable "outcome" represents the proportion of reported cases of pleural tuberculosis whose diagnosis was based on mycobacteriological or histopathological examination of specimens of pleural fluid or pleura (here referred to as high-quality diagnoses), with its corresponding 95% confidence interval (Newcombe-Wilson method).

The explanatory variables were extracted from individual data collected from the SINAN files, which include age, level of education, gender, place of residence, type of admission (recurrence or readmission), clinical data (form of disease, test results, and means of diagnosis), and comorbidities (AIDS, alcoholism, diabetes mellitus, and mental illness). Because of the assumption that all racial classifications are error-prone, racial classification was simplified into two categories in the present study: indigenous and non-indigenous.

For temporal analyses, we used the chi-square test for trend. The difference between proportions was analyzed with Fisher's exact test. Statistical analyses were performed with the Epi Info statistical package, version 7.1.3 for Windows.

Ethical aspects

Individual data on patients reported as having tuberculosis during the period described were delivered to the researchers by the Roraima State Department of Health Tuberculosis Control Program, after the signing of a confidentiality and non-disclosure agreement. The study was approved by the Research Ethics Committee of the Federal University of Roraima (Ruling no. 609,246), which waived the requirement for informed consent because the study used only secondary data.

RESULTS

Between 2005 and 2013, a total of 1,395 cases of tuberculosis were reported in the state of Roraima, Brazil. Of those, 116 (8.3%) were reported as cases of pleural tuberculosis and were included in the present analysis. The mean age of the study population was 39.9 ± 16.6 years. Most patients in the sample were male (n = 82; 70.7%), the most commonly reported level of education was completion of ≤ 9 years of schooling (n = 37; 31.9%), and 12 patients were reported as illiterate (11.1%). Table 1 describes the study sample.

The proportion of reported cases with a high-quality diagnosis was lower in the 2005-2009 period than in the 2010-2013 period, but not statistically significantly so (22.4% vs. 34.5%, respectively; p = 0.67). In addition,

Table 1. Demographic and clinical characteristics of cases of pleural tuberculosis reported between 2005 and 2013, Roraima, Brazil.[a]

Characteristic	Result
Age, years	39.9 ± 16.4
Male gender	82 (70.7)
Level of education	
Illiterate	12 (11.1)
≤ 9 years of schooling	37 (31.9)
High school	25 (21.6)
College	5 (4.3)
No data	37 (31.9)
Race	
Indigenous	21 (18.1)
Non-indigenous	95 (81.9)
Cases reported in the state capital	109 (94.0)
Place of residence	
State capital	66 (56.9)
Rural area	30 (25.9)
Institutionalized in prisons	2 (1.7)
Chest X-ray	
Suspicious (not specified on the reporting form)	105 (90.5)
Not performed	4 (3.5)
Tuberculin skin testing (according to the reporting form)	
Strongly positive	66 (56.9)
Weakly positive	11 (9.5)
Negative	16 (13.8)
Not performed	19 (16.4)
Cases of pleuropulmonary tuberculosis (reported as pulmonary + pleural)	48 (41.4)
Cases of pulmonary + extrapulmonary tuberculosis in a form other than pleural	5 (4.3)
Comorbidities	
AIDS	14 (12.5)
Alcoholism	16 (14.4)
Diabetes	7 (6.3)
Mental illness	5 (4.4)
Positive sputum smear	6 (5.2)
Smear of pleural fluid or a specimen of parietal pleura	
Performed	40 (34.5)
Positive	4 (3.5)
Not performed	74 (63.8)
Culture of pleural fluid or a specimen of parietal pleura	
Performed	54 (46.6)
Positive	3 (2.6)
Not performed	62 (53.5)
Histopathological examination of a specimen of parietal pleura	
Performed	38 (32.8)
Positive or suggestive of tuberculosis	27 (23.3)
Not performed	77 (66.4)
Under way	9 (7.8)
No testing of pleural fluid or specimens of parietal pleura was performed	36 (32.0)

Source: Brazilian Case Registry Database.[11] Developed by the authors, 2014. [a]Values expressed as n (%) or mean ± SD.

there were no statistically significant differences between the 2005-2009 and 2010-2013 groups regarding gender, race, or place of residence. The mean age in the 2005-2009 group was 38.9 years, with a predominance of individuals under 40 years of age (62.0%). In contrast, in the 2010-2013 group, the mean age was 41.1 years, with a predominance of individuals over 40 years of age (55.2%). Table 2 shows the homogeneity of the groups, which minimizes the possibility of interpretation bias in comparing the groups.

Table 2. Comparison between the groups studied. Demographic and clinical characteristics.[a]

Characteristic	Result		p
	2005-2009 group	2010-2013 group	
Age, years	38.9 ± 17.6	41.1 ± 15.1	NS
Male gender	40 (69.0)	42 (72.4)	NS
Race			NS
Indigenous	12 (20.7)	9 (15.5)	
Non-indigenous	46 (79.3)	49 (84.5)	
Place of residence			NS
State capital	36 (62.1)	30 (51.7)	
Rural area	14 (24.1)	16 (27.6)	
High-quality diagnosis	13 (22.4)	20 (34.5)	NS
Other diagnosis	45 (77.6)	38 (65.5)	

Source: Brazilian Case Registry Database.[11] Developed by the authors, 2014. NS: not significant. [a]Values expressed as n (%) or mean ± SD.

The variables gender, age, race, level of education, place of residence, comorbidities, and group (2005-2009 and 2010-2013) did not correlate with the prevalence of cases with a high-quality diagnosis in a univariate analysis. None of the variables met the criterion for inclusion in the multivariate analysis (Table 3).

As shown in Table 3, the only explanatory variable whose prevalence was statistically significant was histopathological examination of a specimen of the parietal pleura (although it was used as a quality-defining criterion, it remained in the table in order to facilitate its comparison with the other criteria), which occurred in 73.7% of the cases ($p < 0.001$). Smear microscopy of a specimen of the pleural fluid or parietal pleura and culture of the same had prevalences of 35.0% ($p = 0.390$) and 29.6% ($p = 0.838$), respectively, among the cases with a high-quality diagnosis in the study sample. For the three aforementioned variables, we performed only a dependence test (Fisher's exact test) in order to avoid possible multicollinearity with the outcome.

DISCUSSION

In 2005, the incidence rate of tuberculosis in the state of Roraima was 36.9/100,000 population, whereas the national incidence rate was 41.4/100,000 population. In contrast, in 2012, Roraima had an incidence rate of 24.5/100,000 population, compared with 37.3/100,000 population nationwide.[11,13] These data reflect the results of the Brazilian National Tuberculosis Control Program in the state, showing that the linear downward trend in incidence was more pronounced statewide than nationwide.

Taking into account cases of extrapulmonary tuberculosis, the incidence rate of tuberculosis in Roraima in 2005 was 8.2/100,000 population, that of pleural tuberculosis being 2.0/100,000 population; in 2013, those rates were 7.9/100,000 and 3.41/100,000 population, respectively, which shows a stabilization of incidence.[11,13] A study conducted by Seiscento et al.,[14] which analyzed epidemiological data on pleural tuberculosis between 1998 and 2005 in the state of São Paulo, Brazil, showed that there were 118,575 reported cases of tuberculosis during the period studied. Of those 118,575 cases, 25,773 (17.8%) were cases of extrapulmonary tuberculosis, pleural tuberculosis being the form most commonly reported (12,545 cases; 48.7%).

Although the overall incidence of tuberculosis shows a linear downward trend in Brazil and in Roraima, the same is not true when we consider only the pleural form of this disease. This was also reported by Seiscento et al.[14] regarding the trend of tuberculosis incidence in the state of São Paulo, Brazil. Likewise, Baumann et al.[15] presented a comprehensive assessment of the epidemiology of pleural tuberculosis in the USA in 2007, corroborating the evidence from the study conducted by Seiscento et al.[14] Baumann et al.[15] showed that, although the incidence of tuberculosis cases decreased in that country between 1993 and 2003, the incidence of pleural tuberculosis cases remained relatively stable in comparison with the total number of tuberculosis cases. Those authors concluded that the increased difficulty and complexity in diagnosing pleural tuberculosis could lead to underreporting of this presentation of the disease and expressed their concern about this fact. In contrast, according to Seiscento et al.,[14] this stability trend is due to the improvement of diagnostic techniques and the significant number of cases of reactivation in their sample, reactivation being correlated with comorbidities, which were present in 32.0% of the patients with pleural tuberculosis in that sample.

Although the aforementioned authors cited the quality and availability of diagnostic methods as factors impacting the incidence of pleural tuberculosis,[14,15] we found no improvement in the quality of diagnosis as a result of the availability of sample collection techniques and methods used for appropriate diagnosis of tuberculosis within the public health care system in the state of Roraima. The prevalence of cases with a high-quality diagnosis in the 2010-2013 group (which were reported after the establishment of the department of thoracic diseases in Roraima) showed an upward, although not statistically significant, trend relative to

Table 3. Univariate analysis of demographic and clinical data with regard to high-quality diagnosis of pleural tuberculosis, Roraima, Brazil, 2005-2013.

Independent variable	Quality of diagnosis				p	OR (95% CI)
	High		Other			
	n	%	n	%		
Age						
< 40 years	18	29.0	44	71.0	NS	1.06 (0.47-2.38)
≥ 40 years	15	27.8	39	72.2		1
Gender						
Male	25	30.5	57	69.5	NS	1.42 (0.57-3.58)
Female	8	23.5	26	76.5		1
Level of education						
Illiterate	3	25.0	9	75.0	NS	0.71 (0.18-2.89)
Low level of education (up to high school)	21	33.3	42	66.7		1.75 (0.51-5.98)
High level of education (college)	1	20.0	4	80.0		0.54 (0.06-5.11)
Race						
Indigenous	5	23.8	16	76.2	NS	0.75 (0.25-2.24)
Non-indigenous	28	29.5	67	70.5		1
Cases reported in the capital city						
Yes	32	29.4	77	70.6	NS	2.49(0.29-21.55)
No	1	14.3	6	85.7		1
Place of residence						
State capital	21	31.8	45	68.2	NS	1.59 (0.66-3.80)
Urban area	21	27.3	56	72.7		1.14 (0.45-2.89)
Rural area	9	30.0	21	70.0		1
Chest X-ray						
Suspicious	29	27.6	76	72.4	NS	0.67 (0.18-2.45)
Not performed	0	0.00	4	100.0		1
Tuberculin skin testing						
Strongly positive	19	28.8	47	71.2		1.15 (0.49-2.67)
Weakly positive	3	27.3	8	72.7	NS	0.98 (0.24-3.95)
Negative	5	25.0	12	75.0		0.85 (0.25-2.87)
Not performed	4	26.3	14	73.7		0.92 (0.30-2.81)
Comorbidities						
AIDS	2	14.3	12	85.7		0.35 (0.73-1.69)
Alcoholism	4	25.0	12	75.0	NS	0.70 (0.21-2.37)
Diabetes	2	28.6	5	71.4		0.90 (0.17-4.94)
Mental illness	1	20.0	4	80.0		0.55 (0.06-5.09)
Positive sputum smear	1	16.7	5	83.3	NS	0.49 (0.55-4.34)
Smear of pleural fluid or a specimen of parietal pleura						
Performed	14	35.0	26	65.0	NS	-
Positive	4	100.0	0	0.00	0.006	-
Not performed	19	25.7	55	74.3	NS	-
Culture of pleural fluid or a specimen of parietal pleura						
Performed	16	29.6	38	70.4	NS	-
Positive	3	100.0	0	0.0	0.021	-
Not performed	17	27.4	45	72.6	NS	-
Histopathological examination of a specimen of parietal pleura						
Performed	28	73.7	10	26.3	< 0.001	-
Positive or suggestive of tuberculosis	27	100.0	0	0.0	< 0.001	-
Not performed	5	6.5	72	93.5	< 0.001	-
Being in the 2005-2009 group	13	22.4	45	77.6	NS	0.55 (0.24-1.25)
Being in the 2010-2013 group	20	34.5	38	65.5	NS	1.82 (0.80-4.14)

Source: Brazilian Case Registry Database.[11] Developed by the authors, 2014.

that observed in the 2005-2009 group. Nevertheless, the prevalence remained low (at approximately one third of cases with a high-quality diagnosis). This evidence allows us to suggest that patients have limited access to such methods. It is of note that 32.0% of the patients reported as having pleural tuberculosis during the study period did not undergo any testing of pleural fluid or specimens of parietal pleura.

Given the fact that the diagnostic resources are available only in the state capital of Roraima, the prevalence of cases with a high-quality diagnosis would be expected to be higher among patients residing in the capital (56.9%) or among patients who were diagnosed at referral hospitals (83.6%), because of the assumption of greater availability of easy access to sample collection techniques and methods used for the appropriate diagnosis of tuberculosis. However, the prevalence of cases with a high-quality diagnosis was not much higher among the patients residing in the state capital than among those residing in other urban areas (31.8%; p = 0.387 vs. 27.3%; p = 0.784). The results were similar even when only the 2010-2013 group was assessed. This observation suggests the need for new patient referral policies—regionally, locally, and within referral centers—so that health system users can have broad access to the services already offered by the health system.

Although the frequency of reports of pleuropulmonary tuberculosis was found to be 41.4% in our sample, sputum smear positivity was found in only 5.2%. Neither of the two variables had a significant impact on the quality of diagnosis. This finding is a cause for concern, given that pleural tuberculosis is often considered a noncommunicable clinical form. In this context, routine screening for pulmonary involvement is not performed, and patients with pleuropulmonary tuberculosis are labeled as having pleural tuberculosis only. If the patient has active tuberculosis, in the peak period of communicability, the risk, in terms of infection among contacts and in terms of hospital biosafety, merits attention and concern.

Various studies have shown that, if more accurate diagnostic methods, such as imaging tests (tomography), collection of induced sputum or bronchoscopy (bronchoalveolar lavage and biopsy), microbiology (culture), and molecular biology tests, were used, concomitant pleural and pulmonary involvement would be confirmed in 50-80% of patients.[16,17] It should be noted that, despite there being no reference to the use of these methods in a systematic way, the pleuropulmonary form was reported in 18.0% of the patients reported as having pleural tuberculosis in the study conducted by Seiscento et al.[14]

According to the data available on the reporting forms analyzed in this study, routine X-ray was the diagnostic method most often used in order to support the diagnosis, having been used in 96.5% of the cases and the results having been considered suspicious in 90.5%. Tuberculin skin testing was performed in 83.6% of the cases, and the result was positive in 79.4%. In agreement with the study conducted by Neves et al.,[18] who analyzed the utility of clinical, radiological, and laboratory variables for the diagnosis of pleural tuberculosis, we found that these explanatory variables did not significantly change the quality of the diagnoses in our sample.

The present study has a limitation. Secondary data analysis is prone to confounding factors and inaccuracies. There is no reference on the SINAN reporting form to pleural fluid cytometry, nor is there reference to determination of adenosine deaminase (ADA) or lactate dehydrogenase activity in pleural fluid. This was a limiting factor in the study, since it was not possible to assess the importance of these methods for the quality of the diagnosis of pleural tuberculosis in Brazil. It is of note that, except for determination of ADA activity, which is unavailable in all public diagnostic facilities in the state of Roraima, the other aforementioned tests are available at referral hospitals in the state.

This limitation was also acknowledged in the study conducted by Seiscento et al.,[14] who reported that 55.6% of the 12,545 reported cases of pleural tuberculosis were cases diagnosed on the basis of unspecified criteria, allowing the assumption that diagnoses were based only on clinical-epidemiological or radiological criteria, biochemical criteria, and cytological criteria that were not recorded in the SINAN data set. In our sample, the frequency of such cases was 71.6%, a worrisome figure when it comes to the reliability of the diagnoses.

It has been observed that, in countries with a high incidence of tuberculosis, an epidemiological history suggestive of exposure, together with elevated protein levels, a lymphocyte/neutrophil ratio > 0.75), and, especially, ADA activity in pleural fluid > 40 U/L, is sufficient to warrant the initiation of treatment,[18,19] especially because highly specific tests can take weeks to produce results.

In view of the fragility of diagnoses in the state of Roraima, the findings of the present study allows us to suggest that determination of ADA activity in pleural, pericardial, and peritoneal fluid should be made available within the public health care system. This suggestion is not intended to replace bacteriological and histopathological methods but rather to provide grounds for the institution of treatment of tuberculosis while tests that are more specific are being processed. Likewise, it is advisable to include a field for reporting the use of the suggested method on the reporting form.

Taking into account the tests recommended by the Brazilian National Tuberculosis Control Program as the tests of choice for a definitive diagnosis of pleural tuberculosis as well as the defining criteria for high-quality diagnosis, the present study can say that bacteriological tests were ordered in 59.5% of the cases, yielding positive results in only 11.2%. Smear microscopy of sputum, pleural fluid, or pleural specimens was positive in only 5.7% and 3.5% of the reported cases, respectively, and culture of the same material

was positive in 2.6%. The fact that smear microscopy and culture of pleural fluid or pleural specimens were requested had no statistically significant impact on the quality of diagnosis.

In the sample studied by Seiscento et al.,[14] bacteriological tests were used in 44.4% of the cases. Approximately 14% of those cases had bacteriological confirmation (positive sputum smear, in 5.6%; positive smear of pleural fluid/pleural tissue, in 3.0%; and positive culture for *M. tuberculosis*, in 5.6%). In contrast, in the sample studied by Baumann et al.,[15] 62.8% of the cases of pleural tuberculosis had at least a culture of tissue/fluid that was positive for *M. tuberculosis*, and 1.7% were sputum smear positive. Those authors acknowledged concern about underreporting owing to decreased yields when only pleural fluid is analyzed.

Histopathological examination of pleural specimens was performed in 32.8% of the reported cases of pleural tuberculosis in the present sample, being positive in 23.3%. The prevalence of having undergone this test among the cases with a high-quality diagnosis was 73.7%. In addition, of the 6 cases in which the diagnosis was changed, 2 underwent histopathological examination, which emphasizes the importance of the method not only to confirm clinical suspicions, but also to establish differential or perhaps comorbid diagnoses. Histology of the pleura was decisive for diagnosis in 30.2% of the reported cases of the disease in the sample studied by Seiscento et al.[14] In contrast, in the sample studied by Baumann et al.,[15] 15.8% of the patients with pleural tuberculosis had a positive result from microscopic examination of pleural tissue, without the criteria for positivity being defined.

We found no data on the clinical progression of the patients treated as having pleural tuberculosis in the SINAN records—only data on treatment outcomes (cure, noncompliance, death, transfer out, change in diagnosis, and multidrug-resistant tuberculosis).[12] Therefore, the fact that there were only 6 cases (5.2%) in which the diagnosis was changed does not ensure that the cases whose diagnosis was based on clinical and radiological criteria, representing most of the sample (71.6%), were actually cases of pleural/pleuropulmonary tuberculosis rather than cases of other diseases that also have pleural involvement.

On the basis of our findings, we conclude that poor quality of diagnosis and limited access of patients to appropriate diagnostic methods result in chronic exposure of the population in Roraima, which has a high prevalence of individuals who are more susceptible to developing tuberculosis, chief among whom are those in indigenous and prison populations. These populations are exposed to the possibility of undergoing long treatments and suffering their potential complications, without a reliable diagnosis. In addition, more disastrously, individuals other than those mentioned above can also have severe, permanent, occupationally limiting pulmonary and pleural sequelae, leading even to death, as a result of delayed or no treatment because of a lack of diagnosis. Furthermore, these facts often perpetuate the chain of disease transmission, which has major consequences for public health and for health care professionals (biosafety).

It is also possible to conclude that the recent provision of services and diagnostic procedures for thoracic diseases in the state of Roraima has not translated to improved quality of diagnosis among the reported cases of pleural or pleuropulmonary tuberculosis. It is therefore evident that there is a need for further studies that will complement the present study, as well as for the development and implementation of public policies that increase the quality of diagnosis and the access to diagnostic methods.

REFERENCES

1. World Health Organization [homepage on the Internet]. Geneva: World Health Organization; [cited 2014 Nov 22]. Global tuberculosis report 2013. {Adobe Acrobat document, 293p.]. Available from: http://apps.who.int/iris/bitstream/10665/91355/1/9789241564656_eng.pdf
2. World Health Organization [homepage on the Internet]. Geneva: World Health Organization [cited 2014 Nov 22]. Global Tuberculosis Control: Epidemiology, Strategy, Financing. WHO report 2009. [Adobe Acrobat document, 314p.]. Available from: http http://www.who.int/tb/publications/global_report/2009/pdf/full_report.pdf
3. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Programa Nacional de Controle da Tuberculose. Manual de recomendações para o controle da tuberculose no Brasil. Brasília: Ministério da Saúde; 2011.
4. Gopi A, Madhavan SM, Sharma SK, Sahn SA. Diagnosis and treatment of tuberculous pleural effusion in 2006. Chest. 2007;131(3):880-9. http://dx.doi.org/10.1378/chest.06-2063
5. Wong PC. Management of tuberculous pleuritis: can we do better? Respirology. 2005;10(2):144-8. http://dx.doi.org/10.1111/j.1440-1843.2005.00689.x
6. Diacon AH, Van de Wal BW, Wyser C, Smedema JP, Bezuidenhout J, Bolliger CT, et al. Diagnostic tools in tuberculous pleurisy: a direct comparative study. Eur Respir J. 2003;22(4):589-91. http://dx.doi.org/10.1183/09031936.03.00017103a
7. Emad A, Rezaian GR. Diagnostic value of closed percutaneous pleural biopsy vs pleuroscopy in suspected malignant pleural effusion or tuberculous pleurisy in a region with a high incidence of tuberculosis: a comparative, age-dependent study. Respir Med. 1998;92(3):488-92. http://dx.doi.org/10.1016/S0954-6111(98)90296-7
8. Campos C, editor. Diversidade socioambiental de Roraima: subsídios para debater o futuro sustentável da região. São Paulo: Instituto Socioambiental; 2011.
9. Brasil. Ministério da Saúde. Fundação Nacional de Saúde. Coordenação de planejamento e avaliação. Relatório de Gestão 2008. Brasília: FUNASA; 2009.
10. Buchillet D. Tuberculose, cultura e saúde pública. Série Antropologia, no. 273, Brasília: DAN/UnB; 2000. p. 1-19.
11. Roraima. Secretaria Estadual de Saúde de Roraima. Núcleo de Controle da Tuberculose. Sistema de Informação de Agravos de Notificação (SINAN). Base de dados relacionados a tuberculose em Roraima de 2005 a 2013 [CD-ROM]. Boa Vista: SINAN; 2014.
12. Souza AL. Diagnóstico tardio da tuberculose em Boa Vista–Roraima: estudo de prevalência e seus determinantes. [thesis]. Roraima: Universidade Federal de Roraima; 2013.
13. Brasil. Instituto Brasileiro de Geografia e Estatística. Censo demográfico 2010: características da população e dos domicílios. Rio de Janeiro: IBGE; 2010.
14. Seiscento M, Vargas FS, Rujula MJ, Bombarda S, Uip DE, Galesi VM. Epidemiological aspects of pleural tuberculosis in the state of São Paulo, Brazil (1998-2005). J Bras Pneumol. 2009;35(6):548-54. http://dx.doi.org/10.1590/S1806-37132009000600008
15. Baumann, MH, Nolan R, Petrini M, Lee YC, Light RW, Schneider

E. Pleural tuberculosis in the United States: incidence and drug resistance. Chest. 2007;131(4):1125-32. http://dx.doi.org/10.1378/chest.06-2352

16. Conde MB, Loivos AC, Rezende VM, Soares SL, Mello FC, Reingold AL, et al. Yield of sputum induction in the diagnosis of pleural tuberculosis. Am J Respir Crit Care Med. 2003;167(5):723-5. http://dx.doi.org/10.1164/rccm.2111019
17. Kim HJ, Lee HJ, Kwon SY, Yoon HI, Chung HS, Lee CT, et al. The prevalence of pulmonary parenchymal tuberculosis in patients with tuberculous pleuritis. Chest. 2006;129(5):1253-8. http://dx.doi.org/10.1378/chest.129.5.1253
18. Neves DD, Dias RM, Cunha AJ, Chibante AM. Efficiency of clinical, radiological and laboratory testing in the diagnosis of pleural tuberculosis. J Bras Pneumol. 2004;30(4):409-16.
19. Porcel JM, Vives M. Differentiating tuberculous from malignant pleural effusions: a scoring model. Med Sci Monit. 2003;9(5):CR175-80.

J Bras Pneumol. 2016;42(2):114-120
http://dx.doi.org/10.1590/S1806-37562015000000192

Correlation between the severity of critically ill patients and clinical predictors of bronchial aspiration

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Submitted: 6 August 2015.
Accepted: 27 January 2016.

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ABSTRACT

Objective: To determine whether the severity of non-neurological critically ill patients correlates with clinical predictors of bronchial aspiration. **Methods:** We evaluated adults undergoing prolonged orotracheal intubation (> 48 h) and bedside swallowing assessment within the first 48 h after extubation. We collected data regarding the risk of bronchial aspiration performed by a speech-language pathologist, whereas data regarding the functional level of swallowing were collected with the American Speech-Language-Hearing Association National Outcome Measurement System (ASHA NOMS) scale and those regarding health status were collected with the Sequential Organ Failure Assessment (SOFA). **Results:** The study sample comprised 150 patients. For statistical analyses, the patients were grouped by ASHA NOMS score: ASHA1 (levels 1 and 2), ASHA2 (levels 3 to 5); and ASHA3 (levels 6 and 7). In comparison with the other patients, those in the ASHA3 group were significantly younger, remained intubated for fewer days, and less severe overall clinical health status (SOFA score). The clinical predictors of bronchial aspiration that best characterized the groups were abnormal cervical auscultation findings and cough after swallowing. None of the patients in the ASHA 3 group presented with either of those signs. **Conclusions:** Critically ill patients 55 years of age or older who undergo prolonged orotracheal intubation (≥ 6 days), have a SOFA score ≥ 5, have a Glasgow Coma Scale score ≤ 14, and present with abnormal cervical auscultation findings or cough after swallowing should be prioritized for a full speech pathology assessment.

Keywords: Deglutition; Deglutition disorders; Intubation, intratracheal; Pneumonia, aspiration; Intensive care units.

INTRODUCTION

Dysphagia after prolonged orotracheal intubation (OTI)—longer than 48 h[1-3]—is defined as the inability to effectively transfer food from the mouth into the stomach.[4] This type of dysphagia has an incidence of 44% to 87%[3,5,6] of cases after extubation, and it can increase morbidity and mortality.[7] According to data collected from hospitals in the USA, the annual cost of patients with dysphagia exceeds US$500 million.[4]

Recently, one of the concerns has been the study of dysphasia and its impact on the health care system.[8-11] Dysphagia after prolonged OTI delays the resumption of oral feeding, increases the risk for lung diseases, and delays hospital discharge.[12,13] In this scenario, early identification of predictors of aspiration is extremely relevant for priority treatment of at-risk patients, with the institution of appropriate measures and promotion of safe and speedy resumption of oral feeding.[14] There are several tests available for the diagnosis of dysphagia after prolonged OTI, including bedside swallowing assessment, performed by a speech-language pathologist, as well as imaging (videofluoroscopy and videoendoscopy).[15] However, it is of note that the use of such tests is not a reality in most treatment centers, in addition to the fact that indications for their use in critically ill patients are limited.[10]

A recent study[15] investigated clinical predictors of dysphagia after prolonged OTI, on the basis of the results of clinical bedside swallowing assessments. The authors concluded that patients presenting with food or liquid escaping from the mouth or nose, multiple swallows, abnormal cervical auscultation findings, choking, altered voice quality, and cough after swallowing should be promptly evaluated before resumption of oral feeding. Other studies using bedside assessments have reported that the following signs are indicative of risk of aspiration: voice quality after swallowing[16,17] and cough after swallowing.[17,18]

It is known that dysphagia severity after prolonged OTI is related to However, there are studies that have assessed the association of dysphagia with other risk factors, such as measures of patient severity of illness.[19-21] In such studies, the authors included the results of instruments that determine patient severity of illness at the time of admission, such as the Sequential Organ Failure Assessment (SOFA) and the Acute Physiology and Chronic Health Evaluation II (APACHE II).[19-21]

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Financial support: None.

ISSN 1806-3713

Two current studies used SOFA scores calculated at ICU admission for investigating their correlations with dysphagia severity.[19,20] Both studies found that patient severity of illness at the time of admission was not associated with dysphagia severity (determined by bedside assessment). Patients with mild dysphagia or normal swallowing had SOFA scores similar to those of patients with severe dysphagia.

Another study,[21] the objective of which was to investigate the demographic and clinical factors associated with dysphagia after prolonged OTI in patients with pulmonary changes, analyzed the results of scales that measure severity of illness (SOFA and APACHE II scores) as possible factors related to post-extubation dysphagia severity. Results of the regression analysis showed that four variables were significant: duration of intubation; upper gastrointestinal comorbidity; SOFA score; and low BMI.

Therefore, the objective of the present study was to determine whether the severity of non-neurological critically ill patients correlates with clinical predictors of bronchial aspiration (bedside swallowing assessment).

METHODS

We conducted a prospective, observational, cross-sectional study, which was approved by the local research ethics committee (Code No. CAPPesq 311784). The data collection procedures began only after obtaining written informed consent from the patients or their legal guardians.

The study participants were patients who underwent bedside swallowing assessment, by physician request, and were being treated in the Department of Speech Therapy of the University of São Paulo School of Medicine *Hospital das Clínicas* Central Institute, located in the city of São Paulo, Brazil, between January of 2013 and January of 2015.

The inclusion criteria were having undergone prolonged OTI (> 48 h)[1-3]; being > 18 years of age; not having or having had a tracheostomy; not having neurological or neurodegenerative disorders; not having a history of esophageal dysphagia; not having lung or neck cancer or having undergone surgical procedures in those regions; and having undergone bedside swallowing assessment within the first 48 h after extubation.

The steps in the data collection process of this study are described below.

Clinical speech pathology assessment of the risk of bronchial aspiration

The risk of bronchial aspiration was determined on the basis of the Dysphagia Risk Evaluation Protocol (DREP).[10,15] The DREP is intended for early bedside assessment of the patient's risk of dysphagia. This protocol involves the controlled administration of water and puree volumes. The final result of the DREP determines whether the patient can receive larger volumes and different textures of foods and liquids, as well as indicating whether monitoring is required for safe feeding. The results observed for each protocol item are recorded as either "pass" or "fail".

A recently published study investigated predictors of dysphagia after prolonged OTI,[15] on the basis of the DREP results for a 5-mL water swallow test. In that study, the authors concluded that the predictors of dysphagia in the study population were food or liquid escaping from the mouth or nose, multiple swallows, abnormal cervical auscultation findings, voice quality after swallowing, cough after swallowing, and choking. Therefore, those DREP items were considered in the analysis and were assessed for correlations with the other data in the study.

Level of swallowing function

Level of swallowing function was determined with the use of the American Speech-Language-Hearing Association National Outcome Measurement System (ASHA NOMS) scale.[22] This scale is a multidimensional tool that assesses the degree of feeding supervision required by and the food/liquid textures that are safe for each patient, producing a single number between 1 and 7. For the purposes of the present study, the ASHA NOMS scale scores were determined after full completion of the DREP and, when necessary, after clinical swallowing assessment. Therefore, level of swallowing function was classified as follows: level 1: the individual is not able to swallow anything safely by mouth, and all nutrition and hydration are received through non-oral means; level 2: the individual is not able to swallow safely by mouth for nutrition and hydration, but may take some consistency, in therapy only, with consistent maximal cues, and an alternative method of feeding is required; level 3: an alternative method of feeding is required as the individual takes less than 50% of nutrition and hydration by mouth, and/or swallowing is safe with use of moderate cues to use compensatory strategies, and/or the individual requires maximum diet restriction; level 4: swallowing is safe, but usually requires moderate cues to use compensatory strategies, and/or the individual has moderate diet restrictions and/or still requires an alternative method of feeding and/or oral supplements; level 5: swallowing is safe with minimal diet restriction and/or occasionally requires minimal cues to use compensatory strategies, the individual may occasionally self-cue, and all nutrition and hydration needs are met by mouth at mealtime; level 6: swallowing is safe, and the individual eats and drinks independently, rarely requires minimal cues to use compensatory strategies, usually self-cues when difficulty occurs, but may need to avoid specific food items (e.g., popcorn and peanuts) and/or require additional time (because of dysphagia); and level 7: the individual's ability to eat independently is not limited by swallow function, which is safe and efficient for all consistencies, and compensatory strategies are effectively used when needed.

Patient severity of illness

Patient severity of illness at the time of clinical speech pathology assessment was determined by using the SOFA score,[23] recorded on the medical chart on the basis of clinical and laboratory test results. This score is a tool that is used on a daily basis in critically ill patients during their ICU stay, to determine the degree of organ dysfunction/failure quantitatively and objectively. The SOFA score is used not to determine patient outcome, but rather to describe complications in critically ill patients. The two major objectives of SOFA are to improve the understanding of organ dysfunction and how impairments in several organs are related to each other and to assess the effects of medical treatment.

To determine patient severity of illness, scores ranging from zero (normal) to four (highest degree of impairment) are assigned to the various organ systems (respiratory, cardiovascular, hematological, hepatic, central nervous system, and renal). Each organ system receives a separate score, and the final score is obtained by summing all scores. The maximum score is 20, which is indicative of the highest degree of severity. The criteria for assigning points are described in Chart 1.

Data analysis

Assumptions of normality of distribution in each group and homogeneity of variances among the groups were tested using the Shapiro-Wilk test and Levene's test, respectively.

To compare SOFA scores among the different levels of swallowing function, we used the Kruskal-Wallis test, and, when multiple comparisons were necessary, we used Dunn's test. Categorical variables were analyzed with the chi-square test and Fisher's exact test. The level of statistical significance was set at 5% ($p \leq 0.05$) for all analyses.

RESULTS

After the inclusion criteria were applied, the final study sample consisted of 150 patients. The underlying diagnoses of the patients included in the study were as follows: lung disease, in 59 patients; multiple trauma without traumatic brain injury, in 18; kidney and liver transplants, in 12; heart disease, in 11; vascular disease, in 11; liver disease, in 10; kidney disease, in 10; infectious disease, in 6; gastroenterological disease, in 5; rheumatic disease, in 5; and endocrine disease, in 3.

The distribution of the patients by level of swallowing function, as determined by the ASHA NOMS scale after bedside speech pathology assessment, was as follows: 3 patients at level 1; 35 at level 2; 22 at level 3; 27 at level 4; 12 at level 5; 10 at level 6; and 41 at level 7. For the purposes of statistical analysis, the patients were grouped as follows: those at levels 1 and 2, ASHA1; those at levels 3 to 5, ASHA2; and those at levels 6 and 7, ASHA3. The group comparison by age and duration of intubation is shown in Table 1.

Statistical analysis using the Kruskal-Wallis test showed significant differences in age between the ASHA1 and ASHA3 groups ($p < 0.001$) and between the ASHA2 and ASHA3 groups ($p = 0.026$), patients in the ASHA3 group being younger than those in the other two groups. Mean duration of intubation (in days) was shortest in the ASHA3 group, and there was a significant difference between that group and the ASHA1 group ($p = 0.001$).

Table 2 shows the comparison of predictors of bronchial aspiration among different levels of swallowing function.

Chart 1. Sequential Organ Failure Assessment scoring system.

Variable	Score				
	0	1	2	3	4
Respiratory system					
PaO_2/FiO_2, mmHg	> 400	≤ 400	≤ 300	≤ 200[a]	≤ 100[a]
Hematological system					
Platelets, $\times 10^3/mm^3$	> 150	≤ 150	≤ 100	≤ 50	≤ 20
Hepatic system					
Bilirubin, mg/dL (μmol/L)	< 1.2 (< 20)	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	> 12.0 (> 204)
Cardiovascular system					
Hypotension	No hypotension	MAP < 70 mmHg	Dopamine ≤ 5 or dobutamine at any dose[b]	Dopamine > 5, epinephrine ≤ 1, or norepinephrine ≤ 0.1[b]	Dopamine > 15, epinephrine > 0.1, or norepinephrine > 0.1[b]
CNS					
Glasgow Coma Scale	15	13-14	10-12	6-9	< 6
Renal system					
Creatinine, mg/dL (μmol/L)	< 1.2 (< 110)	1.2-1.9 (110-170)	2.0-3.4 (171-299)	3.5-4.9 (300-440)	> 5.0 (> 440)
Urine output, mL/day	N/A	N/A	N/A	< 500	< 200

MAP: mean arterial pressure; and SNC central nervous system. [a]With ventilatory support. [b]Adrenergic agents (μg/kg body weight/min) were administered for at least 1 h.

Table 1. Age and duration of intubation in the patients studied.

Variable	Group			p*
	ASHA1	ASHA2	ASHA3	
Age, years	62.00 ± 17.40	55.30 ± 17.48	46.40 ± 18.30	< 0.001
Duration of intubation, days	7.60 ± 3.97	6.20 ± 3.38	4.90 ± 2.70	< 0.001

ASHA1: patients at levels 1 and 2, as scored by the American Speech-Language-Hearing Association National Outcome Measurement System (ASHA NOMS); ASHA2: patients at levels 3, 4, and 5, as scored by ASHA NOMS; and ASHA3: patients at levels 6 and 7, as scored by ASHA NOMS. *ANOVA.

Table 2. Comparison of predictors of bronchial aspiration among levels of swallowing function.

Clinical sign	Result	Group			p*
		ASHA1 (n = 38)	ASHA2 (n = 61)	ASHA3 (n = 51)	
Extraoral loss[a]	Pass	35	57	50	0.402
	Fail	3	4	1	
Multiple swallows	Pass	24	42	44	0.030
	Fail	14	19	7	
Abnormal cervical auscultation findings	Pass	21	52	51	< 0.001
	Fail	17	9	0	
Wet voice	Pass	31	55	51	0.009
	Fail	7	6	0	
Cough	Pass	16	37	50	< 0.001
	Fail	22	24	1	
Choking	Pass	31	52	51	0.008
	Fail	7	9	0	

ASHA1: patients at levels 1 and 2, as scored by the American Speech-Language-Hearing Association National Outcome Measurement System (ASHA NOMS); ASHA2: patients at levels 3, 4, and 5, as scored by ASHA NOMS; and ASHA3: patients at levels 6 and 7, as scored by ASHA NOMS. [a]Food or liquid escaping from the mouth or nose. *Chi-square test.

The results indicated that the predictor "food or liquid escaping from the mouth or nose" did not differentiate among the swallowing function level groups. The predictors "abnormal cervical auscultation findings" and "cough" after swallowing were the indicators that best differentiated among the groups. To determine the groups for which the predictors of aspiration were the most evident, we used Fisher's exact test. In that analysis, the groups were matched for predictors of aspiration—multiple swallows: ASHA1 vs. ASHA2 ($p = 0.559$); ASHA1 vs. ASHA3 ($p = 0.011$); and ASHA2 vs. ASHA3 ($p = 0.030$); abnormal cervical auscultation findings: ASHA1 vs. ASHA2 ($p = 0.001$); ASHA1 vs. ASHA3 ($p < 0.001$); and ASHA2 vs. ASHA3 ($p = 0.004$); wet voice: ASHA1 vs. ASHA2 ($p = 0.236$); ASHA1 vs. ASHA3 ($p = 0.002$); and ASHA2 vs. ASHA3 ($p = 0.031$); cough after swallowing: ASHA1 vs. ASHA2 ($p = 0.072$); ASHA1 vs. ASHA3 ($p < 0.001$); and ASHA2 vs. ASHA3 ($p < 0.001$); and choking: ASHA1 vs. ASHA2 ($p = 0.630$); ASHA1 vs. ASHA3 ($p = 0.002$); and ASHA2 vs. ASHA3 ($p = 0.004$).

Tables 3 and 4 show the results of the comparison of patient severity of illness (SOFA) among levels of swallowing function at the time of speech pathology assessment.

The results of the two analyses indicate that poor swallowing function translates to greater patient severity of illness. It can also be seen that the ASHA1 group (patients who cannot tolerate oral feeding) and the ASHA2 group (patients who require maximum to moderate diet restriction) did not differ regarding patient severity of illness (SOFA score).

To establish which indicators of patient severity of illness could have an impact on swallowing, we sought to determine whether indicators of functioning of the respiratory, cardiovascular, and central nervous systems (SOFA score) correlate with level of swallowing function at the time of speech pathology assessment (Table 5). The results indicated that only changes in the central nervous system correlated with changes in swallowing function, indicating that poor swallowing function translates to central nervous system impairment. In an analysis solely of the indicator of functioning of the central nervous system, Dunn's test indicated that the group with the poorest swallowing function differed from the others: ASHA1 vs. ASHA2 ($p = 0.018$); ASHA1 vs. ASHA3 ($p < 0.001$); and ASHA2 vs. ASHA3 ($p = 0.101$).

DISCUSSION

This study presents the characteristics of the risk of bronchial aspiration in the largest sample of patients after prolonged OTI in Brazil. Establishing priority indicators for post-extubation speech pathology care is essential to reducing hospital costs, optimizing bedside speech pathology assessment, and promoting safe and speedy resumption of oral feeding.

The literature indicates that the impact of age on the occurrence of dysphagia after prolonged OTI is

Table 3. Comparison of patient severity of illness among levels of swallowing function.

Level of wallowing function	Median	IQR	p
ASHA1	5.0	3.75-8.00	0.001
ASHA2	5.0	3.00-7.00	
ASHA3	3.0	2.00-5.00	

IQR: interquartile range; ASHA1: patients at levels 1 and 2, as scored by the American Speech-Language-Hearing Association National Outcome Measurement System (ASHA NOMS); ASHA2: patients at levels 3, 4, and 5, as scored by ASHA NOMS; and ASHA3: patients at levels 6 and 7, as scored by ASHA NOMS. *Kruskal-Wallis test.

similar in young adults and in the elderly[24,25]; both groups seem to differ only in dysphagia resolution, the elderly having a trend toward delayed resumption of oral feeding.[2,18,26] In contrast, the present study showed that predictors of bronchial aspiration were more common in individuals 55 years of age or older.

A previous study reported the impact of aging on the swallowing function, indicating that healthy elderly individuals present with vallecular residuals (laryngeal retention) and that such individuals are usually unaware of retained food in the pharynx.[27] Although pharyngeal clearing is nearly complete in young, asymptomatic individuals, the same is not true for healthy elderly individuals.[27] The mechanisms responsible for the development of pharyngeal retention have yet to be fully determined. According to the literature,[28,29] age-related physiological changes—reduced amplitude of pharyngeal contractions, pharyngeal shortening, reduced tongue propulsion/strength, and reduced soft palate strength, all of which hinder the displacement of the food bolus—may be involved in the impairment of the swallowing process. Those factors could also explain the higher frequency of occurrence of cough and abnormal auscultation findings after swallowing, observed in the present study, in the critically ill patients 55 years of age or older.

The association between duration of orotracheal intubation and dysphagia severity is well documented in the literature.[1,12,19,30,31] This association can be explained by the impact of the tube remaining in the oral cavity, pharynx, and larynx. It is known that chemoreceptors and/or mechanoreceptors, located in the pharyngeal and laryngeal mucosa and involved in the swallowing reflex, can undergo changes due to the presence of an orotracheal tube.[3] Laryngeal sensory impairment, identified by the absence of cough or of any other clinical sign suggestive of aspiration, has been observed in patients during the ingestion of liquids, immediately after extubation and within 4 h after extubation.[32,33] The results of the present study suggest that predictors of aspiration are more common in individuals who remain intubated for 6 days or more.

The present study identified abnormal cervical auscultation findings as a possible predictor of bronchial aspiration. The sounds associated with healthy and pathological swallowing have been identified with the aid of accelerometers and microphones, for analysis of acoustic characteristics[34,35] and determination of the characteristic sounds of swallowing.[35-37] The results regarding the accuracy of the method vary considerably in terms of reliability and validity in comparison with those of imaging.[38] In contrast, it should be taken into consideration that the very interpretation of videofluoroscopy images and results also varies in terms of reliability and reproducibility.[39,40] Regardless of the method adopted to assess swallowing, there is a consensus that specific training in its use is indispensable.

Data analysis indicated that, in the present study, critically ill patients who underwent prolonged OTI and had poorer swallowing function had greater overall

Table 4. Multiple comparisons of patient severity of illness among levels of swallowing function.

Comparison	p
ASHA1 vs. ASHA2	> 0.999
ASHA1 vs. ASHA3	0.003
ASHA2 vs. ASHA3	0.005

ASHA1: patients at levels 1 and 2, as scored by the American Speech-Language-Hearing Association National Outcome Measurement System (ASHA NOMS); ASHA2: patients at levels 3, 4, and 5, as scored by ASHA NOMS; and ASHA3: patients at levels 6 and 7, as scored by ASHA NOMS.*Dunn's test.

Table 5. Comparison of the severity of involvement of the respiratory, cardiovascular, and central nervous systems among levels of swallowing function.

SOFA score	Group			p
	ASHA1 (n = 38)	ASHA2 (n = 61)	ASHA3 (n = 51)	
Respiratory				
0	8	13	14	0.436
1	14	13	15	
2	9	18	7	
3	7	14	13	
4	0	3	2	
Cardiovascular				
0	28	49	47	0.507
1	2	3	1	
2	1	1	1	
3	5	7	1	
4	2	1	1	
CNS				
0	15	40	43	0.001
1	18	18	8	
3	4	2	0	
4	3	1	0	

SOFA: Sequential Organ Failure Assessment; ASHA1: patients at levels 1 and 2, as scored by the American Speech-Language-Hearing Association National Outcome Measurement System (ASHA NOMS); ASHA2: patients at levels 3, 4, and 5, as scored by ASHA NOMS; ASHA3: patients at levels 6 and 7, as scored by ASHA NOMS; and CNS: central nervous system. *Chi-square test.

severity of illness, changes in the central nervous system being the factor with the greatest impact on this difference. As shown in the introduction, the results of the studies that correlated patient severity of illness (SOFA score) with dysphagia severity did not achieve significance.[19,20] However, the item regarding neurological system impairment was not included in the analyses of those studies. The literature has identified that a decreased level of consciousness has impacts on the swallowing mechanism and can lead to aspiration.[2,5,31]

Finally, the limitations of the present study should be acknowledged. First, the study sample consisted of patients from a single institution, and, therefore, the results might have some bias resulting from the therapeutic approaches adopted in the specific protocols. Second, the type of assessment proposed for identifying predictors of bronchial aspiration was based solely on an observational clinical protocol. Determination of the actual occurrence of bronchial aspiration, on the basis of the signs evaluated, was not objectively confirmed by imaging. It is of note that the present study did not exclude full speech pathology assessments, including imaging.

The results of the present study suggest that critically ill patients 55 years of age or older who undergo prolonged OTI (≥ 6 days), have a SOFA score ≥ 5, have a Glasgow Coma Scale score ≤ 14, and present with abnormal cervical auscultation findings or cough after swallowing (5 mL water swallow test at the bedside) should be prioritized for a full speech pathology assessment and, if necessary, referred for imaging confirmation.

REFERENCES

1. Brown CV, Hejl K, Mandaville AD, Chaney PE, Stevenson G, Smith C. Swallowing dysfunction after mechanical ventilation in trauma patients. J Crit Care. 2011;26(1):108.e9-13. http://dx.doi.org/10.1016/j.jcrc.2010.05.036
2. Barquist E, Brown M, Cohn S, Lundy D, Jackowski J. Postextubation fiberoptic endoscopic evaluation of swallowing after prolonged endotracheal intubation: a randomized, prospective trial. Crit Care Med. 2001;29(9):1710-3. http://dx.doi.org/10.1097/00003246-200109000-00009
3. de Larminat V, Montravers P, Dureuil B, Desmonts JM. Alteration in swallowing reflex after extubation in intensive care unit patients. Crit Care Med. 1995;23(3):486-90. http://dx.doi.org/10.1097/00003246-199503000-00012
4. Macht, M, Wimbish T, Clark BJ, Benson AB, Burnham EL, Williams A, et al. Diagnosis and treatment of post-extubation dysphagia: results from a national survey. J Crit Care. 2012;27(6):578-86. http://dx.doi.org/10.1016/j.jcrc.2012.07.016
5. Skoretz SA, Flowers HL, Martino R. The incidence of dysphagia following endotracheal intubation: a systematic review. Chest. 2010;137(3):665-73. http://dx.doi.org/10.1378/chest.09-1823
6. Elpern EH, Scott MG, Petro L, Ries MH. Pulmonary aspiration in mechanically ventilated patients with tracheostomies. Chest. 1994;105(2):563-6. http://dx.doi.org/10.1378/chest.105.2.563
7. Tolep K, Getch CL, Criner GJ. Swallowing dysfunction in patients receiving prolonged mechanical ventilation. Chest. 1996;109(1):167-72. http://dx.doi.org/10.1378/chest.109.1.167
8. Altman KW, Yu GP, Schaefer SD. Consequence of dysphagia in the hospitalized patient: impact on prognosis and hospital resources. Arch Otolaryngol Head Neck Surg. 2010;136(8):784-9. http://dx.doi.org/10.1001/archoto.2010.129
9. Brazilian recommendations of mechanical ventilation 2013. Part 2. J Bras Pneumol. 2014;40(5):458-86. http://dx.doi.org/10.1590/S1806-37132014000500003
10. Moraes, DP, Sassi FC, Mangilli LD, Zilberstein B, de Andrade CR. Clinical prognostic indicators of dysphagia following prolonged orotracheal intubation in ICU patients. Crit Care. 2013;17(5):R243. http://dx.doi.org/10.1186/cc13069
11. Hu X, Yi ES, Ryu JH. Diffuse aspiration bronchiolitis: analysis of 20 consecutive patients. J Bras Pneumol. 2015;41(2):161-6. http://dx.doi.org/10.1590/S1806-37132015000004516
12. Barker J, Martino R, Reichardt B, Hickey EJ, Ralph-Edwards A. Incidence and impact of dysphagia in patients receiving prolonged endotracheal intubation after cardiac surgery. Can J Surg. 2009;52(2):119-24.
13. Ward EC, Green K, Morton AL. Patterns and predictors of swallowing resolution following adult traumatic brain injury. J Head Trauma Rehabil. 2007;22(3):184-91. http://dx.doi.org/10.1097/01.HTR.0000271119.96780.f5
14. Altman KW, Yu GP, Schaefer SD. Consequence of dysphagia in the hospitalized patient: impact on prognosis and hospital resources. Arch Otolaryngol Head Neck Surg. 2010;136(8):784-9. http://dx.doi.org/10.1001/archoto.2010.129
15. Medeiros GC, Sassi FC, Mangilli LD, Zilberstein B, Andrade CR. Clinical dysphagia risk predictors after prolonged orotracheal intubation. Clinics (Sao Paulo). 2014;69(1):8-14. http://dx.doi.org/10.6061/clinics/2014(01)02
16. Martino R, Silver F, Teasell R, Bayley M, Nicholson G, Streiner DL, et al. The Toronto Bedside Swallowing Screening Test (TOR-BSST): development and validation of a dysphagia screening tool for patients with stroke. Stroke. 2009;40(2):555-61. http://dx.doi.org/10.1161/STROKEAHA.107.510370
17. Edmiaston J, Connor LT, Steger-May K, Ford AL. A simple bedside stroke dysphagia screen, validated against videofluoroscopy, detects dysphagia and aspiration with high sensitivity. J Stroke Cerebrovasc Dis. 2014;23(4):712-6. http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2013.06.030
18. Bordon A, Bokhari R, Sperry J, Testa D 4th, Feinstein A, Ghaemmaghami V. Swallowing dysfunction after prolonged intubation: analysis of risk factors in trauma patients. Am J Surg. 2011;202(6):679-82. http://dx.doi.org/10.1016/j.amjsurg.2011.06.030
19. Macht M, Wimbish T, Clark BJ, Benson AB, Burnham EL, Williams A, et al. Postextubation dysphagia is persistent and associated with poor outcomes in survivors of critical illness. Crit Care. 2011;15(5):R231. http://dx.doi.org/10.1186/cc10472
20. Macht M, King CJ, Wimbish T, Clark BJ, Benson AB, Burnham EL, et al. Post-extubation dysphagia is associated with longer hospitalization in survivors of critical illness with neurologic impairment. Crit Care. 2013;17(3):R119. http://dx.doi.org/10.1186/cc12791
21. Brodsky, BM, Gellar JE, Dinglas VD, Colantuoni E, Mendez-Tellez PA, Shanholtz C, et al. Duration of oral endotracheal intubation is associated with dysphagia symptoms in acute lung injury patients. J Crit Care. 2014;29(4):574-9. http://dx.doi.org/10.1016/j.jcrc.2014.02.015
22. American Speech-Language-Hearing Association; National Outcome Measurement System (NOMS). Adult Speech-Language Pathology Training Manual. Rockville, MD: American Speech-Language-Hearing Association; 1998.
23. Moreno R, Vincent JL, Matos R, Mendonça A, Cantraine F, Thijs L, et al. The use of maximum SOFA score to quantify organ dysfunction/failure in intensive care. Results of a prospective, multicenter study. Working Group on Sepsis related Problems of the ESICM. Intensive Care Med. 1999;25(7):686-96. http://dx.doi.org/10.1007/s001340050931
24. McMicken BL, Muzzy CL. Prognostic indicators of functional outcomes in first time documented acute stroke patients following standard dysphagia treatment. Disabil Rehabil. 2009;31(26): 2196-203. http://dx.doi.org/10.3109/09638280902956894
25. Schroeder MF, Daniels SK, McClain M, Corey DM, Foundas AL. Clinical and cognitive predictors of swallowing recovery in stroke. J Rehabil Res Dev. 2006;43(3):301-10. http://dx.doi.org/10.1682/JRRD.2004.12.0154
26. Leder SB, Suiter DM. An epidemiologic study on aging and dysphagia in the acute care hospitalized population: 2000-2007. Gerontology. 2009;55(6):714-8. http://dx.doi.org/10.1159/000235824
27. Yoshikawa M, Yoshida M, Nagasaki T, Tanimoto K, Tsuga K, Akagawa

Y, et al. Aspects of swallowing in healthy dentate elderly persons older than 80 years. J Gerontol A Biol Med Sci. 2005;60(4):506-9. http://dx.doi.org/10.1093/gerona/60.4.506

28. Kallman DA, Plato CC, Tobin JD. The role of muscle loss in the age-related decline of grip strength: cross-sectional and longitudinal perspectives. J Gerontol. 1990;45(3):M82-8. http://dx.doi.org/10.1093/geronj/45.3.M82
29. Dejaeger E, Pelemans W, Ponette E, Joosten E. Mechanisms involved in postdeglutition retention in elderly. Dysphagia. 1997;12(2):63-7. http://dx.doi.org/10.1007/PL00009520
30. Skoretz SA, Yau TM, Ivanov J, Granton JT, Martino R. Dysphagia and associated risk factors following extubation in cardiovascular surgical patients. Dysphagia. 2014;29(6):647-54. http://dx.doi.org/10.1007/s00455-014-9555-4
31. Kwok AM, Davis JW, Cagle KM, Sue LP, Kaups KL. Post-extubation dysphagia in trauma patients: it's hard to swallow. Am J Surg. 2013;206(6):924-7; discussion 927-8. http://dx.doi.org/10.1016/j.amjsurg.2013.08.010
32. Burgess GE 3rd, Cooper JR Jr, Marino RJ, Peuler MJ, Warriner RA 3rd. Laryngeal competence after tracheal extubation. Anesthesiology. 1979;51(1):73-7. http://dx.doi.org/10.1097/00000542-197907000-00016
33. Stauffer JL, Olson DE, Petty TL. Complications and consequences of endotracheal intubation and tracheotomy. A prospective study of 150 critically ill adult patients. Am J Med. 1981;70(1):65-76. http://dx.doi.org/10.1016/0002-9343(81)90413-7
34. Morinièri S, Beutter P, Boiron M. Sound component duration of healthy human pharyngoesophageal swallowing: a gender comparison study. Dysphagia. 2006;21(3):175-82. http://dx.doi.org/10.1007/s00455-006-9023-x
35. Cichero JA, Murdoch BE. Acoustic signature of the normal swallow: characterization by age, gender, and bolus volume. Ann Otol Rhinol Laryngol. 2002;111(7 Pt 1):623-32. http://dx.doi.org/10.1177/000348940211100710
36. Zenner PM, Losinski DS, Millis RH. Using cervical auscultation in the clinical dysphagia examination in long-term care. Dysphagia. 1995;10(1):27-31. http://dx.doi.org/10.1007/BF00261276
37. Lazareck LJ, Moussavi ZM. Classification of normal and dysphagic swallows by acoustical means. IEEE Trans Biomed Eng. 2004;51(12):2103-12. http://dx.doi.org/10.1109/TBME.2004.836504
38. Mann G, Hankey GJ. Initial clinical and demographic predictors of swallowing impairment following acute stroke. Dysphagia. 2001;16(3):208-15. http://dx.doi.org/10.1007/s00455-001-0069-5
39. Kuhlemeier KV, Yates P, Palmer JB. Intra- and interrater variation in the evaluation of videofluorographic swallowing studies. Dysphagia. 1998;13(3):142-7. http://dx.doi.org/10.1007/PL00009564
40. McCullough GH, Wertz RT, Rosenbek JC, Mills RH, Webb WG, Ross KB. Inter- and intrajudge reliability for videofluoroscopic swallowing evaluation measures. Dysphagia. 2001;16(2):110-8. http://dx.doi.org/10.1007/PL00021291

J Bras Pneumol. 2016;42(2):121-129
http://dx.doi.org/10.1590/S1806-37562015000000078

Exercise performance and differences in physiological response to pulmonary rehabilitation in severe chronic obstructive pulmonary disease with hyperinflation

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Submitted: 7 April 2015.
Accepted: 4 November 2015.

Study carried out in the Disciplina de Pneumologia, Instituto do Coração, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.

ABSTRACT

Objective: Pulmonary rehabilitation (PR) improves exercise capacity in most but not all COPD patients. The factors associated with treatment success and the role of chest wall mechanics remain unclear. We investigated the impact of PR on exercise performance in COPD with severe hyperinflation. **Methods:** We evaluated 22 COPD patients (age, 66 ± 7 years; FEV_1 = 37.1 ± 11.8% of predicted) who underwent eight weeks of aerobic exercise and strength training. Before and after PR, each patient also performed a six-minute walk test and an incremental cycle ergometer test. During the latter, we measured chest wall volumes (total and compartmental, by optoelectronic plethysmography) and determined maximal workloads. **Results:** We observed significant differences between the pre- and post-PR means for six-minute walk distance (305 ± 78 vs. 330 ± 96 m, $p < 0.001$) and maximal workload (33 ± 21 vs. 39 ± 20 W; $p = 0.02$). At equivalent workload settings, PR led to lower oxygen consumption, carbon dioxide production (VCO_2), and minute ventilation. The inspiratory (operating) rib cage volume decreased significantly after PR. There were 6 patients in whom PR did not increase the maximal workload. After PR, those patients showed no significant decrease in VCO_2 during exercise, had higher end-expiratory chest wall volumes with a more rapid shallow breathing pattern, and continued to experience symptomatic leg fatigue. **Conclusions:** In severe COPD, PR appears to improve oxygen consumption and reduce VCO_2, with a commensurate decrease in respiratory drive, changes reflected in the operating chest wall volumes. Patients with severe post-exercise hyperinflation and leg fatigue might be unable to improve their maximal performance despite completing a PR program.

Keywords: Pulmonary disease, chronic obstructive/rehabilitation; Exercise therapy; Respiratory therapy.

INTRODUCTION

Pulmonary rehabilitation (PR) is one of the most effective interventions in the management of COPD and produces significant improvements in exercise performance, with a reduction in breathlessness,[1-3] in patients with varying degrees of disease severity.[4] However, not all patients benefit from PR programs.[5] The reasons for this are complex; some patients decline to enroll in such programs, and some others initially recruited drop out, often due to factors related to expectation, smoking status, or perceived disability.[6] Relatively little is known about why some patients who complete the planned course of a PR program fail to improve.[7]

Most studies of PR programs have shown that, although rehabilitation has no effect on lung function, it can reduce carbon dioxide production (VCO_2) and increase the lactate threshold.[6,8] It has been reported that lung and chest wall volumes decrease during exercise.[1,8,9] It remains unclear whether that is an effect of a reduced ventilatory demand for a given amount of work or whether rehabilitation changes the way in which COPD patients who have chronic hyperinflation breathe. The effect may be most relevant when resting hyperinflation is more severe. However, there are relatively few data about the impact of PR in hyperinflated patients with extremely poor initial exercise tolerance. We hypothesized that the main effect of PR in such patients would be to decrease the metabolic stimulus for ventilation during exercise and that any changes in the inspiratory (operating) chest wall volume would be secondary. In addition, we anticipated that the patients in whom there was no increase in CO_2 production during exercise (lack of such an increase being a marker of an impaired muscle performance) would not benefit from PR. Therefore, we aimed to investigate the impact that a general PR program has on exercise performance in COPD patients with severe hyperinflation and, consequently, worse baseline exercise performance than that of the COPD patients who have typically been studied.

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Financial support: None.

METHODS

Patients and procedures

This was an exploratory observational study involving a convenience sample of 22 patients with moderate to very severe COPD[10] and a residual volume > 150% predicted. All were current or former smokers, with a post-bronchodilator FEV_1/FVC ratio < 0.7 and FEV_1 < 70% of the predicted value. No patient had had an exacerbation in the last six weeks. All were treated with inhaled corticosteroids and long-acting bronchodilators, as well as short-acting rescue therapy when necessary. The exclusion criteria were having been diagnosed with asthma, requiring supplemental oxygen at rest, and having any concurrent illness that could limit exercise performance (including heart failure and neuromuscular disorders). The study was approved by the Research Ethics Committee of Aintree University Hospital, in Liverpool, England, and all participating patients gave written informed consent.

All measurements were performed before and after eight weeks of PR. Spirometry and lung volume measurements were performed using a plethysmograph (1085D; Medical Graphics Corporation, St. Paul, MN, USA), in accordance with the American Thoracic Society/European Respiratory Society recommendations.[11,12] Maximal voluntary ventilation (MVV) was determined indirectly as the product of $FEV_1 \times 37.5$.[13] All variables are expressed as a percentage of the predicted value for age.[14,15]

Each patient performed two six-minute walk tests in accordance with the American Thoracic Society recommendations.[16] The six-minute walk distance (6MWD) was measured and compared with that obtained for an age-matched reference population evaluated in a study conducted in the city of Liverpool, United Kingdom.[17] Peripheral oxygen saturation and heart rate were recorded with a pulse oximeter (PULSOX 3i; Konica Minolta, Ramsey, NJ, USA). During the test, subjects were asked to rate their breathlessness and leg fatigue, on a modified Borg scale,[18] once every minute.

Optoelectronic plethysmography (OEP) was applied (see below), after which patients were seated on a cycle ergometer (Corival; Lode, Groningen, the Netherlands) and asked to execute three slow vital capacity maneuvers, followed by 2 min of quiet breathing, to establish baseline values for the chest wall volumes. Subjects then undertook an incremental exercise test on a cycle ergometer, pedaling without a load for 2 min, then with incremental load increases of 5 watts/min until exhaustion. Subjects were breathing through a mouthpiece with a nose clip, and breath-by-breath ventilatory variables were derived from the flow signal detected with a pneumotachograph (preVent; Medical Graphics Corporation). Oxygen consumption (VO_2) and VCO_2 were measured with a paramagnetic sensor and an infrared carbon dioxide analyzer, respectively, as part of an exercise testing system (CardioO$_2$ system; Medical Graphics Corporation). During the exercise, subjects were asked to rate their breathlessness and leg fatigue, on a modified Borg scale,[18] once every minute. The results were compared with those obtained for an age-matched population.[19] The flow signal was synchronized with that of the motion analyzer used for OEP and transferred to a personal computer for subsequent analysis. Peripheral oxygen saturation was measured by pulse oximetry (Biox 3700e; Ohmeda, Louisville, CO, USA). Heart rate was determined on the basis of the R-R interval from a 4-lead electrocardiogram.

The kinematic data of the chest wall were analyzed with an OEP system (BTS Bioengineering, Milan, Italy). A complete description of the process has previously been published.[20,21] In brief, the volume displacements of the two compartments of the chest wall were measured through the use of 89 retroreflective markers placed on the trunk at established anatomical reference points.[20] Three-dimensional coordinates of the markers were calculated with stereophotogrammetry and then linked with a mesh of triangles representing the surface of the trunk. The volume of the trunk enclosed by the defined surfaces was obtained through Gauss' theorem.

PR program

The PR program consisted of two supervised 60-min sessions and one unsupervised 60-min session of exercise per week, over a period of eight weeks. Patients performed aerobic upper and lower limb exercise, which included peripheral muscle strengthening and whole body endurance exercises delivered by a combination of cycle ergometry and corridor walking exercise. The patients trained to a symptom-limited intensity equivalent to a level of 3 to 4 on the modified Borg scale and were allowed 1-2 min of rest between each exercise. Patients were encouraged to increase the time spent on each exercise at each session. An individually tailored home exercise program was provided for the unsupervised session. After each supervised exercise session, there was also an education session focusing on aspects of behavior and lifestyle. This regime has previously been shown to improve exercise capacity in patients with a wide range of COPD severity.[22] The attendance at each supervised session was documented and patients used a home diary to confirm adherence with the unsupervised portion of the program.

Data analysis

The chest wall was modeled in two compartments: rib cage and abdomen. The total volume displaced by the chest wall was calculated as the sum of the volumes swept by the two individual compartments. The boundaries between those two compartments were represented by the lower costal margin. The total lung capacity (TLC) was plotted to indicate the operating constraints on the chest wall volumes during cycling and was obtained as the sum of inspiratory capacity and the chest wall volume at the end of expiration.

We devised an a priori definition of post-PR improvement in exercise performance: an increase in the peak workload achieved during the incremental exercise test. We also conducted a post-hoc comparison in which post-PR improvement was defined as a clinically significant increase in the 6MWD.[16] To evaluate the physiological responses to PR at equivalent workloads, we compared metabolic, ventilatory, and symptomatic variables, as well as the operating chest wall volumes, during conditions of quiet breathing, unloaded pedaling, and equivalent workload (50% and maximum), using the shortest cycling test workload as a reference value. Thus, for patients who achieved a higher workload after PR than before ("improvers"), the selected workload was obtained from the pre-PR incremental exercise test, whereas for those who did not ("non-improvers"), the selected workload was obtained from the post-PR test.

Statistical analysis

Results are presented as mean ± SD or as median and ranges for symptom scores and 6MWD. Values at peak exercise were compared by paired t-test and the Wilcoxon test for parametric and non-parametric distribution, respectively. Pre- and post-PR time courses on incremental exercise test were compared at equivalent workload settings with two-way repeated-measures analysis of variance. The level of statistical significance was set at $p < 0.05$. The estimation of the sample size was impaired because there is lack of studies involving OEP and PR. To our knowledge, there have been only two studies of OEP and PR in COPD,[1,23] both of which investigated the effects of PR on operating volumes. Our sample was larger than those evaluated in either of those two studies.

RESULTS

Of the 22 patients evaluated, 15 were male. According to the Global Initiative for Chronic Obstructive Lung Disease staging system,[16] all of the patients had moderate to severe COPD (stage II = 5; stage III = 12; and stage IV = 5), with substantial resting hyperinflation. There were no dropouts. As can be seen in Table 1, the overall pre-PR exercise performance was markedly impaired, with a mean peak workload < 25% predicted. Before PR, the mean peak VO_2 showed a modest relationship with FEV_1 as a percentage of the predicted value ($r = 0.48$, $p = 0.02$). Table 1 also shows that cycle exercise was limited by a combination of dyspnea and leg fatigue, a high mean pre-PR peak minute ventilation (V_E)/MVV ratio (88.2 ± 20.1%) suggesting that ventilatory limitation was an important reason for exercise cessation. In addition, the mean pre-PR 6MWD was well below the predicted value (28.7 ± 6.8% of predicted).

There were no significant post-PR changes in spirometry parameters or lung volumes at rest (Table 1). The mean values for peak ventilation, tidal volume, and respiratory rate were similar before and after PR, as were the intensity of symptoms and the 6MWD (Table 1).

Analyzing the equivalent workload conditions, based on the highest load achieved in the pre-PR incremental exercise test, we found that VO_2 and VCO_2 were both lower after PR, with a corresponding significant drop in V_E, as shown in Figure S1 of the supplementary file (available online at **http://www.jornaldepneumologia.com.br/detalhe_anexo.asp?id=45**). This post-PR reduction in ventilation was due to decreases in tidal volume (−2.7 ± 20.3%) and respiratory rate (−5.9 ± 16.3%). There was no significant difference between the pre- and post-PR values for the V_E/VCO_2 slope (31.8 ± 4.1 vs. 33.3 ± 3.8, $p > 0.05$). Breathlessness and leg fatigue during cycling were also similar before and after PR ($p > 0.05$ for both).

The end-expiratory chest wall volume (EECWV) increased during exercise. At peak exercise, the end-inspiratory chest wall volume (EICWV) approached TLC. The PR program had no effect of the behavior on the chest wall volumes or on the timing of the increase in the EECWV (Figure 1A). Given the lower ventilation after exercise at any given workload, the tidal volume was lower and this is in line with the decrease in EICWV in the isovolumic comparisons. However, the regional distribution of tidal volume did change after rehabilitation, despite a significant reduction in the volume of the rib cage compartment and a non-significant increase in abdominal volume (Figures 1B and 1C).

In 16 patients (72.7%), the workload was higher after PR than before (46 ± 17 vs. 36 ± 22 W, $p < 0.05$). The gender distribution was comparable between the two groups, females accounting for 5 (31.2%) of the 16 patients in the improver group and for 2 (33.3%) of the 6 patients in the non-improver group. Although all of the patients attended the same number of training sessions, as well as having similar anthropometric and spirometric characteristics before PR, the post-PR lung volumes (functional residual capacity and TLC) tended to be higher in the non-improvers (Table 2). There were no significant differences between the pre- and post-PR lung function, within or between subgroups ($p > 0.05$ for both). The differences in exercise performance between the two subgroups were reflected in the 6MWD (Table 3). However the post-PR change in the response to the incremental exercise test was not very predictive of that, several of the patients in the non-improver group showing considerable increases in their 6MWD. In comparison with the improvers, the non-improvers showed lower metabolic and ventilatory responses to incremental exercise before PR ($p < 0.05$) and did not show an increase in their whole body VO_2 during exercise, as can be seen in Figure S2 of the supplementary file (available online at **http://www.jornaldepneumologia.com.br/detalhe_anexo.asp?id=45**). In addition, the non-improvers reported greater leg fatigue at maximal

Table 1. Demographic characteristics at baseline, together with BMI, spirometry parameters, and lung volumes, as well as exercise performance values (for an incremental exercise test on a cycle ergometer and for the six-minute walk test), before and after pulmonary rehabilitation, in patients with COPD (n = 22).[a]

Variable	Pre-PR	Post-PR	p
Age, years	65.9 ± 7.1		
Male gender, n (%)	15 (68.2)		
BMI, kg/m^2	24.4 ± 5.9	24.7 ± 5.7	0.21
FEV_1			
L	1.00 ± 0.26	1.01 ± 0.33	0.77
% of the predicted value	37.1 ± 11.8	2.53 ± 0.79	0.72
FVC			
L	2.49 ± 0.68	2.53 ± 0.79	0.67
% of the predicted value	66.2 ± 13.5	67.3 ± 15.6	0.71
FEV_1/FVC ratio, %	42.5 ± 11.8	41.5 ± 10.0	0.39
IC			
L	1.74 ± 0.54	1.79 ± 0.51	0.45
% of the predicted value	64.2 ± 16.0	66.2 ± 16.4	0.32
FRC			
L	6.29 ± 2.10	6.10 ± 1.64	0.55
% of the predicted value	189.2 ± 46.3	184.2 ± 38.1	0.57
TLC			
L	8.07 ± 2.28	7.84 ± 1.75	0.49
% of the predicted value	128.9 ± 23.4	125.7 ± 17.7	0.51
RV			
L	5.35 ± 1.91	5.18 ± 1.45	0.62
% of the predicted value	239.8 ± 69.4	233.9 ± 59.1	0.68
RV/TLC ratio	0.65 ± 0.07	0.65 ± 0.07	0.92
Peak incremental exercise values			
Workload			
W	33 ± 21	39 ± 20	0.02
% of the predicted value	23.3 ± 13.7	29.0 ± 13.2	0.01
VO_2			
L/min	0.74 ± 0.18	0.72 ± 0.20	0.43
% of the predicted value	44.7 ± 16.6	42.6 ± 14.4	0.23
VCO_2, L/min	0.77 ± 0.22	0.73 ± 0.25	0.15
V_E, L/min	32.8 ± 7.2	31.1 ± 9.4	0.07
V_E/MVV ratio, %	88.2 ± 20.1	83.2 ± 23.5	0.04
V_T, L	1.03 ± 0.31	1.00 ± 0.35	0.34
RR, breaths/min	31 ± 6	30 ± 5	0.7
T_I, s	0.81 ± 0.19	0.81 ± 0.18	0.9
T_E, s	1.25 ± 0.24	1.26 ± 0.28	0.9
T_I/Ttot ratio, %	39.2 ± 4.6	39.2 ± 5.2	0.9
SpO_2, %	92 ± 2	94 ± 8	0.3
Post-6MWT values			
6MWD			
m, median (range)	305 (170-425)	330 (230-490)	0.001
% of the predicted value	28.7 ± 6.8	33.3 ± 8.0	0.001
Borg dyspnea score	3 (1.3)	3 (4.6)	0.8
Borg leg fatigue score	2 (3.0)	1 (4.1)	0.7
SpO_2, %	92 ± 2	92 ± 2	0.003

PR: pulmonary rehabilitation; IC: inspiratory capacity; FRC: functional residual capacity; TLC: total lung capacity; RV: residual volume; VO_2: oxygen consumption; VCO_2: carbon dioxide production; V_E: minute ventilation; MVV: maximal voluntary ventilation; V_T: tidal volume; RR: respiratory rate; T_I: inspiratory time, T_E: expiratory time; Ttot: total respiratory time; 6MWT: six-minute walk test; and 6MWD: six-minute walk distance. [a]Values expressed as mean ± SD, except where otherwise indicated.

exercise in the pre-PR incremental exercise test than did the improvers ($p < 0.05$).

Although the change in end-exercise total chest wall volume under an equivalent workload was no different

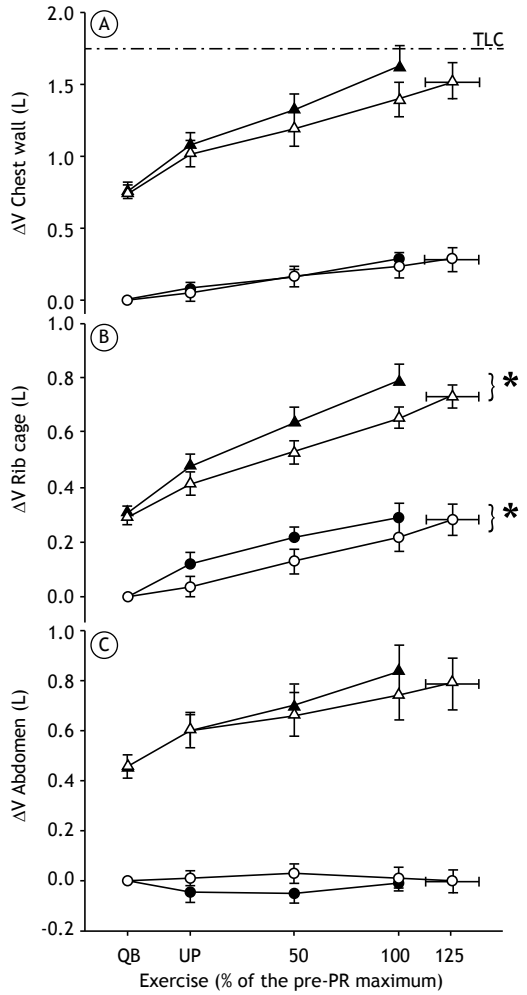

Figure 1. Changes, before and after pulmonary rehabilitation (PR), in the inspiratory (operating) volume of the chest wall (A), rib cage (B), and abdomen (C) during incremental exercise at an equivalent workload, defined as the percentage of the maximum workload achieved during the pre-PR incremental exercise test. White symbols: before PR; black symbols: after PR; ΔV: volume change from resting state; TLC (---): total lung capacity, measured before PR; triangles: end-inspiratory volumes; circles: end-expiratory volumes; QB: quiet breathing; and UP: unloaded pedaling. *p < 0.05 vs. pre-PR value.

after PR in the improver group or in the non-improver group (Figures 2A and 2B, respectively), a significant post-PR decrease in rib cage operating volume was seen in the former and not in the latter (Figures 2C and 2D, respectively). In addition, the end-expiratory volume of the abdominal compartment during submaximal exercise was higher in the improvers than in the non-improvers (Figures 2E and 2F, respectively), although the difference did not reach statistical significance. We saw the same changes in end-expiratory lung volume when the response to rehabilitation was categorized by the ability to increase walking distance by 30 m or more, a recently proposed minimum clinically important difference.[16] The ventilatory pattern also differed between the two subgroups, the improvers showing a post-PR change to a less rapid and less shallow breathing pattern at an equivalent V_E.

DISCUSSION

Most patients with COPD report reduced exercise tolerance and show varying degrees of dynamic hyperinflation during exercise.[24,25] That change has been observed even in patients with mild COPD.[26] After PR, the rate of rise of end-expiratory lung volume during exercise appears to decrease, at least in some patients,[2,8] whereas it has also been shown that chest wall volumes were reduced after a PR program in which the respiratory rate at an equivalent workload fell.[1] Our data for COPD patients with even more marked resting hyperinflation suggest that this is not always the case, even when an equivalent degree of improvement in workload is achieved. In addition, some of our subjects continued to be limited despite PR, possibly as a consequence of hyperinflation and the accompanying impairment of the extrapulmonary peripheral muscles.

Our patients are similar to those with severe COPD evaluated in other studies, save for their more marked degree of resting hyperinflation, with a mean functional residual capacity of 6.29 L, compared with the 5.56 L reported in the literature,[1] which contributed to their relatively poor exercise performance. Although we followed an incremental exercise test protocol similar to that described by Georgiadou et al.,[1] pre-PR workloads were higher in the subjects evaluated by those authors than in our subjects. Our patients exercised with a high fraction of their MVV at peak exercise, and their end-inspiratory lung volume reached their predicted TLC. After PR, there was a small yet statistically significant increase in peak workload similar to that reported in other studies employing incremental exercise tests,[1,8] and that was reflected in a similar improvement in the 6MWD. For a given workload, VO_2 and VCO_2 both decreased after PR in our patients, suggesting that a true training effect had occurred. However, because the V_E/VCO_2 slope was not changed after PR, it is likely that the lower ventilation seen at the equivalent workload was a consequence mainly of the lower metabolic stimulus (reduced VCO_2).

Like other authors, we observed no relationship between the timing of the change in chest wall volume and the response to PR. In a recent study, we observed that changes in the EECWV during exercise are associated with the presence of paradoxical movement of the lower rib cage at rest.[27] The data obtained in the present study suggest that although this might be undesirable in terms of energy expenditure, it does not influence the ability to achieve a training effect, at least in hyperinflated patients. Although the total EECWV was unaffected by PR, there was a post-PR decrease in the rib cage volumes, with less recruitment of the abdominal compartment during exercise. The end-expiratory abdominal volume remained constant and there was a proportionate decrease in the volume

Table 2. Comparison between COPD patients who improved after pulmonary rehabilitation and those who did not, in terms of baseline age, BMI, spirometry parameters, and lung volumes.[a,b]

Variable at baseline	Post-PR improvers (n = 16)	Post-PR non-improvers (n = 6)
Age, years	65.5 ± 6.8	67.1 ± 8.4
BMI, kg/m^2	25.1 ± 6.4	22.5 ± 4.5
FEV_1		
L	1.01 ± 0.29	1.00 ± 0.19
% of the predicted value	37.4 ± 12.2	36.5 ± 10.1
FVC		
L	2.40 ± 0.62	2.73 ± 0.84
% of the predicted value	64.3 ± 12.6	71.5 ± 15.7
FEV_1/FVC ratio, %	44.1 ± 12.9	38.3 ± 7.6
IC		
L	1.75 ± 0.42	1.61 ± 0.47
% of the predicted value	63.4 ± 12.3	56 ± 10.7
FRC		
L	5.67 ± 2.48	6.68 ± 1.02
% of the predicted value	174.3 ± 54.1	204.2 ± 13.0
TLC		
L	7.42 ± 2.66	8.29 ± 1.39
% of the predicted value	122.1 ± 26.0	135.2 ± 10.7
RV		
L	4.93 ± 2.19	5.48 ± 0.82
% of the predicted value	228.0 ± 82.6	242.0 ± 23.7
RV/TLC ratio, %	64.8 ± 7.3	66.7 ± 9.1

PR: pulmonary rehabilitation; IC: inspiratory capacity; FRC: functional residual capacity; TLC: total lung capacity; and RV: residual volume. [a]Values expressed as mean ± SD. [b]There were no statistical differences between the two subgroups for any of these variables.

contained within the rib cage compartment at any given workload. Although the EECWV was unaffected by PR in either subgroup, this new behavior in the rib cage and abdominal compartments after PR, resulting in a more physiological pattern and less distortion of the total chest wall, was seen only in the improvers. However, in the study conducted by Georgiadou et al.,[1] who evaluated patients in Athens, Greece, rib cage and abdominal volumes at equivalent workloads both decreased after PR as a result of a change in the breathing pattern and an increase in expiratory time. These discrepancies might reflect differences in the resting lung volumes, our hyperinflated subjects tending to show a reduction in tidal volume rather than in the respiratory rate. Another possible explanation is that the exercise regimes employed may have been different, particularly because some of the patients evaluated by Georgiadou et al.[1] underwent an interval training regime rather than a general physical exercise program.

In the present study, there was a high level of adherence to treatment. Nevertheless, some patients failed to improve in terms of their response to the incremental exercise test or their 6MWD. In general, the non-improvers exercised to a lower peak workload before PR and tended to have more severe resting hyperinflation than did the improvers, although the small numbers of patients in each of the subgroups precluded any inferences regarding statistical significance. More striking was the pre-PR inability of the non-improvers to increase their VCO_2 during exercise. Previous studies have suggested that there are differences among patients in terms of the ability of peripheral muscles to increase their VO_2 during exercise,[19] which could explain why some COPD patients are limited by peripheral muscle fatigue rather than by ventilatory factors.[28-30] Although we did not collect data related to peripheral muscle strength, the fact that the non-improvers reported significantly higher pre-PR levels of muscle fatigue than did the improvers is consistent with such a mechanism. The changes in regional operating lung volumes were confined to the patients who improved their exercise performance, suggesting that such changes were secondary to the reduced overall metabolic drive to breathing at any given workload. After PR, the improvers had a relatively slower and deeper breathing pattern at any V_E, which could explain why these patients were able to exercise for longer without further increasing their reported levels of breathlessness. However, whether the change in rib cage volume was a result of a reduction in the activation of the muscles acting on that compartment or a consequence of a reduced central respiratory drive cannot be answered on the basis of our findings in the present study. In contrast, the non-improvers reported higher degrees of muscle fatigue before PR, which were still present at lower absolute workloads after PR. The fact that the non-improvers showed no improvement in VO_2 and no decrease in VCO_2 could

Table 3. Comparison between COPD patients who improved after pulmonary rehabilitation and those who did not, in terms of pre- and post-pulmonary rehabilitation exercise performance on an incremental exercise test and the six-minute walk test.[a]

Variable	Post-PR improvers (n = 16)		Post-PR non-improvers (n = 6)	
	Pre-PR	Post-PR	Pre-PR	Post-PR
Peak incremental exercise values				
Workload				
W	36 ± 22	46 ± 17*	27 ± 18	21 ± 13†
% of the predicted value	24.8 ± 14.3	34.2 ± 10.3*	19.1 ± 12	15.1 ± 9.6
VO_2, L/min	0.76 ± 0.18	0.77 ± 0.21	0.70 ± 0.19	0.60 ± 0.15
VCO_2, L/min	0.81 ± 0.23	0.80 ± 0.25	0.69 ± 0.20	0.53 ± 0.12†
V_E, L/min	33.7 ± 8.1	33.7 ± 9.7	30.4 ± 3.6	24.3 ± 4.1*
V_E/MVV ratio, %	87.9 ± 18.6	87.0 ± 21.2	89.1 ± 25.7	72.8 ± 28.3*
V_T, L	1.08 ± 0.34	1.09 ± 0.37	0.92 ± 0.20	0.76 ± 0.14†
RR, breaths/min	32 ± 6	30 ± 6	30 ± 3	30 ± 4
T_I, s	0.79 ± 0.19	0.81 ± 0.18	0.86 ± 0.18	0.83 ± 0.21
T_E, s	1.24 ± 0.27	1.27 ± 0.31	1.25 ± 0.15	1.22 ± 0.19
T_I/Ttot ratio	0.39 ± 0.04	0.39 ± 0.05	0.39 ± 0.05	0.39 ± 0.06
SpO_2, %	93 ± 2	94 ± 2	92 ± 2	92 ± 1
Post-6MWT values				
6MWD				
m, median (range)	310 (170-425)	338 (230-490)*	285 (190-340)	290 (230-466)
% of the predicted value	29.8 ± 7.2	34.5 ± 7.7*	25.7 ± 5.0	30.2 ± 8.7
Borg dyspnea score, median (range)	3 (0-5)	3 (0.5-5)	3.5 (2-5)	3 (2-9)
Borg leg fatigue score, median (range)	2 (0-5)	1 (0-5)	1.75 (0-4)	1.5 (0-7)
SpO_2, %	92 ± 3	90 ± 4*	92 ± 1	88 ± 2

PR: pulmonary rehabilitation; VO_2: oxygen consumption; VCO_2: carbon dioxide production; V_E: minute ventilation; MVV: maximal voluntary ventilation; V_T: tidal volume; RR: respiratory rate; T_I: inspiratory time, T_E: expiratory time; Ttot: total respiratory time; 6MWT: six-minute walk test; and 6MWD: six-minute walk distance. [a]Values expressed as mean ± SD, except where otherwise indicated. *$p < 0.05$ vs. pre-PR value. †$p < 0.05$ vs. post-PR improvers.

explain why they also showed no post-PR changes in V_E or regional chest wall volumes.

Our study has certain limitations. We used a relatively arbitrary threshold to define improvers and non-improvers in terms of the response to the incremental exercise test, given that there is no established minimum clinically important difference for that test. However, our findings were unchanged when we separated patients according to the ability to achieve a clinically important improvement in the 6MWD after PR. In addition, the protocol involved incremental rather than constant-load exercise, which could have decreased its sensitivity to detect post-PR improvements in exercise capacity. Nevertheless, the use of incremental exercise allowed us to analyze variables at different exercise intensities over the course of the test. Furthermore, we did not specifically identify peripheral muscle weakness, although that would be a plausible explanation for the differences we observed. Future studies of COPD patients who do not improve after PR, however they are defined, should include objective measurements of peripheral muscle fatigue. The small number of patients who did not improve after our PR is encouraging given our selection of individuals with significant hyperinflation. Finally, we did not measure ventilatory muscle strength, which could have had some effect on the operating volumes during exercise.

In summary, we have shown that in COPD patients with resting hyperinflation the major effect that PR has on exercise capacity is that of improving VO_2 and reducing VCO_2, with a commensurate decrease in respiratory drive. The changes in operating lung volumes reflect this reduction in respiratory drive for a given workload. When severe hyperinflation is present, the ability to reduce operating lung volumes with a reduction in respiratory drive is more limited, although subtle changes in the distribution of volume between the rib cage and abdominal compartments could be a useful way to delay the onset of limiting symptoms. Such changes occurred only in patients in whom an objective training effect could be demonstrated. It is encouraging to see that a majority of patients with severe COPD can improve after completing a conventional non-specific exercise program. However, certain patients (those with significant resting hyperinflation) might require a different approach to rehabilitation and those in whom breathlessness or leg fatigue is a dominant symptom at low workloads might require specific peripheral muscle training.

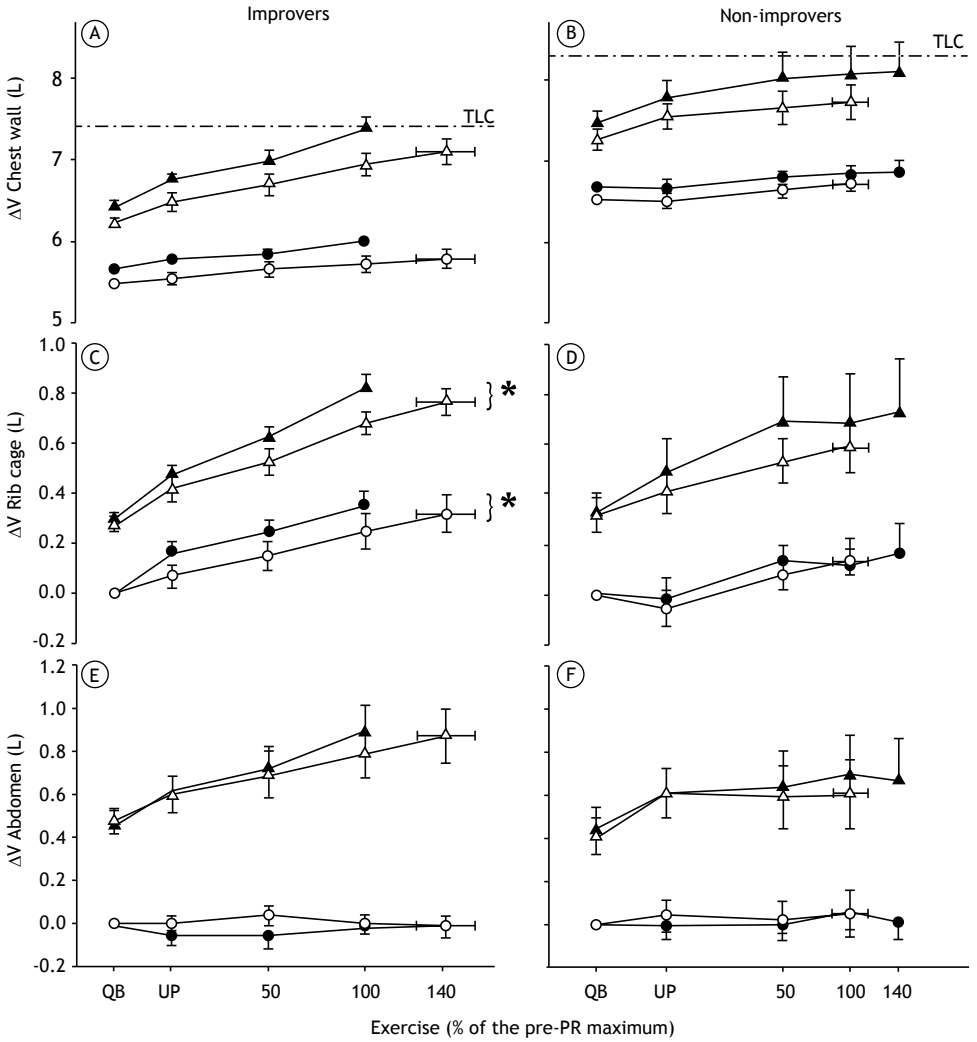

Figure 2. Comparison between COPD patients who improved after pulmonary rehabilitation (PR) and those who did not, in terms of pre- and post-PR changes in the inspiratory (operating) volume of the chest wall (A and B), rib cage (C and D), and abdomen (E and F) during incremental exercise at an equivalent workload, defined as the percentage of the maximum workload achieved during the pre-PR incremental exercise test. White symbols: before PR; black symbols: after PR; ΔV: volume change from resting state; TLC (---): total lung capacity, measured before PR; triangles: end-inspiratory volumes; circles: end-expiratory volumes; QB: quiet breathing; and UP: unloaded pedaling. *p < 0.05 vs. pre-PR value.

REFERENCES

1. Georgiadou O, Vogiatzis I, Stratakos G, Koutsoukou A, Golemati S, Aliverti A, et al. Effects of rehabilitation on chest wall volume regulation during exercise in COPD patients. Eur Respir J. 2007;29(2):284-91. http://dx.doi.org/10.1183/09031936.00121006
2. Gigliotti F, Coli C, Bianchi R, Romagnoli I, Lanini B, Binazzi B, et al. Exercise training improves exertional dyspnea in patients with COPD: evidence of the role of mechanical factors. Chest. 2003;123(6):1794-802. http://dx.doi.org/10.1378/chest.123.6.1794
3. Vogiatzis I, Zakynthinos S. The physiological basis of rehabilitation in chronic heart and lung disease. J Appl Physiol (1985). 2013;115(1):16-21. http://dx.doi.org/10.1152/japplphysiol.00195.2013
4. Berry MJ, Rejeski WJ, Adair NE, Zaccaro D. Exercise rehabilitation and chronic obstructive pulmonary disease stage. Am J Respir Crit Care Med. 1999;160(4):1248-53. http://dx.doi.org/10.1164/ajrccm.160.4.9901014
5. Troosters T, Gosselink R, Decramer M. Exercise training in COPD: how to distinguish responders from nonresponders. J Cardiopulm Rehabil. 2001;21(1):10-7. http://dx.doi.org/10.1097/00008483-200101000-00004
6. Casaburi R, Patessio A, Ioli F, Zanaboni S, Donner CF, Wasserman K. Reductions in exercise lactic acidosis and ventilation as a result of exercise training in patients with obstructive lung disease. Am Rev Respir Dis. 1991;143(1):9-18. http://dx.doi.org/10.1164/ajrccm/143.1.9
7. Vogiatzis I. Strategies of muscle training in very severe COPD patients. Eur Respir J. 2011;38(4):971-5. http://dx.doi.org/10.1183/09031936.00075011
8. Porszasz J, Emtner M, Goto S, Somfay A, Whipp BJ, Casaburi R. Exercise training decreases ventilatory requirements and exercise-induced hyperinflation at submaximal intensities in patients with COPD. Chest. 2005;128(4):2025-34. http://dx.doi.org/10.1378/chest.128.4.2025
9. Puente-Maestu L, Abad YM, Pedraza F, Sánchez G, Stringer WW. A controlled trial of the effects of leg training on breathing pattern and dynamic hyperinflation in severe COPD. Lung. 2006;184(3):159-67. http://dx.doi.org/10.1007/s00408-005-2576-x
10. Rabe KF, Hurd S, Anzueto A, Barnes PJ, Buist SA, Calverley P, et al. Global strategy for the diagnosis, management, and prevention of

chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med. 2007;176(6):532-55. http://dx.doi.org/10.1164/rccm.200703-456SO

11. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J. 2005;26(2):319-38. http://dx.doi.org/10.1183/09031936.05.00034805
12. Wanger J, Clausen JL, Coates A, Pedersen OF, Brusasco V, Burgos F, et al. Standardisation of the measurement of lung volumes. Eur Respir J. 2005;26(3):511-22. http://dx.doi.org/10.1183/09031936.05.00035005
13. ERS Task Force, Palange P, Ward SA, Carlsen KH, Casaburi R, Gallagher CG, et al. Recommendations on the use of exercise testing in clinical practice. Eur Respir J. 2007;29(1):185-209.
14. Roca J, Burgos F, Sunyer J, Saez M, Chinn S, Antó JM, et al. References values for forced spirometry. Group of the European Community Respiratory Health Survey. Eur Respir J. 1998;11(6):1354-62. http://dx.doi.org/10.1183/09031936.98.11061354
15. Stocks J, Quanjer PH. Reference values for residual volume, functional residual capacity and total lung capacity. ATS Workshop on Lung Volume Measurements. Official Statement of The European Respiratory Society. Eur Respir J. 1995;8(3):492-506. http://dx.doi.org/10.1183/09031936.95.08030492
16. Holland AE, Spruit MA, Troosters T, Puhan MA, Pepin V, Saey D, et al. An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease. Eur Respir J. 2014;44(6):1428-46. http://dx.doi.org/10.1183/09031936.00150314
17. Gibbons WJ, Fruchter N, Sloan S, Levy RD. Reference values for a multiple repetition 6-minute walk test in healthy adults older than 20 years. J Cardiopulm Rehabil. 2001;21(2):87-93. http://dx.doi.org/10.1097/00008483-200103000-00005
18. Borg GA. Psychophysical bases of perceived exertion. Med Sci Sports Exerc. 1982;14(5):377-81. http://dx.doi.org/10.1249/00005768-198205000-00012
19. Koch B, Schäper C, Ittermann T, Spielhagen T, Dörr M, Völzke H, et al. Reference values for cardiopulmonary exercise testing in healthy volunteers: the SHIP Study. Eur Respir J. 2009;33(2):389-97. http://dx.doi.org/10.1183/09031936.00074208
20. Cala SJ, Kenyon CM, Ferrigno G, Carnevali P, Aliverti A, Pedotti A, et al. Chest wall and lung volume estimation by optical reflectance motion analysis. J Appl Physiol (1985). 1996;81(6):2680-9.
21. Aliverti A, Stevenson N, Dellacà RL, Lo Mauro A, Pedotti A, Calverley PM. Regional chest wall volumes during exercise in chronic obstructive pulmonary disease. Thorax. 2004;59(3):210-6. http://dx.doi.org/10.1136/thorax.2003.011494
22. Walker PP, Burnett A, Flavahan PW, Calverley PM. Lower limb activity and its determinants in COPD. Thorax. 2008;63(8):683-9. http://dx.doi.org/10.1136/thx.2007.087130
23. Romagnoli I, Gigliotti F, Lanini B, Bruni GI, Coli C, Binazzi B, et al. Chest wall kinematics and breathlessness during unsupported arm exercise in COPD patients. Respir Physiol Neurobiol. 2011;178(2):242-9. http://dx.doi.org/10.1016/j.resp.2011.06.014
24. O'Donnell DE, Revill SM, Webb KA. Dynamic hyperinflation and exercise intolerance in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2001;164(5):770-7. http://dx.doi.org/10.1164/ajrccm.164.5.2012122
25. Calverley PM. Dynamic hyperinflation: is it worth measuring? Proc Am Thorac Soc. 2006;3(3):239-44. http://dx.doi.org/10.1513/pats.200508-084SF
26. Ofir D, Laveneziana P, Webb KA, Lam YM, O'Donnell DE. Mechanisms of dyspnea during cycle exercise in symptomatic patients with GOLD stage I chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2008;177(6):622-9. http://dx.doi.org/10.1164/rccm.200707-1064OC
27. Aliverti A, Quaranta M, Chakrabarti B, Albuquerque AL, Calverley PM. Paradoxical movement of the lower ribcage at rest and during exercise in COPD patients. Eur Respir J. 2009;33(1):49-60. http://dx.doi.org/10.1183/09031936.00141607
28. Saey D, Debigare R, LeBlanc P, Mador MJ, Cote CH, Jobin J, et al. Contractile leg fatigue after cycle exercise: a factor limiting exercise in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2003;168(4):425-30. http://dx.doi.org/10.1164/rccm.200208-856OC
29. Man WD, Soliman MG, Gearing J, Radford SG, Rafferty GF, Gray BJ, et al. Symptoms and quadriceps fatigability after walking and cycling in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2003;168(5):562-7. http://dx.doi.org/10.1164/rccm.200302-162OC
30. Aliverti A, Macklem PT. The major limitation to exercise performance in COPD is inadequate energy supply to the respiratory and locomotor muscles. J Appl Physiol (1985). 2008;105(2):749-51; discussion 755-7.

J Bras Pneumol. 2016;42(2):130-135
http://dx.doi.org/10.1590/S1806-37562015000000102

ORIGINAL ARTICLE

Association between physical activity in daily life and pulmonary function in adult smokers

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Submitted: 15 June 2015.
Accepted: 30 November 2015.

Study carried out in the Departamento de Ciências do Movimento Humano, Laboratório de Epidemiologia e Movimento Humano – EPIMOV – Universidade Federal de São Paulo, Santos (SP) Brasil.

ABSTRACT

Objective: To determine whether the level of physical activity in daily life (PADL) is associated with pulmonary function in adult smokers. **Methods:** We selected 62 adult smokers from among the participants of an epidemiological study conducted in the city of Santos, Brazil. The subjects underwent forced spirometry for pulmonary function assessment. The level of PADL was assessed by the International Physical Activity Questionnaire and triaxial accelerometry, the device being used for seven days. The minimum level of PADL, in terms of quantity and intensity, was defined as 150 min/week of moderate to vigorous physical activity. Correlations between the studied variables were tested with Pearson's or Spearman's correlation coefficient, depending on the distribution of the variables. We used linear multiple regression in order to analyze the influence of PADL on the spirometric variables. The level of significance was set at 5%. **Results:** Evaluating all predictors, corrected for confounding factors, and using pulmonary function data as outcome variables, we found no significant associations between physical inactivity, as determined by accelerometry, and spirometric indices. The values for FVC were lower among the participants with arterial hypertension, and FEV_1/FVC ratios were lower among those with diabetes mellitus. Obese participants and those with dyslipidemia presented with lower values for FVC and FEV_1. **Conclusions:** Our results suggest that there is no consistent association between physical inactivity and pulmonary function in adult smokers. Smoking history should be given special attention in COPD prevention strategies, as should cardiovascular and metabolic comorbidities.

Keywords: Smoking; Respiratory function tests; Motor activity; Accelerometry.

INTRODUCTION

Smoking is a major public health problem worldwide. In the 20th century, tobacco use killed 100 million people worldwide. Smoking accounts for 5.4 million deaths per year worldwide, and it is estimated that it will account for more than 8.0 million deaths per year in 2030. Approximately 80% of these deaths will occur in developing countries, and smoking is currently the leading cause of preventable death worldwide.[1]

The impact of tobacco use on health is well known, tobacco use accounting for 90% of all cases of lung cancer, 75% of all cases of chronic bronchitis, and 25% of all cases of ischemic heart disease.[2] Individuals who smoke more than 20 cigarettes per day are significantly different from nonsmokers in terms of their FEV_1.[3] This is due to the fact that smoking causes acute lung changes, including changes in airflow resistance, cough, and airway irritation.[4]

Lung function decline is less pronounced in smokers who engage in moderate- to high-intensity physical activity.[5] Studies have shown that regular physical activity is effective in preventing chronic diseases such as cardiovascular disease, diabetes, cancer, hypertension, obesity, depression, and osteoporosis. It has been suggested that there is a significant association between physical activity and health status, increased physical fitness resulting in additional health benefits.[6] Other studies have shown that endurance training in nonsmokers results in adaptations of the cardiorespiratory and neuromuscular systems that increase the supply of oxygen to the mitochondria, thus contributing to maintaining physical fitness.[7,8] It has been suggested that smoking reduces cardiorespiratory fitness and lung function.[9,10] In addition, significant differences have been found between physically active and physically inactive smokers regarding fatigue immediately after the six-minute walk test and during the recovery period, at two minutes after the test.[11]

Regular physical exercise can counter the negative effects of smoking through an anti-inflammatory and antioxidant mechanism. Physical activity and smoking

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Financial support: This study received financial support from the *Fundação de Amparo à Pesquisa do Estado de São Paulo* (FAPESP, São Paulo Research Foundation; Grant 2011/07282-6). Miriane Lilian Barboza and Alan Carlos Brisola Barbosa receive financial support from the *Programa Institucional de Bolsas de Iniciação Científica* of the Brazilian *Conselho Nacional de Desenvolvimento Científico e Tecnológico* (CNPq, National Council for Scientific and Technological Development).

ISSN 1806-3713

interact antagonistically: inflammatory markers that are produced in the lung and are related to a decline in cardiorespiratory fitness are suppressed by physical exercise.[5]

Physical activity can be assessed by a variety of methods, including direct observation, questionnaires, self-report diaries, and motion sensors, such as pedometers and accelerometers.[12] Objective assessment is performed by motion sensors, which are instruments that are used in order to detect body motion and determine the level of physical activity in daily life (PADL) over a period of time. Accelerometers are real-time motion capture sensors that are sensitive to acceleration.[13]

Few studies have examined the preventive effect of physical activity on the lung function of smokers, the level of PADL having been determined on the basis of self-reports, face-to-face interviews, or physical activity questionnaires. Using pedometers, Furlanetto et al.[11] found that the mean number of daily steps was significantly lower in adult smokers than in adult controls, the former also having lower physical capacity, worse lung function, and greater sensation of fatigue. However, there is a lack of studies in which the level of PADL in smokers is more accurately determined with the use of triaxial accelerometers.

There is evidence that a higher level of PADL reduces smoking-related complications. However, there is a need for further clarification of the association between the level of PADL and lung function in smokers. If this association is found to be consistent, preventive strategies can be devised. Longitudinal studies of the role that a higher level of objectively measured PADL has in preventing lung function decline in smokers could contribute to preventing smoking-related complications, which consume a significant proportion of health care resources in Brazil and the world.[14]

We hypothesized that smokers who have a higher level of PADL (more accurately determined by triaxial accelerometry) have relatively preserved lung function, regardless of their smoking history. Confirmation of our hypothesis would support the need for strategies to increase the level of PADL in smokers in order to reduce the damage caused by smoking. Therefore, we sought to determine whether the level of PADL, as determined by triaxial accelerometry, was associated with lung function in adult smokers.

METHODS

This was a cross-sectional study involving a convenience sample of adult smokers selected from among the participants of a study conducted in the Federal University of São Paulo Laboratory of Epidemiology and Human Movement, located in the city of Santos, Brazil. The study included 62 adult smokers who were 20 years of age or older and had no cardiac, respiratory, or metabolic diseases limiting their exercise capacity. In brief, this was a population-based epidemiological study whose primary objective was to determine the association of sedentary behavior and physical inactivity with the development of chronic diseases. The exclusion criteria were as follows: a spirometric diagnosis of COPD; problems indicating inability to perform PADL adequately; being a smoker with a smoking history of fewer than 1.5 pack-years or more than 50 pack-years; and being a former smoker.[15]

The following demographic variables were analyzed: age; gender; race; place of birth; level of education; and socioeconomic status. After being selected for inclusion, all participants were informed of the procedures, discomfort, and risks associated with the present study and gave written informed consent. The study project was approved by the Federal University of São Paulo Human Research Ethics Committee (Protocol no. 186.796).

Initial clinical evaluation included history taking for previous health problems and use of medications. The risk of cardiovascular events was determined on the basis of the following risk factors: age; family history; smoking history; hypertension; dyslipidemia or hypercholesterolemia; diabetes or hyperglycemia; obesity; and sedentary lifestyle.

Smoking status was determined by self-report, and smoking history was calculated by multiplying the duration of smoking in years by the number of cigarettes smoked per day and dividing the result by 20 (the number of cigarettes in one pack). Individuals who reported current smoking and having smoked 100 or more cigarettes in their lifetime at the time of the study were defined as smokers.[15]

After anthropometric measurements, including weight, height, and BMI calculation, all participants were evaluated as described below.

Lung function was assessed by forced spirometry (Quark PFT; Cosmed, Rome, Italy). FEV_1, FVC, FEV_1/FVC, and PEF were determined in accordance with the American Thoracic Society criteria.[16] Spirometric indices were expressed as absolute values and as a percentage of reference values.[17]

The level of PADL was determined by the International Physical Activity Questionnaire (IPAQ), which assesses total energy expenditure in metabolic equivalent task-minutes per week (MET-min/wk) and time spent in daily physical activity. PADL was classified as vigorous, moderate, or light, measured in MET-min/wk, and divided into four domains: work; transport; household chores; and recreation and leisure. The total IPAQ score is calculated by summing the individual domain scores. The IPAQ-long form was used, consisting of 27 questions regarding physical activity. The participants were instructed to answer the questions on the basis of the week prior to the administration of the IPAQ.[18] The level of PADL was also assessed with a widely used triaxial accelerometer (GT3X ActiGraph; MTI, Pensacola, FL, USA).[19-22] A triaxial accelerometer measures the duration and intensity of physical activity. The participants were instructed to wear the device on an elastic belt placed on their dominant hip and left

in place for seven days. A valid day was defined as at least 12 h of accelerometer use. All participants were instructed to remove the device before engaging in water-based activities, such as bathing and swimming, and at bedtime. Only the data from the participants who used the accelerometer for at least four valid days were analyzed.[19] On the basis of its intensity, physical activity was classified as follows: physical inactivity or light physical activity, fewer than 3.00 MET-min/wk; moderate physical activity, 3.00-5.99 MET-min/wk; hard physical activity, 6.00-8.99 MET-min/wk; and very hard physical activity, ≥ 9.00 MET-min/wk.[23] The minimum level of PADL, in terms of quantity and intensity, was defined as 150 min/week of moderate to vigorous physical activity.[24] The participants who were unable to achieve that level of PADL were considered to be physically inactive.

In the present study, statistical analysis was performed with the IBM SPSS Statistics software package, version 23 (IBM Corporation, Armonk, NY, USA). The Kolmogorov-Smirnov test was used in order to determine the normality of continuous variables. Data are presented as mean ± standard deviation or as median (interquartile range).

The study sample size was calculated on the basis of the number of independent variables of interest for inclusion in the multiple regression model. Outcome variables in the regression models included percent predicted FEV_1 and FVC. The models were adjusted for age, gender, weight, height, and six other variables. Smoking history was considered to be the main predictor. Possible predictors were initially evaluated in categories. Demographic and anthropometric characteristics were taken into consideration, as were cardiovascular risk factors. After the bivariate analysis, the variables that were found to be significantly associated with the spirometric indices were included in the multiple regression model, as follows: age; gender; presence of hypertension; presence of diabetes mellitus; IPAQ household chores domain score; daily energy expenditure in kcal; and physical inactivity.

The Student's t-test or the Mann-Whitney test was used in order to compare the spirometric indices between males and females according to the presence of comorbidities, such as hypertension, diabetes mellitus, dyslipidemia, obesity, and physical inactivity.

Correlations between the studied variables were tested with Pearson's or Spearman's correlation coefficient, depending on the distribution of the variables. The level of significance was set at 5%.

RESULTS

Among the 62 volunteers in the study sample, obese individuals and females predominated (Table 1). There were significant differences between males and females regarding smoking history, weight, and BMI.

Table 2 shows the correlations between PADL and lung function, FVC having been found to correlate significantly with the IPAQ household chores domain score, energy expenditure in kcal/day, and hard physical activity in h ($p < 0.05$ for all). The aforementioned variables were also found to correlate significantly with FEV_1. The household chores domain scores were the only IPAQ domain scores that correlated significantly with lung function. PEF was found to correlate significantly with the IPAQ household chores domain score, light physical activity, and hard physical activity. Table 3 shows the bivariate association between lung function data and cardiovascular risk factors. FVC was found to be reduced in the participants with arterial hypertension, and the FEV_1/FVC ratio was found to be reduced in those with diabetes mellitus. Obese participants and those with dyslipidemia were found to have reduced FVC and FEV_1. No significant associations were found between physical inactivity, as determined by accelerometry, and spirometric indices.

Evaluating all predictors, corrected for confounding factors, and using lung function data (FVC and FEV_1, both in % of predicted) as outcome variables, we found that the variables that remained in the model as predictors of lung function were smoking history and the presence of diabetes, as predictors of FVC, and smoking history and the presence of arterial hypertension, as predictors of FEV_1 (Table 4).

DISCUSSION

The present study investigated the association between the level of PADL and lung function in adult smokers without respiratory disease. The level of PADL was directly assessed by triaxial accelerometry over the course of seven days. To our knowledge, there is little information regarding the use of triaxial accelerometry for determining the level of PADL. After adjustment for the main confounding factors, no association was found between an adequate level of PADL and better lung function.

As expected, smoking history was a predictor of worse FVC and FEV_1, even after having been adjusted for confounding factors. Studies have shown that smoking history is the main predictor of reduced FEV_1 in smokers with a normal FEV_1/FVC ratio.[25] Smoking is also associated with dysregulation of gene expression in the small airway epithelium and accelerates the aging of the airways, as well as being the principal factor responsible for progressive lung function decline.[26]

Lallukka et al.[27] conducted a cohort study and concluded that smoking and physical inactivity are associated with disability retirement and that even hard physical activity is not sufficient to eliminate the adverse effects that smoking has on health. Elderly smokers have reduced exercise capacity when compared with elderly never-smokers, and tobacco exposure is associated with reduced quality of life regardless of the level of physical activity.[28] Smoking is associated with evidence of mild obstruction and accelerates lung function decline in adolescents. Female adolescents are possibly more vulnerable to the effects of smoking on lung function than are male adolescents.[29] We believe

Table 1. General characteristics of the sample (N = 62).[a]

Variable	Males (n = 20)	Females (n = 42)
Age, years	47 ± 14	53 ± 8
Smoking history, pack-years	12.7 (3.2-20.0)*	22.5 (11.7-40.0)
Weight, kg	80.2 ± 12.3*	74.6 ± 19.9
Height, cm	1.71 ± 0.07*	1.57 ± 0.07
BMI, kg/m^2	27.4 ± 4.5*	29.8 ± 7.07
Risk factors, n (%)		
Hypertension	4 (20)	13 (31)
Obesity	5 (25)	20 (47)
Diabetes	2 (10)	10 (23)
Dyslipidemia	5 (25)	18 (42)
Physical inactivity	7 (35)	14 (33)

[a]Data presented as mean ± SD or median (interquartile range), except where otherwise indicated. *p< 0.05.

Table 2. Statistical correlations between lung function and physical activity in daily life.

Lung function	Physical activity in daily life						
	IPAQ-HC[a]	EE, kcal/day	WST, h	WLPA, h	WMPA, h	WVPA, h	WVVPA, h
FVC, L	0.432*	0.320*	0.182	0.203	0.104	0.375*	0.034
FEV_1, L	0.400*	0.330*	0.218	0.186	0.103	0.346*	0.036
FEV_1/FVC	0.110	0.064	0.205	0.064	0.023	0.071	0.018
FEV_1/FVC, % predicted	0.057	0.046	0.241	0.059	0.012	0.084	0.001
PEF, L/min	0.451*	0.191	0.246	0.264*	0.052	0.392*	0.008

IPAQ-HC: International Physical Activity Questionnaire household chores domain score; EE: energy expenditure; WST: weekly sedentary time; WLPA: weekly light physical activity; WMPA: weekly moderate physical activity; WVPA: weekly vigorous physical activity; and WVVPA: weekly very vigorous physical activity. [a]Energy expenditure measured in metabolic equivalent task-minutes per week. *p < 0.05.

Table 3. Relationship between lung function data and cardiovascular risk factors.

Risk factors		Lung function data				
		FVC, L	FVC, % predicted	FEV_1, L	FEV_1, % predicted	FEV_1/FVC, % predicted
Arterial hypertension	Yes	2.81 ± 0.62*	86 ± 14	2.22 ± 0.53	84 ± 16	78 ± 6
	No	3.72 ± 0.10*	94 ± 12	2.88 ± 0.89	95 ± 12	82 ± 5
Diabetes mellitus	Yes	2.74 ± 0.85	83 ± 10	2.29 ± 0.69	86 ± 10	84 ± 2*
	No	3.47 ± 1.03	94 ± 12	2.80 ± 0.87	94 ± 15	80 ± 6*
Dyslipidemia	Yes	2.98 ± 0.67*	92 ± 12	2.44 ± 0.52*	93 ± 13	82 ± 5
	No	3.53 ± 1.16*	92 ± 13	2.85 ± 0.98*	92 ± 15	80 ± 6
Obesity	Yes	2.94 ± 0.59*	88 ± 11	2.41 ± 0.52*	89 ± 14	81 ± 6
	No	3.58 ± 1.19*	95 ± 13	2.90 ± 0.99*	94 ± 14	80 ± 5
Physical inactivity	Yes	3.27 ± 1.11	92 ± 15	2.62 ± 0.97	91 ± 18	79 ± 6
	No	3.35 ± 1.00	92 ± 12	2.74 ± 0.81	93 ± 12	82 ± 5

*p < 0.05.

Table 4. Multivariate regression results with the main predictors of lung function.[a]

Outcome	Predictors	Coefficient	Standard error	p	ΔR	R^2
FVC, % predicted	Smoking history	−0.218	0.065	0.001	0.110	0.246
	Diabetes mellitus	−12.266	3.763	0.002	0.136	
FEV_1, % predicted	Smoking history	−0.202	0.074	0.009	0.135	0.225
	Arterial hypertension	−9.883	3.781	0.011	0.090	

[a]Model adjusted for age, gender, weight, height, hypertension, diabetes, physical inactivity (determined by triaxial accelerometry), and International Physical Activity Questionnaire score.

that the benefits of PADL were not enough to make up for the damage caused by smoking.

We observed a crucial association between the presence of diabetes mellitus and lung function in our participants. Our results are in agreement with those of previous studies.[30,31] Lung volume changes reducing lung compliance and DLCO have been described in patients with diabetes. This is probably due to a reduction in pulmonary capillary blood volume as a result of diabetes mellitus. Impaired lung function in

individuals with diabetes suggests that the lung is a "target organ" in diabetes mellitus.[32] Systematic reviews have examined lung function in patients with diabetes mellitus. Reduced FEV_1 and FVC have been found to be associated with type 1 diabetes and type 2 diabetes.[33] Our results suggest that this association remains significant even in smokers with varying history of smoking. Therefore, diabetes mellitus should be considered a major risk factor for lung function decline and, eventually, COPD. According to the aforementioned studies, moderate to high levels of regular physical activity are associated with reduced lung function decline and reduced risk of COPD in smokers.[5,34] This difference can be attributed to the methods used in order to determine the level of PADL. In the present study, we used triaxial accelerometry, which precisely measures the amount and intensity of PADL. The aforementioned studies involved the use of questionnaires. Despite the size of those studies, the major limitation of questionnaires is that they overestimate the level of PADL. Triaxial motion sensors can overcome some of the limitations of self-report instruments, are not affected by random and systematic errors introduced by interviewees and interviewers, and provide valid and reliable estimates of basic features such as the frequency, duration, and intensity of physical activity, as well as the pattern of physical activity.[35] An accurate assessment of physical activity is extremely important when the relationship between exposure to physical activity and a range of health outcomes (e.g., cardiovascular disease, hypertension, and obesity) is examined.[36] In addition, self-reported physical activity is highly susceptible to inaccuracy because self-report instruments depend on the ability of individuals to recall and report their physical activity.[23] Our results suggest the need for longitudinal epidemiological studies to investigate the association between lung function and PADL, the latter being more accurately assessed by motion sensors.

The major limitation of the present study is its convenience sample, which can explain the predominance of females and the difference in smoking history between males and females. However, the sample size was sufficient to adjust the regression models to the main confounders of clinical interest.

Our results suggest that there is no association between physical inactivity and lung function in adult smokers, as well as reinforcing the importance of smoking cessation and preventing comorbidities such as diabetes mellitus and arterial hypertension in order to prevent lung function decline and COPD. Therefore, health professionals should focus on health promotion instructions and strategies, as well as on preventing comorbidities in smokers and the general population.

ACKNOWLEDGMENTS

The authors would like to thank the Angiocorpore Institute of Cardiovascular Medicine for their support.

REFERENCES

1. World Health Organization. WHO Report on the Global Tobacco Epidemic 2008: The Mpower Package. Geneva: World Health Organization; 2008.
2. Wünsch Filho V, Mirra AP, López RV, Antunes LF. Tobacco smoking and cancer in Brazil: evidence and prospects [Article in Portuguese]. Rev Bras Epidemiol. 2010;13(2):175-87. http://dx.doi.org/10.1590/S1415-790X2010000200001
3. Urrutia I, Capelastegui A, Quintana JM, Mu-iozguren N, Basagana X, Sunyer J, et al. Smoking habit, respiratory symptoms and lung function in young adults. Eur J Public Health. 2005;15(2):160-5. http://dx.doi.org/10.1093/eurpub/cki113
4. Tantisuwat A, Thaveeratitham P. Effects of smoking on chest expansion, lung function, and respiratory muscle strength of youths. J Phys Ther Sci. 2014;26(2):167-70. http://dx.doi.org/10.1589/jpts.26.167
5. Garcia-Aymerich J, Lange P, Benet M, Schnohr P, Antó JM. Regular physical activity modifies smoking-related lung function decline and reduces risk of chronic obstructive pulmonary disease: a population-based cohort study. Am J Respir Crit Care Med. 2007;175(5):458-63. http://dx.doi.org/10.1164/rccm.200607-896OC
6. Warburton DE, Nicol CW, Bredin SS. Health benefits of physical activity: the evidence. CMAJ. 2006;174(6):801-9. http://dx.doi.org/10.1503/cmaj.051351
7. Cheng YJ, Macera CA, Addy CL, Sy FS, Wieland D, Blair SN. Effects of physical activity on exercise tests and respiratory function. Br J Sports Med. 2003;37(6):521-8. http://dx.doi.org/10.1136/bjsm.37.6.521
8. Jones AM, Carter H. The effect of endurance training on parameters of aerobic fitness. Sports Med. 2000;29(6):373-86. http://dx.doi.org/10.2165/00007256-200029060-00001
9. Hashizume K, Kusaka Y, Kawahara K. Effects of cigarette smoking on endurance performance levels of 16- to 19-year-old males. Environ Health Prev Med. 1999;4(2):75-80. http://dx.doi.org/10.1007/BF02931998
10. Lee CL, Chang WD. The effects of cigarette smoking on aerobic and anaerobic capacity and heart rate variability among female university students. Int J Womens Health. 2013;5:667-79. http://dx.doi.org/10.2147/IJWH.S49220
11. Furlanetto KC, Mantoani LC, Bisca G, Morita AA, Zabatiero J, Proença M, et al. Reduction of physical activity in daily life and its determinants in smokers without airflow obstruction. Respirology. 2014;19(3):369-75. http://dx.doi.org/10.1111/resp.12236
12. Atkin AJ, Gorely T, Clemes SA, Yates T, Edwardson C, Brage S, et al. Methods of measurement in epidemiology: sedentary behaviour. Int J Epidemiol. 2012;41(5):1460-71. http://dx.doi.org/10.1093/ije/dys118
13. Pitta F, Troosters T, Probst VS, Spruit MA, Decramer M, Gosselink R. Quantifying physical activity in daily life with questionnaires and motion sensors in COPD. Eur Respir J. 2006;27(5):1040-55. http://dx.doi.org/10.1183/09031936.06.00064105
14. Pinto M, Ugá MA. Os custos de doenças tabaco-relacionadas para o Sistema Único de Saúde. Cad Saude Publica. 2010;26(6):1234-45. http://dx.doi.org/10.1590/S0102-311X2010000600016
15. Santos JD, Silveira DV, Oliveira DF, Caiaffa WT. Instruments used to evaluate smoking habits: a systematic review [Article in Portuguese]. Cien Saude Colet. 2011;16(12):4707-20. http://dx.doi.org/10.1590/S1413-81232011001300020
16. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J. 2005;26(2):319-38. http://dx.doi.org/10.1183/09031936.05.00034805
17. Pereira CA, Sato T, Rodrigues SC. New reference values for forced spirometry in white adults in Brazil. J Bras Pneumol. 2007;33(4):397-406. http://dx.doi.org/10.1590/S1806-37132007000400008
18. Hallal PC, Gomez LF, Parra DC, Lobelo F, Mosquera J, Florindo AA, et al. Lessons learned after 10 years of IPAQ use in Brazil and Colombia. J Phys Act Health. 2010;7 Suppl 2:S259-64.
19. Troiano RP, Berrigan D, Dodd KW, Mâsse LC, Tilert T, McDowell M. Physical activity in the United States measured by accelerometer. Med Sci Sports Exerc. 2008;40(1):181-8. http://dx.doi.org/10.1249/mss.0b013e31815a51b3

20. Trost SG, Way R, Okely AD. Predictive validity of three ActiGraph energy expenditure equations for children. Med Sci Sports Exerc. 2006;38(2):380-7. http://dx.doi.org/10.1249/01.mss.0000183848.25845.e0
21. Evenson KR, Wen F, Metzger JS, Herring AH. Physical activity and sedentary behavior patterns using accelerometry from a national sample of United States adults. Int J Behav Nutr Phys Act. 2015;12:20. http://dx.doi.org/10.1186/s12966-015-0183-7
22. Loprinzi PD, Walker JF. Nicotine Dependence, Physical Activity, and Sedentary Behavior among Adult Smokers. N Am J Med Sci. 2015;7(3):94-9. http://dx.doi.org/10.4103/1947-2714.153920
23. Freedson PS, Melanson E, Sirard J. Calibration of the Computer Science and Applications, Inc. accelerometer. Med Sci Sports Exerc. 1998;30(5):777-81. http://dx.doi.org/10.1097/00005768-199805000-00021
24. American College of Sports Medicine. ACSM's guidelines for exercise testing and prescription. 8th ed. Philadelphia: Lippincott Williams & Wilkins; 2009.
25. Masuko H, Sakamoto T, Kaneko Y, Iijima H, Naito T, Noguchi E, et al. Lower FEV1 in non-COPD, nonasthmatic subjects: association with smoking, annual decline in FEV1, total IgE levels, and TSLP genotypes. Int J Chron Obstruct Pulmon Dis. 2011;6:181-9.
26. Walters MS, De BP, Salit J, Buro-Auriemma LJ, Wilson T, Rogalski AM, et al. Smoking accelerates aging of the small airway epithelium. Respir Res. 2014;15:94. http://dx.doi.org/10.1186/s12931-014-0094-1
27. Lallukka T, Rahkonen O, Lahelma E, Lahti J. Joint associations of smoking and physical activity with disability retirement: a register-linked cohort study. BMJ Open. 2015;5(7):e006988. http://dx.doi.org/10.1136/bmjopen-2014-006988
28. Mesquita R, Gonçalves CG, Hayashi D, Costa Vde S, Teixeira Dde C, de Freitas ER, et al. Smoking status and its relationship with exercise capacity, physical activity in daily life and quality of life in physically independent, elderly individuals. Physiotherapy. 2015;101(1):55-61. http://dx.doi.org/10.1016/j.physio.2014.04.008
29. Gold DR, Wang X, Wypij D, Speizer FE, Ware JH, Dockery DW. Effects of cigarette smoking on lung function in adolescent boys and girls. N Engl J Med. 1996;335(13):931-7. http://dx.doi.org/10.1056/NEJM199609263351304
30. Cazzola M, Calzetta L, Rogliani P, Lauro D, Novelli L, Page CP, et al. High glucose enhances responsiveness of human airways smooth muscle via the Rho/ROCK pathway. Am J Respir Cell Mol Biol. 2012;47(4):509-16. http://dx.doi.org/10.1165/rcmb.2011-0449OC
31. Shah SH, Sonawane P, Nahar P, Vaidya S, Salvi S. Pulmonary function tests in type 2 diabetes mellitus and their association with glycemic control and duration of the disease. Lung India. 2013;30(2):108-12. http://dx.doi.org/10.4103/0970-2113.110417
32. Sandler M. Is the lung a 'target organ' in diabetes mellitus? Arch Intern Med. 1990;150(7):1385-8. http://dx.doi.org/10.1001/archinte.1990.00390190051006
33. Kinney GL, Black-Shinn JL, Wan ES, Make B, Regan E, Lutz S, et al. Pulmonary function reduction in diabetes with and without chronic obstructive pulmonary disease. Diabetes Care. 2014;37(2):389-95. http://dx.doi.org/10.2337/dc13-1435
34. Pelkonen M, Notkola IL, Lakka T, Tukiainen HO, Kivinen P, Nissinen A. Delaying decline in pulmonary function with physical activity: a 25-year follow-up. Am J Respir Crit Care Med. 2003;168(4):494-9. http://dx.doi.org/10.1164/rccm.200208-954OC
35. Ortlieb S, Gorzelniak L, Nowak D, Strobl R, Grill E, Thorand B, et al. Associations between multiple accelerometry-assessed physical activity parameters and selected health outcomes in elderly people--results from the KORA-age study. PLoS One. 2014;9(11):e111206. http://dx.doi.org/10.1371/journal.pone.0111206
36. Caspersen CJ. Physical activity epidemiology: concepts, methods, and applications to exercise science. Exerc Sport Sci Rev. 1989;17:423-73. http://dx.doi.org/10.1249/00003677-198900170-00015

J Bras Pneumol. 2016;42(2):136-142
http://dx.doi.org/10.1590/S1806-37562015000000166

Asthma treatment in children and adolescents in an urban area in southern Brazil: popular myths and features

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Submitted: 13 July 2015.
Accepted: 3 November 2015.

Study carried out at the Pontifícia Universidade Católica do Rio Grande do Sul – PUCRS – Porto Alegre (RS) Brasil.

ABSTRACT

Objective: To describe the frequency of popular myths about and features of asthma treatment in children and adolescents in an urban area in southern Brazil. **Methods:** The parents or legal guardians of public school students (8-16 years of age) completed a specific questionnaire regarding their understanding of asthma, asthma control, and treatment characteristics. The sample included parents or legal guardians of students with asthma (n = 127) and healthy controls (n = 124). **Results:** The study involved 251 parents or legal guardians, of whom 127 (68.5%) were the mothers and 130 (51.8%) were White. The mean age of these participants was 38.47 ± 12.07 years. Of the participants in the asthma and control groups, 37 (29.1%) and 26 (21.0%), respectively, reported being afraid of using asthma medications, whereas 61 (48%) and 56 (45.2%), respectively, believed that using a metered dose inhaler can lead to drug dependence. However, only 17 (13.4%) and 17 (13.7%) of the participants in the asthma and control groups, respectively, reported being afraid of using oral corticosteroids. In the asthma group, 55 students (43.3%) were diagnosed with uncontrolled asthma, only 41 (32.3%) had a prescription or written treatment plan, and 38 (29.9%) used asthma medications regularly. **Conclusions:** Popular myths about asthma treatment were common in our sample, as were uncontrolled asthma and inappropriate asthma management. Further studies in this field should be conducted in other developing countries, as should evaluations of pediatric asthma treatment programs in public health systems.

Keywords: Asthma/therapy; Asthma/prevention & control; Child health.

INTRODUCTION

Asthma is the most common chronic disease in children.[1] In the last two decades, International Study of Asthma and Allergies in Childhood (ISAAC) studies have shown the impact and importance of asthma worldwide, asthma being a childhood disease that can affect 15-25% of schoolchildren in many different countries.[2,3] In addition, although there are drugs that are effective in controlling the disease in most patients, studies have shown that many children with asthma have uncontrolled disease.[4] Environmental control measures, medication use, psychological support, and health education for patients and their families should be aimed at achieving asthma control. In addition, continued treatment adherence is required.[1] Therefore, a major clinical and public health challenge is to achieve disease control in children with asthma, asthma control resulting in significant improvement in the quality of life of such patients.

Independently of patient age or disease severity, treatment adherence is essential to maintain asthma control. Factors contributing to treatment nonadherence are many and complex, including socioeconomic status and physician-patient relationship, as well as cultural, psychological, and individual factors, together with factors associated with patient understanding of asthma treatment.[5,6] Patients should understand asthma and its treatment and have a written treatment plan to be used in case of disease exacerbation. The optimal treatment for asthma is that which results in asthma control and stable disease with the lowest possible dose of medication (inhaled corticosteroids).[1]

Parents or caregivers are responsible for disease management in children and adolescents with asthma. Parental knowledge of asthma, aggravating factors (and how to identify them), triggering factors (and how to control them), and asthma medications (and how to use them correctly) can influence treatment adherence and symptom management. Misinformation and, in particular, popular myths can lead to treatment nonadherence and, consequently, an increase in the number of hospitalizations and emergency room visits,

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Financial support: This investigator-initiated study received financial support from the *Coordenação de Aperfeiçoamento de Pessoal de Nível Superior* (CAPES, Office for the Advancement of Higher Education), the *Fundação de Amparo à Pesquisa do Estado do Rio Grande do Sul* (FAPERGS, Foundation for the Support of Research in the State of Rio Grande do Sul), the Brazilian *Conselho Nacional de Desenvolvimento Científico e Tecnológico* (CNPq, National Council for Scientific and Technological Development), and Novartis Brazil.

ISSN 1806-3713

which result in high costs to health care systems and society (direct and indirect costs).[7]

Among the various factors contributing to a poor understanding of and a belief in popular myths about asthma treatment are the lack of effective asthma education programs and the lack of training of health professionals in managing the disease. Therefore, from a geographic and cultural standpoint, it is necessary to determine the level of understanding of asthma (and the popular myths about the disease) in each distinct population in order to inform educational programs aimed at increasing adherence to treatment and the correct use of medications, resulting in a better prognosis, improved quality of life, and increased life expectancy.[8]

Although clinical trial results and international guidelines suggest that asthma control can be achieved, there is a significant gap between therapeutic goals and the level of asthma control in "real life".[1] Therefore, it is necessary to identify the most common myths about the management of asthma in children and adolescents in sociogeographically distinct populations.[9] To date, there have been no published studies evaluating the frequency of popular myths about asthma among parents or legal guardians of children and adolescents with the disease. Data on popular myths about asthma treatment in children and adolescents can aid in developing educational strategies and dispelling myths that can hinder the management of the disease. In this context, the objective of the present study was to evaluate the prevalence of myths about asthma and asthma treatment among parents of children and adolescents with the disease, as well as to describe the features of asthma treatment and the level of asthma control in children and adolescents in an urban area in southern Brazil.

METHODS

This was a cross-sectional, descriptive, analytical study conducted between February and December of 2013 and evaluating public school students (8-16 years of age) in the city of Porto Alegre, Brazil, the primary objective of which was to determine the impact of asthma in children and adolescents in an urban area in southern Brazil. Data collection was divided into three phases: 1) characterization and prevalence of asthma; 2) asthma phenotypes; and 3) myths and truths about asthma treatment.

The public schools and schoolchildren in the present study were randomly selected. A total of seven public schools were selected in Porto Alegre. The sample size was calculated on the basis of the ISAAC studies,[2,3] with a confidence interval of at least 95% and a sampling error of up to 5%. A total of 2,500 schoolchildren were required for phase 1 of the study. For phases 2 and 3, 576 schoolchildren (288 schoolchildren with asthma and 288 healthy schoolchildren; 1:1) were required.

This article discusses popular myths about asthma treatment in southern Brazil, i.e., data collected in phase 3 of the study, from parents of public school children in Porto Alegre. Schoolchildren with asthma and healthy controls were characterized in phase 1 of the study, during which asthma prevalence and socioeconomic status were analyzed and the schoolchildren and their parents or legal guardians were generally classified (in terms of gender, age, race/ethnicity, level of education, gestational age at birth, presence of other chronic diseases, and physical or cognitive limitations, among others). The Brazilian Economic Classification Criterion questionnaire[10] was used in order to stratify the participants by socioeconomic class (from A to E), class A being the highest and class E the lowest. The ISAAC questions and criteria were used in order to classify asthma,[11] consisting of four central questions regarding symptoms and physician-diagnosed asthma ever, as well as symptoms and asthma medication use in the last 12 months. Race/ethnicity was self-reported as White (Caucasian), Black (African), Brown (Mulatto), Red (Indigenous), or Yellow (Asian). The exclusion criteria for schoolchildren were as follows: having a chronic disease other than asthma; having been born prematurely; and having cognitive/motor deficits that could affect the study outcomes.

In phase 3 of the study, the level of asthma control was assessed by the Global Initiative for Asthma (GINA) asthma control questions.[1] The participating parents or legal guardians completed two questionnaires, which were aimed at identifying myths and truths about asthma treatment: a clinical questionnaire consisting of questions regarding health status and adherence to asthma treatment; and a questionnaire consisting of specific questions regarding myths and truths about asthma treatment, which was developed by our research group and consists of six yes/no questions, respondents being asked to explain their affirmative answers (Chart 1). The latter questionnaire was completed not only by the parents/legal guardians of the schoolchildren with asthma but also by those of the children who were healthy. This was due to the fact that, in phase 2 of the study, parents/legal guardians of healthy controls were found to have direct or indirect contact with asthma patients; that is, they themselves or a relative had asthma. The questions regarding the treatment of asthma were answered only by the parents/legal guardians of children and adolescents with asthma.

The present study was approved by the local research ethics committee (Protocol no. 73585/12) and the Porto Alegre Municipal Department of Health Research Ethics Committee (Protocol no. 793/12). The parents or legal guardians of the participating schoolchildren gave written informed consent. For statistical analysis, descriptive and categorical variables were expressed as absolute and relative frequencies. Continuous variables were expressed as mean and standard deviation. The chi-square test was used in order to compare the two groups, the level of significance being set at $p < 0.05$.

RESULTS

In phase 1 of the study, the participation rate was 86.24% (2,500/2,899), asthma prevalence

Chart 1. Questionnaire regarding myths and truths about asthma.

Questions	Yes[a]	No
1. Are you afraid of using a "puffer/spray"[b] for the treatment of asthma in your child?		
2. Are you afraid of using inhaled corticosteroids for the treatment of asthma in your child?		
3. Do you believe that the use of a "puffer/spray" for the treatment of asthma can lead to addiction?		
4. Do you use a nebulizer for the treatment of asthma in your child?		
5. Do you believe that nebulizers are more effective than "puffers/sprays" for the treatment of asthma in your child?		
6. Do you believe that physical activity can aid in the treatment of asthma in your child?		

[a]If the answer is yes, please explain why. [b]Puffer/spray = metered dose inhaler.

being estimated at 20.4% (511/2,500). Of the 576 schoolchildren required for phase 3, 251 (127 children with asthma and 124 controls) participated in that phase (participation rate, 43.58%). The mean age of the participants was 10.36 ± 2.05 years, and 134 (53.4%) were female. Of the 251 parents or legal guardians who participated in the study, 127 (68.5%) were the mothers. In addition, 181 (72.1%) belonged to socioeconomic class C, and 130 (51.8%) were White. Furthermore, 51 (20.31%) reported that the mothers had been diagnosed with asthma. Of those 51 mothers, 41 (32.28%) were in the asthma group and 10 (8.00%) were in the control group. Also in phase 3 of the study, 60 children/adolescents (52.6%) were found to have uncontrolled asthma on the basis of the GINA criteria for asthma control. Figure 1 shows a detailed flowchart of patient participation in each phase of the study.

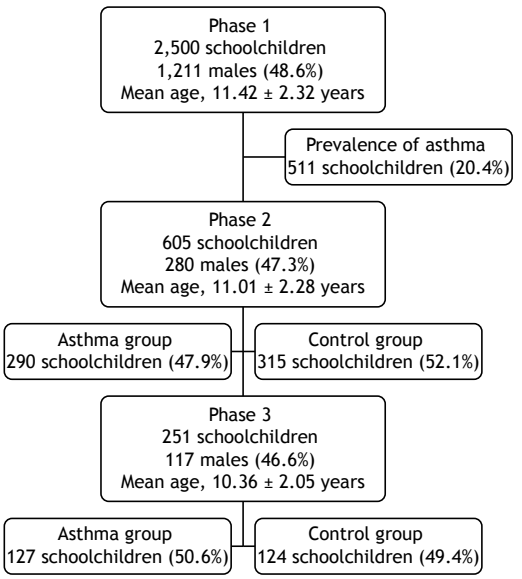

Figure 1. Flowchart of the three phases of the study.

For the evaluation of parental understanding of myths about asthma in children and adolescents, parents or legal guardians in the asthma and control groups were interviewed. Of the participants in the asthma and control groups, 37 (29.1%) and 26 (21.0%), respectively, reported being afraid of using metered dose inhalers (MDIs) for the treatment of asthma in their children. In addition, 61 (48.0%) and 56 (45.2%), respectively, believed that using an MDI can lead to addiction (drug dependence). Furthermore, 17 (13.4%) and 17 (13.7%), respectively, reported being afraid of using oral corticosteroids for the treatment of asthma in their children. Moreover, 84 (66.1%) and 63 (50.8%), respectively, reported regular nebulizer use for the treatment of asthma in their children. Finally, 38 (29.1%) and 51 (41.7%), respectively, believed that physical activity is harmful to the health of asthma patients and should not be prescribed as an adjunct in the treatment of asthma. These results are shown in Table 1.

For the evaluation of parental understanding of asthma treatment, only the parents or legal guardians in the asthma group answered the pertinent questions; 67 (52.8%) reported that their children had had a medical consultation or emergency room visit for asthma in the last 12 months, and 9 (23.7%) reported that their children had visited "witch doctors or faith healers" in that period. Only 41 (32.3%) had a prescription or written treatment plan, and 38 (29.9%) used asthma medications regularly. Of those, 28 (72.4%) admitted to forgetting to use their asthma medications regularly, 37 (97.4%) used medications provided free of charge by the public health care system, and only 9 (23.7%) used their bronchodilators with a spacer. In addition, 52 (40.9%) reported having used inhaled corticosteroids in the last 12 months, whereas 57 (44.9%) reported having used oral corticosteroids in that period. Furthermore, 69 (54.3%) reported nebulizer use. With regard to physical activity, 17 (13.4%) of the schoolchildren used asthma medications before engaging in physical activity.

Figure 2 shows the results of our analysis of the association of myths and truths about asthma with the treatment of the disease, the questions having been answered by the parents or legal guardians in the asthma group. In the last 12 months, there were no associations between being afraid of using an MDI and using an MDI (29.1% vs. 40.9%; $p = 0.782$); between being afraid of using oral corticosteroids and using oral corticosteroids (13.4% vs. 44.9%; $p = 0.249$); between considering nebulizer use better than MDI use (66.1% vs. 54.3%; $p = 0.741$); or between considering physical activity an adjunct in the treatment of asthma and using asthma medications before engaging in physical activity (70.1% vs. 13.4%; $p = 0.519$).

Table 2 shows a comparison between the schoolchildren with controlled asthma (n = 54) and those with uncontrolled asthma (n = 60) regarding myths about asthma, asthma treatment, medical monitoring, and asthma attacks, no differences being found between myths about asthma treatment and the treatment of asthma in the last 12 months, the exception being MDI use (30.2% vs. 55.0%, respectively; p = 0.008). With regard to asthma exacerbations in the last 12 months, a comparison between the schoolchildren with uncontrolled asthma and those with controlled asthma showed that medical consultations for asthma symptoms (wheezing, dyspnea, or cough) had been more common in the former than in the latter (66.7% vs. 45.3%; p = 0.023), as had wheezing during or after physical activity (71.2% vs. 41.5%; p = 0.002) and wheezing at rest without having engaged in physical activity (61.7% vs. 35.8%; p = 0.006).

DISCUSSION

Our results show that, in the city of Porto Alegre, many parents of children and adolescents with asthma believe in popular myths about the treatment of asthma. In addition, most admitted that they do not adhere to the prescribed treatment. A minority of the schoolchildren had a prescription or written treatment plan, and less than one third used prophylaxis; however, most of the parents or legal guardians reported that they were not afraid of using oral corticosteroids for the treatment of asthma in their children. In a population in which the prevalence of asthma is high (20.4% of the children/adolescents studied had asthma) and nearly half have uncontrolled asthma, the aforementioned findings reveal a bleak outlook for public health, and this requires changes in government strategies for asthma programs.

Parental knowledge of asthma in children and adolescents appears to be poor, particularly in developing countries. In a study conducted in southern Brazil, Zhang et al.[12] showed that over 90% of parents of asthma patients lack knowledge of the disease. This is a worrisome scenario in developing countries and requires further studies. In the present study, the number of parents or legal guardians of asthma patients who believed that MDI use can be significantly harmful to health was higher than that of those of healthy controls, and nearly half (48%) believed that "the puffer is addictive", with no significant difference in comparison with the control group. Many of the parents or legal guardians in the asthma group reported being afraid of using asthma medications in their children. In contrast, a minority (13%) of parents or legal guardians in the asthma and control groups reported being afraid of using oral corticosteroids for

Table 1. Participant responses regarding myths and truths about the treatment of asthma, by group (asthma group, n = 127; control group, n = 124).

Response	Asthma group		Control group		p*
	n	%	n	%	
Afraid of using MDIs for the treatment of asthma	37	29.1	26	21.0	0.009
Rationale: MDIs are addictive and harmful to the heart	29	22.8	21	16.9	
Afraid of using oral corticosteroids for the treatment of asthma	17	13.4	17	13.7	0.180
Rationale: oral corticosteroids are too strong	45	35.4	80	64.5	
Afraid that MDI use can lead to drug dependence (addiction)	61	48.0	56	45.2	0.240
Rationale: has relatives or friends who are addicted to MDIs	27	21.3	28	22.6	
Uses a nebulizer for the treatment of asthma	84	66.1	63	50.8	0.003
Rationale: believes that nebulizers are more effective than MDIs	43	33.9	47	37.9	
Believes that physical activity can aid in the treatment of asthma	89	70.1	73	58.9	0.002
Rationale: physical activity contributes to physical fitness	76	59.8	81	65.3	

MDI: metered dose inhaler (puffer/spray). *Chi-square test.

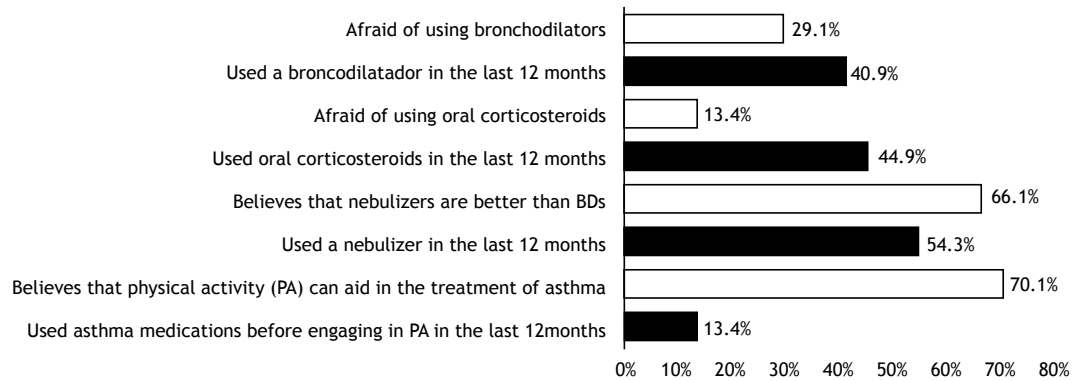

Figure 2. Asthma treatment characteristics in the patients studied.

Table 2. Comparison of myths about asthma, asthma treatment, medical monitoring, and asthma exacerbations between the groups of patients with controlled asthma (n = 54) and uncontrolled asthma (n = 60).

Variable	Controlled asthma		Uncontrolled asthma		p*
	n	%	n	%	
Myths and truths about asthma					
Is afraid of using MDIs for the treatment of asthma	17	31.5	17	28.3	0.715
Believes that MDI use for the treatment of asthma can lead to addiction	29	53.7	28	46.7	0.409
Is afraid of using oral corticosteroids for the treatment of asthma	5	9.3	9	15.0	0.395
Uses a nebulizer for the treatment of asthma	42	77.8	38	63.3	0.094
Believes that nebulizers are more effective than MDIs for the treatment of asthma	22	40.7	19	31.7	0.316
Believes that physical activity can aid in the treatment of asthma	37	68.5	48	80.0	0.169
Asthma treatment in the last 12 months					
The student uses asthma medications regularly	15	31.9	21	36.2	0.647
The student received MDI-delivered medications for the treatment of asthma	16	30.2	33	55.0	0.008
The student received oral corticosteroids for the treatment of asthma	22	41.5	32	53.3	0.211
The student received nebulizer-delivered inhaled medications for the treatment of asthma	26	49.1	40	66.7	0.059
The student used asthma medications before engaging in physical activity	5	9.4	12	20.0	0.119
Medical monitoring and asthma attacks in the last 12 months					
The student is followed at an outpatient clinic or public health care clinic for asthma	8	16.3	17	28.8	0.127
The student has a written treatment plan or prescription for asthma attacks	19	40.4	19	32.2	0.383
The student had a consultation for asthma (wheezing, dyspnea, or cough)	24	45.3	40	66.7	0.023
The student had wheezing during or after physical activity	22	41.5	42	71.2	0.002
The student had wheezing at rest, without having engaged in physical activity	19	35.8	37	61.7	0.006

MDI: metered dose inhaler (puffer/spray). *Chi-square test.

the treatment of asthma in their children, nearly half of the children and adolescents with asthma having used oral corticosteroids in the last 12 months. Currently, oral corticosteroids are reserved for patients with severe exacerbations. Increased oral corticosteroid use appears to be associated with long-term changes in bone mineral density in children and adolescents.[13] According to the 2014 revision of the GINA guidelines, short-acting β_2 agonists are safe for use in adults and children/adolescents and oral corticosteroids should be reserved for acute episodes of severe or complicated asthma, in which there is an incomplete response or worsening of symptoms after the use of short-term β_2 agonists.[1]

Another interesting finding of our study is that the vast majority of the parents or legal guardians in the asthma group reported that nebulizer use made them feel more confident and active in treating asthma. In addition, many reported feeling safer because treatment with nebulizers is more "natural", i.e., not as harmful to the health of children and adolescents as is treatment with bronchodilators. Zhang et al.[12] found that nonspecialists in children and adolescents with asthma prescribe nebulizers more often than they do other asthma medication delivery devices. Despite the technical ease of use of nebulizers, 80.6% of the parents were found to use them incorrectly at home, errors including nebulizer use during sleep and incorrect mask placement. For nearly two decades, nebulizers have not been the devices of choice for delivering inhaled asthma therapy to children and adolescents, regardless of their age.[14] Therefore, the use of MDIs with a spacer should be encouraged, and parents and patients should receive ongoing training in how to use MDIs correctly.

Most of our sample received their asthma medications free of charge. This finding could suggest that government provision of free medications is not enough to maintain population health. Effective public policies for the education, diagnosis, and monitoring of children and adolescents with asthma, together with a structured program for training not only health professionals but also patients and their parents or legal guardians, contribute to demystifying asthma treatment; myths and misconceptions are likely to have a negative impact on patient adherence to treatment, which is essential for improving patient quality of life.

Our results regarding asthma treatment in children and adolescents are not encouraging. As shown in Figure 2, only one third of the children and adolescents with asthma in the present study used prophylaxis or had a prescription or written treatment plan, nearly half had used oral corticosteroids at least once in the last 12 months, and three quarters of all parents or legal guardians admitted to forgetting to administer asthma medications to their children on a regular basis. No significant associations were found between popular myths about asthma treatment and the treatments

used. After the asthma group was divided into the controlled asthma group and the uncontrolled asthma group, no differences were found between popular myths and the treatments used, the exception being MDI use in the last 12 months: children and adolescents with uncontrolled asthma used MDIs more often than did those with controlled asthma. In addition, medical visits for asthma symptoms and asthma symptoms at rest or during physical activity were significantly more common in the uncontrolled asthma group than in the controlled asthma group (Table 2).

In a recent study conducted in Saudi Arabia,[15] the level of knowledge of asthma among parents of children with the disease was compared with the prevalence of controlled and uncontrolled asthma, and significant differences were found between the two groups regarding prolonged MDI use, the rationale being that MDIs can affect or harm the heart and should be administered only in the period between asthma attacks. The study found substantial gaps in knowledge among parents of children with asthma, including a lack of understanding of the disease, misconceptions regarding inhalers for the delivery of asthma medications, and misconceptions regarding asthma medication use. The aforementioned findings are consistent with ours, given that most of the parents or legal guardians in the present study reported being afraid of using MDIs prophylactically, believing that MDIs can cause heart problems and using MDI-delivered medication as rescue medication in children and adolescents with uncontrolled asthma (Table 2).

Most of our sample received their asthma medications free of charge. This is an indirect datum suggesting that government provision of free medications is not enough to maintain population health. Effective public policies for the education, diagnosis, and monitoring of children and adolescents with asthma, together with a structured program for training not only health professionals but also patients and their parents or legal guardians, contribute to demystifying asthma treatment; myths and misconceptions are likely to have a negative impact on patient adherence to treatment, which is essential for improving patient quality of life.

One limitation of our study is that there was a large loss to follow-up in phase 3; of the 605 schoolchildren who participated in phase 2, only 251 participated in phase 3. This was due to the fact that the schoolchildren were tested at primary health care clinics when they were not at school, and the presence of parents or legal guardians was required. However, for personal or professional reasons, the parents or legal guardians were often unable to accompany their children to the clinics. This bias might have selected, during that phase of the study, patients with disease that is more severe; however, the internal validity of the study is not affected if it is accepted that children and adolescents with disease that is more severe could have been selected for inclusion in the study sample. However, given the lack of published data on popular myths about asthma, which are highly prevalent in developing countries, the results of the present study are important and might lead to further studies, aimed at informing public programs for the management of asthma in children and adolescents.

In conclusion, our study shows that popular myths about asthma are common in the families of children and adolescents with asthma in a city in southern Brazil. Some of these myths can have a negative impact on the treatment and quality of life of these patients. Therefore, the lack of association between popular myths about asthma and the use of asthma medications in the present study indicates the need for studies involving larger samples. The continued development of asthma education programs for patients and the general population can serve as a strategy for gaining a deeper understanding of childhood asthma and improving asthma control in many countries, having a positive impact on public health.

REFERENCES

1. Global Initiative for Asthma [homepage on the Internet]. Bethesda: Global Strategy for Asthma Management and Prevention 2014; c2014 [cited 2015 Oct 1]. Available from: http://www.ginasthma.org/documents/4
2. Asher M, Weiland S. The International Study of Asthma and Allergies in Childhood (ISAAC). ISAAC Steering Committee. Clin Exp Allergy. 1998;28 Suppl 5:52-66; discussion 90-1. http://dx.doi.org/10.1046/j.1365-2222.1998.028s5052.x
3. Asher MI, Montefort S, Björkstén B, Lai CK, Strachan DP, Weiland SK, et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. Lancet. 2006;368(9537):733-43. Erratum in Lancet. 2007 Sep 29;370(9593):1128.
4. Carroll WD, Wildhaber J, Brand PL. Parent misperception of control in childhood/adolescent asthma: the Room to Breathe survey. Eur Respir J. 2012;39(1):90-6. http://dx.doi.org/10.1183/09031936.00048911
5. Klok T, Kaptein AA, Duiverman EJ, Brand PL. It's the adherence, stupid (that determines asthma control in preschool children). Eur Respir J. 2014;43(3):783-91. http://dx.doi.org/10.1183/09031936.00054613
6. Bourdin A, Halimi L, Vachier I, Paganin F, Lamouroux A, Gouitaa M, et al. Adherence in severe asthma. Clin Exp Allergy. 2012;42(11):1566-74. http://dx.doi.org/10.1111/j.1365-2222.2012.04018.x
7. Lougheed MD, Lemière C, Dell SD, Ducharme FM, FitzGerald JM, Leigh R, et al. Canadian Thoracic Society Asthma Management Continuum--2010 Consensus Summary for children six years of age and over, and adults. Can Respir J. 2010;17(1):15-24.
8. O'Laughlen MC, Rance K, Rovnyak V, Hollen PJ, Cabana MD. National Asthma Education Prevention Program: survey of nurse practitioners' knowledge, attitudes, and behaviors. J Ped Health Care. 2013;27(2):e17-24. http://dx.doi.org/10.1016/j.pedhc.2011.07.005
9. Martínez-Gimeno A. Onions, myths, beliefs, fashion and reality in asthma. Allergol Immunopathol (Madr). 2009;37(6):309-13. http://dx.doi.org/10.1016/j.aller.2009.10.004
10. Associação Brasileira de Empresas de Pesquisa--ABEP. [homepage on the Internet]. São Paulo: ABEP [cited 2015 Oct 1]. Critério de Classificação Econômica Brasil. Available from: http://www.abep.org/criterioBrasil.aspx
11. Strachan D, Sibbald B, Weiland S, Aït-Khaled N, Anabwani G, Anderson HR, et al. Worldwide variations in prevalence of symptoms of allergic rhinoconjunctivitis in children: the International Study of Asthma and Allergies in Childhood

(ISAAC). Pediatr Allergy Immunol. 1997;8(4):161-76. http://dx.doi.org/10.1111/j.1399-3038.1997.tb00156.x

12. Zhang L, Costa MG, Ávila LH, Bonfanti T, Ferruzzi EH. Asthma related knowledge among parents of asthmatic children at the moment of admission to a specialized service [Article in Portuguese]. Rev Assoc Med Bras. 2005;51(6):342-7. http://dx.doi.org/10.1590/S0104-42302005000600018
13. Donatti TL, Koch VH, Takayama L, Pereira RM. Effects of glucocorticoids on growth and bone mineralization. J Pediatr (Rio J). 2011;87(1):4-12. http://dx.doi.org/10.1590/S0021-75572011000100002
14. O'Callaghan C, Barry PW. How to choose delivery devices for asthma. Arch Dis Child. 2000;82(3):185-7. http://dx.doi.org/10.1136/adc.82.3.185
15. BinSaeed AA. Caregiver knowledge and its relationship to asthma control. J Asthma. 2014;51(8):870-5. http://dx.doi.org/10.3109/02770903.2014.906608

J Bras Pneumol. 2016;42(2):143-145
http://dx.doi.org/10.1590/S1806-37562015000000195

Influence of age and gender on the profile of exhaled volatile organic compounds analyzed by an electronic nose

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Submitted: 20 August 2015.
Accepted: 30 November 2015.

Study carried out in the Disciplina di Malattie dell'Apparato Respiratorio, Dipartimento di Scienze Mediche di Base, Neuroscienze e Organi di Senso, Scuola di Medicina, Università degli Studi di Bari, Bari, Italy.

ABSTRACT

We aimed to investigate the effects of age and gender on the profile of exhaled volatile organic compounds. We evaluated 68 healthy adult never-smokers, comparing them by age and by gender. Exhaled breath samples were analyzed by an electronic nose (e-nose), resulting in "breathprints". Principal component analysis and canonical discriminant analysis showed that older subjects (≥ 50 years of age) could not be distinguished from younger subjects on the basis of their breathprints, as well as that the breathprints of males could not distinguished from those of females (cross-validated accuracy, 60.3% and 57.4%, respectively).Therefore, age and gender do not seem to affect the overall profile of exhaled volatile organic compounds measured by an e-nose.

Keywords: Breath tests; Volatile organic compounds; Electronic nose.

Since the discovery of electronic noses, or e-noses, and of their application in the molecular profiling of exhaled breath (i.e., creation of breathprints), great advances have been made with respect to the discrimination of diseases through the comparison of overall breathprints. Numerous studies have shown the potential for applying exhaled volatile organic compound (VOC) profiling in three classes of respiratory diseases: lung cancer, respiratory infections, and obstructive lung diseases. After the ability of e-noses to sniff out these diseases was proven, the question of what constitutes the exhaled markers of those pathologies was raised. Because e-noses assess the overall mixture of VOCs in exhaled breath, no primary discriminating markers can be specified as being suggestive of the pathophysiological pathways involved. In addition, likely sources of signal interference must be identified and corrected for, because they are potentially confounding factors.[1] The exhaled VOC profile can be influenced by disease-associated factors, such as airway caliber and airway inflammation; treatment-associated factors, such as medication use; and patient-associated factors, such as age, gender, comorbidities, pregnancy, diet, and smoking.[2] Concerning age and gender, these two factors are known to alter VOC levels.[2] Previous studies on e-nose exhaled breath profiling in several diseases have suggested that age does not affect the overall VOC profile.[3,4] However, to our knowledge, there have been no studies specifically addressing e-nose analysis of exhaled biomarkers in relation to age and gender differences in healthy subjects. Therefore, the aim of the present study was to investigate the effects of age and gender on exhaled breath VOC profiles, as analyzed by an e-nose, in a population of healthy adults.

In this cross-sectional study, exhaled breath samples were obtained from 68 healthy adults between 20 and 68 years of age. Participants were volunteers recruited from among hospital staff members. We selected an equal number of individuals < 50 years of age (n = 34) and ≥ 50 years of age (n = 34). Of the 68 volunteers, 32 (47.1%) were male. All were never-smokers, none had a history of chest symptoms, and all were free of any known disease. All had an FEV_1 > 70% of the predicted value and an FEV_1/FVC ratio > 80%. None had experienced any upper or lower respiratory tract infections in the 4 weeks prior to the study. We evaluated the study sample by age group (< 50 vs. ≥ 50 years of age) and by gender. The study was approved by the Research Ethics Committee of the University of Bari School of Medicine, in the city of Bari, Italy (Protocol no. 46403/15), and all participating subjects gave written informed consent.

All measurements were obtained during a single visit. Subjects were asked to refrain from eating and drinking, as well as from engaging in strenuous physical exercise, for at least for 3 h before the visit.

Spirometry was performed by a trained lung function technician, in accordance with the latest European Respiratory Society recommendations,[5] and the equipment (MasterScreen Pneumo; Jaeger; Würzburg, Germany) was calibrated daily. For all subjects, FEV_1 and FVC were measured. Exhaled breath analysis was performed as previously described.[3] In brief, after 5 min of tidal breathing through a 3-way non-rebreathing valve connected to an inspiratory VOC filter (A2; North Safety, Middelburg, the Netherlands), subjects exhaled a single vital capacity volume into a Tedlar bag connected to an e-nose.

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Financial support: None.

We used a commercially available, handheld e-nose (Cyranose 320; Smith Detections, Pasadena, CA, USA) with a nanocomposite array of 32 organic polymer sensors. When the sensors are exposed to a mixture of VOCs, the polymers swell, inducing a change in their electrical resistance. The raw data are captured as the changes in resistance of each of the 32 sensors in an onboard database, producing a distribution profile (breathprint) that describes the VOC mixture and can be analyzed with pattern-recognition algorithms.[6]

The estimated sample size was based on data from previous studies.[3,4,7] We calculated the sample size by estimating the standard error of the percentage of correctly classified patients:

$$SE = \sqrt{(C(100 - C)/n)}$$

where *SE* is the standard error, *C* is the percentage of patients classified correctly, and *n* is the estimated sample size. The reliability of the percentage correct classification is dependent on the standard error, which is itself a function of p. If the percentage of patients classified correctly is between 50% and 75%, the current sample sizes per subgroup provide standard errors between 8% and 9%. The raw data were analyzed with the Statistical Package for the Social Sciences, version 16.0 (SPSS Inc., Chicago, IL, USA). Data were reduced to a set of principal components capturing the largest amount of variance of the original 32 sensors. To select the principal components which best discriminated among the groups, we used one-way ANOVA. Afterwards, these principal components were then used in a canonical discriminant analysis (CDA), in order to classify cases into a categorical partition. Using the "leave-one-out" method, we calculated the cross-validated accuracy (CVA), which is expressed as a percentage. The CVA provides an estimate of how accurately a predictive model will perform in practice. For each case, the probability of a positive diagnosis was calculated on the basis of the linear canonical discriminant function.

The characteristics of the study population, as a whole and by age group, are described in Table 1. No significant differences were found for FEV_1, although there was a slight difference between the two age groups in terms of the BMI. The two-dimensional principal component analysis plot showed that the breathprints of older subjects could not be distinguished from those of younger subjects (Figure 1). The CDA of those data showed a CVA of 60.3%, indicating that the difference was not significant. Similarly, the breathprints of males could not be distinguished from those of females (Figure 1), the CDA showing a CVA of 57.4%, also indicating a less than significant difference.

Our results suggest that, although aging modifies the individual components of exhaled breath, the overall VOC profile, as measured by an e-nose, does not differ between age groups. Likewise, gender seems to have no influence on the exhaled VOC spectrum.

To our knowledge, this is the first study specifically addressing e-nose-analyzed exhaled biomarkers in relation to age and gender in well-characterized healthy subjects. Research on age- and gender-specific metabolic dissimilarities is essential for understanding the physiological and metabolic phenotype of healthy subjects. It is known that the number of neutrophils in induced sputum increase with advancing age,[8,9] as does the CD4+/CD8+ lymphocyte ratio in BAL fluid.[10] These data are consistent with those of studies showing that, with aging, oxidative stress increases and clearance of cytochrome p450 decreases.[11] In addition, various studies have shown gender-specific metabolomic profiles in the urine and serum of healthy subjects.[12] However, there have been few studies focusing on exhaled human breath. Furthermore, studies employing gas chromatography-mass spectrometry analysis have demonstrated that there are age-related changes in the VOC profile of exhaled air in healthy individuals.[13] Bikov et al. found a significant correlation between e-nose-analyzed breathprints and age only in lung cancer patients.[7] Conversely, studies have shown that the ability of an e-nose to distinguish among healthy controls, individuals with asthma, and individuals with COPD is not influenced by differences in age.[3,4] Only a few studies have identified gender-specific VOCs in human exhaled breath, as analyzed by gas chromatography-mass spectrometry.[14,15] A very recent study using an e-nose showed that gender has an effect on the classification of breathprints in high-risk smokers.[16]

How can we explain our results? Human exhaled breath contains more than 3,000 VOCs deriving from physiologic and pathophysiological mechanisms operating via metabolic pathways.[8] In accordance with the findings of previous studies, our data suggest that, despite the presence of age- and gender-specific VOCs in healthy human exhaled breath, the overall VOC profile does not seem to be influenced by either age or gender.

What are the implications of our findings? Our results indicate that careful age- and gender-matching might not be necessary in future comparative studies.

Table 1. Clinical characteristics of a sample of healthy adult never-smokers.[a]

Characteristic	All subjects (n = 68)	< 50 years of age (n = 34)	≥ 50 years of age (n = 34)	p*
Female gender, n (%)	36 (52.9)	7 (20.6)	12 (35.3)	-
Age (years)	43.2 ± 11.3	33.1 ± 8.0	55.6 ± 4.7	< 0.01
FEV_1 (% of predicted)	104.7 ± 11.8	106.2 ± 11.3	103.3 ± 12.3	ns
BMI (kg/m^2)	25.25 ± 3.3	24.8 ± 3.8	25.7 ± 2.9	< 0.05

[a]Values are expressed as mean ± SD, except where otherwise indicated. *ANOVA between the two groups.

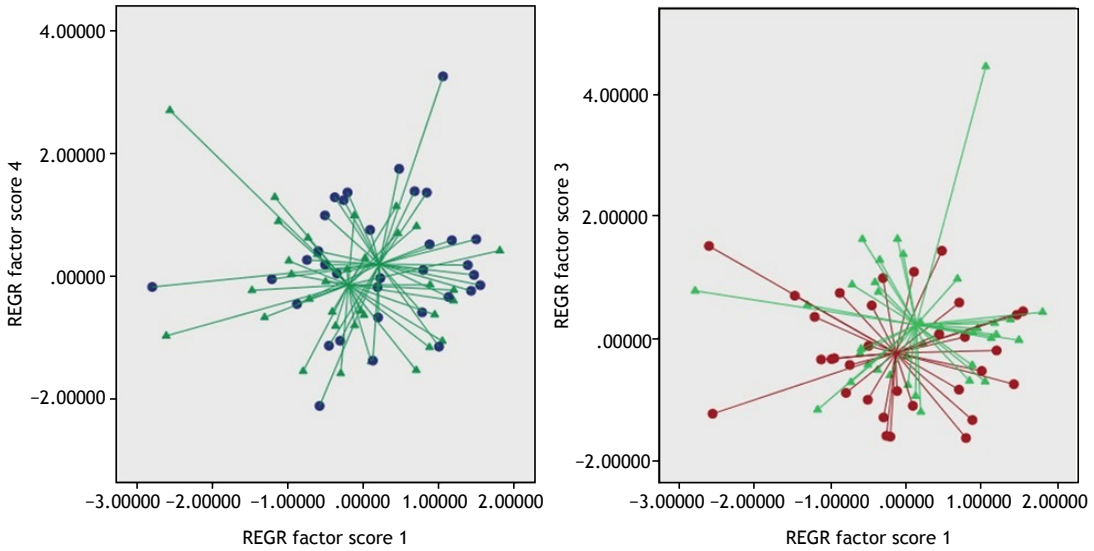

Figure 1. Two dimensional principal component analysis plot, showing that exhaled breath profiles (breathprints) of subjects ≥ 50 years of age (left, triangles) are indistinguishable from those of subjects < 50 years of age (left, circles). Similarly the breathprints of male subjects (right, circles) could not be distinguished from those of female subjects (right, triangles). REGR: relative elemental growth rate.

Nevertheless, further studies with larger populations are needed in order to confirm our findings and to investigate other possible confounding factors, such as pregnancy, medication, diet, and smoking.

REFERENCES

1. Friedrich MJ. Scientists seek to sniff out diseases: electronic "noses" may someday be diagnostic tools. JAMA. 2009;301(6):5856. http://dx.doi.org/10.1001/jama.2009.90
2. van der Schee MP, Paff T, Brinkman P, van Aalderen WM, Haarman EG, Sterk PJ. Breathomics in lung disease. Chest. 2015;147(1):224-31. http://dx.doi.org/10.1378/chest.14-0781
3. Dragonieri S, Schot R, Mertens BJ, Le Cessie S, Gauw SA, Spanevello A, et al. An electronic nose in the discrimination of patients with asthma and controls. J Allergy Clin Immunol. 2007;120(4):856-62. http://dx.doi.org/10.1016/j.jaci.2007.05.043
4. Fens N, de Nijs SB, Peters S, Dekker T, Knobel HH, Vink TJ, et al. Exhaled air molecular profiling in relation to inflammatory subtype and activity in COPD. Eur Respir J. 2011;38(6):1301-9. http://dx.doi.org/10.1183/09031936.00032911
5. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardization of spirometry. Eur Respir J. 2005;26(2):319-38. http://dx.doi.org/10.1183/09031936.05.00034805
6. Röck F, Barsan N, Weimar U. Electronic nose: current status and future trends. Chem Rev. 2008;108(2);705-25. http://dx.doi.org/10.1021/cr068121q
7. Bikov A, Hernadi M, Korosi BZ, Kunos L, Zsamboki G, Sutto Z, et al. Expiratory flow rate, breath hold and anatomic dead space influence electronic nose ability to detect lung cancer. BMC Pulm Med. 2014;14:202. http://dx.doi.org/10.1186/1471-2466-14-202
8. Thomas RA, Green RH, Brightling CE, Birring SS, Parker D, Wardlaw AJ, et al. The influence of age on induced sputum differential cell counts in normal subjects. Chest. 2004;126(6):1811-4. http://dx.doi.org/10.1016/S0012-3692(15)31427-6
9. Malerba M, Balbi B, Spanevello A. Aging and induced-sputum cells. Chest. 2005;128(6):4049-50. http://dx.doi.org/10.1378/chest.128.6.4049
10. Meyer KC, Ershler W, Rosenthal NS, Lu XG, Peterson K. Immune dysregulation in the aging human lung. Am J Respir Crit Care Med. 1996;153(3):1072-9. http://dx.doi.org/10.1164/ajrccm.153.3.8630547
11. Scheller U, Zimmer T, Kärgel E, Schunck WH. Characterization of the n-alkane and fatty acid hydroxylating cytochrome P450 forms 52A3 and 52A4. Arch Biochem Biophys. 1996;328(2):245-54. http://dx.doi.org/10.1006/abbi.1996.0170
12. Jain RB. Distributions of selected urinary metabolites of volatile organic compounds by age, gender, race/ethnicity, and smoking status in a representative sample of U.S. adults. Environ Toxicol Pharmacol. 2015;40(2):471-9. http://dx.doi.org/10.1016/j.etap.2015.07.018
13. Philips M, Cataneo RN, Greenberg J, Gunawardena R, Naidu A, Rahbari-Oskoui F. Effect of age on the breath methylated alkane contour, a display of apparent new markers of oxidative stress. J Lab Clin Med. 2000;136(3):243-9. http://dx.doi.org/10.1067/mlc.2000.108943
14. Ben-Zaken Cohen S, Paré PD, Man SF, Sin DD. The growing burden of chronic obstructive pulmonary disease and lung cancer in women: examining sex differences in cigarette smoke metabolism. Am J Respir Crit Care Med. 2007;176(2):113-20. http://dx.doi.org/10.1164/rccm.200611-1655PP
15. Das MK, Bishwal SC, Das A, Dabral D, Varshney A, Badireddy VK, et al. Investigation of gender-specific exhaled breath volatome in humans by GCxGC-TOF-MS. Anal Chem. 2014;86(2):1229-37. http://dx.doi.org/10.1021/ac403541a
16. McWilliams A, Beigi P, Srinidhi A, Lam S, MacAulay CE. Sex and Smoking Status Effects on the Early Detection of Early Lung Cancer in High-Risk Smokers Using an Electronic Nose. IEEE Trans Biomed Eng. 2015;62(8):2044-54. http://dx.doi.org/10.1109/TBME.2015.2409092

J Bras Pneumol. 2016;42(2):146-154
http://dx.doi.org/10.1590/S1806-37562016042020068

REVIEW ARTICLE

New anticoagulants for the treatment of venous thromboembolism

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Submitted: 2 March 2016.
Accepted: 22 March 2016.

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ABSTRACT

Worldwide, venous thromboembolism (VTE) is among the leading causes of death from cardiovascular disease, surpassed only by acute myocardial infarction and stroke. The spectrum of VTE presentations ranges, by degree of severity, from deep vein thrombosis to acute pulmonary thromboembolism. Treatment is based on full anticoagulation of the patients. For many decades, it has been known that anticoagulation directly affects the mortality associated with VTE. Until the beginning of this century, anticoagulant therapy was based on the use of unfractionated or low-molecular-weight heparin and vitamin K antagonists, warfarin in particular. Over the past decades, new classes of anticoagulants have been developed, such as factor Xa inhibitors and direct thrombin inhibitors, which significantly changed the therapeutic arsenal against VTE, due to their efficacy and safety when compared with the conventional treatment. The focus of this review was on evaluating the role of these new anticoagulants in this clinical context.

Keywords: Blood coagulation; Venous thromboembolism\therapy; Venous thromboembolism\prevention and control.

INTRODUCTION

Worldwide, venous thromboembolism (VTE) is the third leading cause of cardiovascular mortality, surpassed only by myocardial infarction and stroke,[1,2] and affects patients in various populations, including the pediatric population.[3,4] Deep vein thrombosis (DVT) is the most prevalent presentation of VTE, and its most severe form is acute pulmonary thromboembolism (PTE).[5] In both situations, the main treatment consists of full anticoagulation and is aimed at reducing VTE recurrence. Studies conducted in the 1960s systematically showed that anticoagulants reduce mortality when administered to patients with VTE in general[6] and to those with PTE in particular.[7]

Despite the fact that the anticoagulation cascade (Figure 1) has long been known, the choice of drugs that could actually influence it was initially limited. Although traditional anticoagulants were effective in the treatment of VTE,[8] practical difficulties in their management led to the development of new drugs for this purpose. Two groups of oral anticoagulants—factor Xa inhibitors (rivaroxaban, apixaban, and edoxaban) and direct thrombin inhibitors (dabigatran)—have recently been made available, and the evidence that justifies their use in VTE will be discussed below.

CLASSIC ANTICOAGULATION AND WARFARIN

The American College of Chest Physicians (ACCP) recommends, for teaching purposes, that VTE treatment be divided into three periods: an initial period, from diagnosis to the seventh day; a long-term period; and an extended period. In the initial period, an intravenous anticoagulant (unfractionated heparin) or a subcutaneous anticoagulant (enoxaparin, nadroparin, dalteparin, tinzaparin, or fondaparinux) is classically used. Subsequently, in the long-term period, intravenous or subcutaneous therapy is switched to oral therapy, which should be maintained for at least 3 months. The most extensively studied drugs in this condition are vitamin K antagonists, of which warfarin is the most prominent representative. Warfarin produces its effect by interfering with the cyclic interconversion of vitamin K and vitamin K 2,3-epoxide, thus blocking vitamin K-dependent coagulation factor synthesis (factors II, VII, IX, and X). Therefore, the anticoagulant effect of warfarin does not occur until the factors already present in the circulation are metabolized, a process that typically takes 36-72 h. During the first days of warfarin treatment, prolongation of the prothrombin time reflects only the loss of factor VII (the half-life of which is 5-7 h), and this does not represent adequate anticoagulation, given that the intrinsic clotting pathway remains functional. Efficient blockade of this pathway takes about 5 days (hence the ACCP recommendation to maintain intravenous or subcutaneous anticoagulant therapy during this period). After 3 months, at the end of the long-term period, the need to continue anticoagulant therapy should be assessed, and, that being the case, this extended period should last as long as the benefits of anticoagulation (prevention of VTE recurrence) surpass its potential harms (risk of bleeding).[9]

Warfarin treatment in the long-term and extended periods has proven to be effective in preventing VTE

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Financial support: None.

ISSN 1806-3713

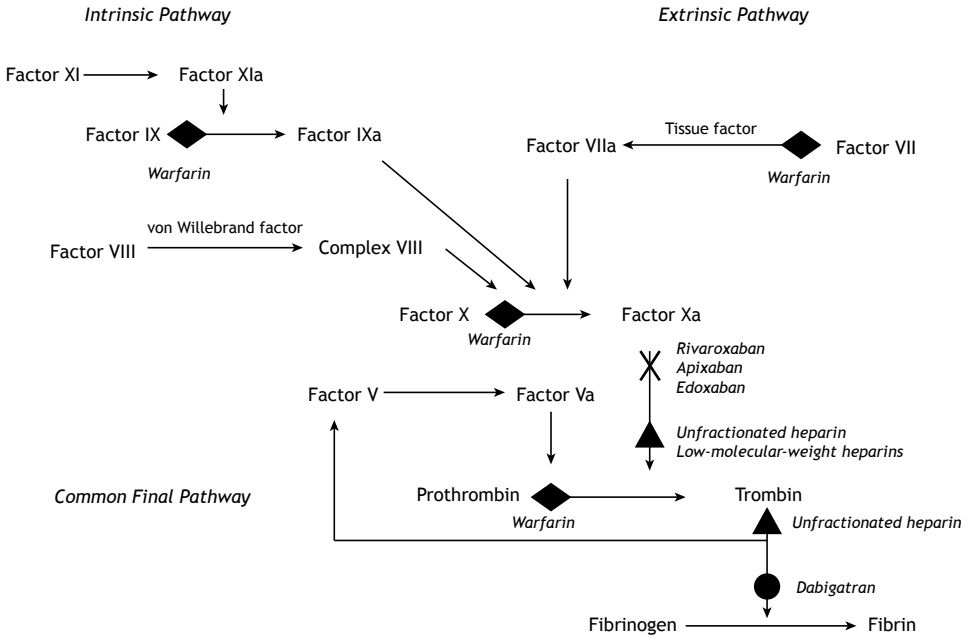

Figure 1. Anticoagulation cascade with the sites of action of the anticoagulants.

recurrence.[10,11] A meta-analysis of 8 randomized studies involving 2,994 patients with PTE showed that patients who were treated with warfarin for an extended period were less likely to have recurrence (OR = 0.18; 95% CI: 0.13-0.26) than were those in whom warfarin was discontinued after 1-4 months of treatment.[12]

Despite being effective, the use of warfarin has a number of drawbacks.[13] Given the narrow therapeutic range of warfarin, there is a need for constant monitoring of its action, which is not always feasible. Recent data from the first cohort of the Global Anticoagulant Registry in the Field (GARFIELD) studyshow that, among 6,047 patients on vitamin K antagonists, monitoring of drug action via the international normalized ratio (INR) was recorded for only 3,952 patients, and only 1,660 had a therapeutic level that met the current recommendation, with a time in therapeutic range (TTR) above 60%.[14] This is particularly true in Brazil. The Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) study showed that, whereas worldwide the mean TTR of the 6,000 patients on warfarin was 64%, it was only 54% among those in Brazil[15]; that is, even in a situation that is closer to optimal than is clinical practice, within an international research protocol, the reality is that maintaining a warfarin-treated patient within an appropriate therapeutic range is costly and complex.

Another difficulty with the use of warfarin is the issue of safety. As with any anticoagulant, there is the fear of bleeding as a side effect of its use.[16] An argument in favor of the use of warfarin is the theoretical possibility of monitoring the intensity of anticoagulation, via the INR (prothrombin time test results). Therefore, if a patient had an INR within the therapeutic range (between 2 and 3), the risk of bleeding would be minimal or nonexistent. However, evidence from the most recent studies shows that, whereas patients with a TTR above 60% have a lower rate of VTE recurrence, the same is not true for the bleeding rates.[17] In other words, keeping INR levels stable and within the recommended range does not reduce the risk of bleeding; it affects only the risk of recurrence.

Other drawbacks of the use of warfarin include multiple food and drug interactions, impairment of patient quality of life, and difficulty of management for physicians, which ultimately implies suboptimal therapy, given the fear of adverse events.[13]

Based on the problems experienced in the use of vitamin K antagonists, it is possible to devise some theoretical characteristics of an optimal anticoagulant: oral administration; a rapid onset of action; a short half-life; a wide therapeutic margin; therapeutic effect prediction with a fixed dose or based on body weight; few drug or food interactions; monitoring not required (but possible if desired); well-established pharmacokinetics in the presence of hepatic or renal failure; easily reversible effects in the presence of bleeding; and cost-effectiveness. These principles have led, in the last decade, to the emergence of new anticoagulants (Table 1) with properties aimed at filling such gaps, thereby improving outpatient anticoagulation in patients with VTE, which, in the last 50 years, has remained at the same level and has been based on the use of vitamin K antagonists.

DABIGATRAN

Dabigatran is a direct thrombin (or factor II) inhibitor. It is an oral drug that is administered in prodrug form,

with no interaction with food. Its onset of action occurs within 2 h of administration, and its half-life is 12-17 h. Because 80% of dabigatran is excreted by the kidneys, its use is contraindicated in patients with a creatinine clearance < 30 mL/min. Its bioavailability is 3-7% of the administered dose. Dabigatran causes clinically relevant dyspepsia in 5-10% of cases, and concomitant proton pump inhibitor use reduces dabigatran absorption by 20-30%.[18]

Dabigatran was the first new anticoagulant to be systematically evaluated for the treatment of VTE. In one study,[19] 2,539 patients with acute VTE (70% with DVT, 20% with PTE, and 10% with both) were randomized, after being treated with full-dose enoxaparin for 5 days, to receive either dabigatran 150 mg every 12 h or warfarin. After 6 months of treatment, dabigatran proved to be as effective as warfarin in preventing VTE recurrence (2.4% vs. 2.1%; p < 0.001 for non-inferiority). Dabigatran proved to be superior to the conventional treatment in terms of "any bleeding" (16.1% vs. 21.9%; 95% CI: 0.59-0.85) and to be equivalent to it in terms of "major bleeding" (1.6% vs. 1.9%; 95% CI: 0.45-1.48). Of the patients on dabigatran, 9% had to discontinue treatment because of adverse events, compared with 6.8% of the patients on warfarin (p = 0.05).[19]

The initial data on dabigatran were quite encouraging. Dabigatran proved to be as effective as and potentially safer than the conventional treatment of VTE, if not in the initial period then at least in the long-term period. Extended treatment of VTE with dabigatran was evaluated in two randomized, double-blind trials.[20] In those trials, patients who had been on full anticoagulation for at least 3 months were randomized to receive dabigatran, warfarin, or placebo for 18 months, on average. In the dabigatran vs. warfarin study, 26 of a total of 1,430 patients in the dabigatran group (1.8%) had VTE recurrence, compared with 18 of 1,426 patients in the warfarin group (1.3%; p = 0.01 for non-inferiority). Major bleeding occurred at similar rates (0.9% in the dabigatran group vs. 1.8% in the warfarin group; 95% CI: 0.27-1.02). In terms of "all types of bleeding", dabigatran proved to be superior to warfarin (relative risk [RR] = 0.54; 95% CI: 0.41-0.71). Of note in that study is that patients in the dabigatran group had a higher rate of acute coronary syndrome events than did those in the warfarin group (0.9% vs. 0.2%; p = 0.02). In the dabigatran vs. placebo study, VTE recurred in 3 of 681 patients (0.4%) in the dabigatran group and in 37 of 681 patients (5.6%) in the placebo group (p < 0.001). Major bleeding occurred in 0.3% of the patients in the dabigatran group and in none of those in the placebo group. "Any bleeding" occurred in 5.3% of the patients in the dabigatran group and in 1.8% of those in the placebo group (RR = 2.92; 95% CI: 1.52-5.60). There were no differences in the rate of acute coronary syndrome events.[20]

Although the finding related to coronary events in long-term studies was striking, as was some difficulty in profiling adverse events, especially adverse gastrointestinal events, dabigatran proved to be a viable, effective, and potentially safer alternative to warfarin for the treatment of VTE, both in the long-term period and in the extended period. Caution is recommended if dabigatran is used in patients with a history of

Table 1. Studies of new oral anticoagulants for the treatment of venous thromboembolism.

Drug	Mechanism	Study	Doses	Treatment duration, months	Efficacy (fatal VTE recurrence; non-inferiority))	Safety (MB or MRB)
Dabigatran	Thrombin inhibitor	Schulman et al.[19]	Enoxaparin/ dabigatran 150 mg every 12 h	6	Dabigatran (2.4%) vs. warfarin (2.1%)	MB: dabigatran (1.6%) vs. warfarin (1.9%)
Dabigatran		Schulman et al.[47]	Enoxaparin/ dabigatran 150 mg every 12 h	6	Dabigatran (2.3%) vs. warfarin (2.2%)	MB: dabigatran (0.3%) vs. warfarin (0.0%)
Rivaroxaban	Factor Xa inhibitor	EINSTEIN Investigators et al.[21]	Rivaroxaban 15 mg every 12 h for 3 weeks; 20 mg/day	3, 6, or 12	Rivaroxaban (2.1%) vs. warfarin (3.0%)	MRB: rivaroxaban (8.1%) vs. warfarin (8.1%)
Rivaroxaban		EINSTEIN Investigators et al.[22]	Rivaroxaban 15 mg every 12 h for 3 weeks; 20 mg/day	3, 6, or 12	Rivaroxaban (2.1%) vs. warfarin (1.8%)	MRB: rivaroxaban (10.3%) vs. warfarin (11.4%)
Apixaban	Factor Xa inhibitor	Agnelli et al.[23,24]	Apixaban 10 mg every 12 h for 7 days; 5 mg every 12 h	6	Apixaban (2.3%) vs. warfarin (2.7%)	MB: apixaban (0.6%) vs. warfarin (1.8%)
Edoxaban	Factor Xa inhibitor	Hokusai-VTE Investigators et al.[25]	Low-molecular-weight heparin for 5 days; edoxaban 60 mg/day	3-12	Edoxaban (3.2%) vs. warfarin (3.5%)	MRB: edoxaban (8.5%) vs. warfarin (10.3%)

VTE: venous thromboembolism; MB: major bleeding; and MRB: major/relevant bleeding.

coronary artery disease, dyspepsia, or renal failure. The recommended dose for VTE treatment with dabigatran, following a 5-day course of parenteral or subcutaneous anticoagulation, is 150 mg every 12 h. If the estimated creatinine clearance is < 30 mL/min, dabigatran is contraindicated. Patients with a creatinine clearance of 30-50 mL/min and > 80 years of age should use a 110-mg dose every 12 h, as should those who are at high risk of bleeding. A 110-mg dose every 12 h can also be considered for patients > 80 years of age even if they have a creatinine clearance > 50 mL/min.

RIVAROXABAN

Rivaroxaban is a factor Xa antagonist. It is an oral drug that is administered in its active form. Its onset of action occurs within 2-3 h of administration. The bioavailability of rivaroxaban is increased when it is administered with food (66% without food and 100% with food); it is therefore recommended that it be administered with food. No significant dyspeptic effects or reduction in rivaroxaban absorption are observed with concomitant use of proton pump inhibitors. Approximately 35% of rivaroxaban is excreted by the kidneys; its half-life is 5-9 h in young individuals and 11-13 h in elderly individuals. There is interaction with drugs that are metabolized by (hepatic) cytochrome CYP3A4, such as ketoconazole, ritonavir, clarithromycin, and erythromycin.[18]

The first randomized study evaluating rivaroxaban in patients with VTE was published in 2010. The EINSTEIN program produced significant advances in this field in two aspects: patients with DVT[21] and patients with PTE[22] were evaluated separately, the latter being known to be patients with different severity of disease and different prognoses; and the protocols of the randomized trials were the first to propose replacing the intravenous or subcutaneous anticoagulation of the initial phase after the diagnosis of VTE directly with an oral drug, inaugurating the single drug approach. Therefore, the proposal was to treat the episode of VTE (either DVT or PTE) with a single oral drug from diagnosis through the long-term period (up to 3 months) and the extended period.

In the study published in 2010, called EINSTEIN-DVT,[21] 3,449 patients with DVT were randomized to receive either rivaroxaban (15 mg every 12 h for 3 weeks, followed by 20 mg every 24 h for 3, 6, or 12 months after the diagnosis of acute VTE) or enoxaparin (1 mg/kg every 12 h for at least 5 days, followed by warfarin for the same period). Rivaroxaban proved to be as effective as the conventional treatment in terms of the rate of VTE recurrence (2.1% vs. 3.0%; $p < 0.001$ for non-inferiority). The bleeding rate was identical in the two groups (8.1%). In addition, the same study included a group called EINSTEIN-Extension, in which, after being treated for VTE for at least 3 months, 1,196 patients were randomized to receive either rivaroxaban or placebo for 12 months. There was VTE recurrence in 1.3% of the patients who received rivaroxaban, compared with 7.1% of the patients in the placebo group ($p < 0.001$), and 0.7% of the patients in the rivaroxaban group had nonfatal major bleeding, compared with none in the placebo group ($p = 0.11$).[21]

In 2012, the EINSTEIN-PE (Pulmonary Embolism) study was published.[22] In that study, 4,832 patients with acute PTE were randomized to receive either rivaroxaban (15 mg every 12 h for 3 weeks, followed by 20 mg/day for 3, 6, or 12 months after the diagnosis of acute PTE) or enoxaparin (1 mg/kg every 12 h for at least 5 days, followed by warfarin for the same period). Rivaroxaban proved to be as effective as the conventional treatment with warfarin in terms of the rate of VTE recurrence (2.1% vs. 1.8%; $p = 0.003$ for non-inferiority). The bleeding rate in the rivaroxaban and conventional treatment groups was 10.3% and 11.4%, respectively ($p = 0.23$). However, rivaroxaban had a quite favorable result in terms of "major bleeding" when compared with warfarin: 1.1% vs. 2.2% (RR = 0.49; 95% CI: 0.31-0.79; $p = 0.003$). This benefit in terms of major bleeding occurred early in therapy and is therefore not due only to the presence of warfarin in the conventional treatment. Even in the initial period of enoxaparin therapy, rivaroxaban had a better safety profile than did the conventional treatment. It is worth emphasizing that patients who had hemodynamic instability or required thrombolytic therapy were not included in that study.[22]

The studies comprising the EINSTEIN program showed that rivaroxaban was as effective as the conventional treatment (enoxaparin in the acute phase and warfarin in the long-term and extended periods) in the treatment of acute VTE, providing significant benefits in the rate of major bleeding. Therefore, it became possible to administer a single drug, from the time the diagnosis is made, for the treatment of both DVT and PTE, with similar efficacy to and with potentially greater safety than that of the conventional treatment.

For the treatment of VTE, rivaroxaban should be used at a dose of 15 mg every 12 h for 3 weeks. Thereafter, for the long-term and extended treatment periods, a dose of 20 mg/day is recommended. During these periods, if the patient has a creatinine clearance of 15-50 mL/min or is > 75 years of age, the recommended dose is 15 mg/day. For patients with a creatinine clearance < 15 mL/min, the use of rivaroxaban in not recommended. The convenient dosing schedule (a single daily dose) is a factor to be considered, because it can influence patient adherence to the treatment, improving its results. However, it is important to emphasize to patients that strict adherence to rivaroxaban therapy is necessary, given that missing even a single dose is sufficient to reverse its anticoagulant effect, leaving patients unprotected and therefore susceptible to having another VTE event.

APIXABAN

Apixaban is a factor Xa antagonist. It is an oral drug that is administered in its active form. Its onset of action

occurs within 3 h of administration. The bioavailability of apixaban is 50% and does not depend on food. No significant dyspeptic effects or reduction in apixaban absorption are observed with concomitant use of proton pump inhibitors. Approximately 27% of apixaban is excreted by the kidneys, and its half-life is 12 h. There is mild interaction with drugs that are metabolized by (hepatic) cytochrome CYP3A4.[18]

In 2013, the results of the Apixaban for the initial Management of PuLmonary embolism and deep-vein thrombosis as fIrst-line therapY (AMPLIFY) trial were published.[23] In that trial, 5,395 patients with acute VTE (65% with DVT, 25% with PTE; and 10% with both) were randomized to receive either apixaban (10 mg every 12 h for 7 days, followed by 5 mg every 12 h for 6 months); or conventional anticoagulant therapy—subcutaneous enoxaparin followed by warfarin. Again the choice was to use a single drug, from the time the diagnosis of VTE was made. Apixaban was as effective as the conventional treatment in terms of VTE recurrence (2.3% vs. 2.7%; $p < 0.001$ for non-inferiority). Apixaban had a better safety profile, with a rate of major bleeding of 0.6%, compared with 1.8% for the conventional treatment (RR = 0.31; 95% CI: 0.17-0.55; $p < 0.001$).

Another study, the AMPLIFY-Extension trial, was published in 2013.[24] In that study, 2,486 patients with VTE who had completed 6 to 12 months of treatment with anticoagulants were randomized to receive apixaban 2.5 mg every 12 h, apixaban 5 mg every 12 h, or placebo (all of which were administered for 12 months). The rate of VTE recurrence was 8.8% in the placebo group, 1.7% in the apixaban 2.5 mg group, and 1.7% in the apixaban 5 mg group ($p < 0.001$ for both comparisons with the placebo group). The safety results reported in that study were also quite significant: the rates of major bleeding were 0.5%, 0.2%, and 0.1%, respectively, in the placebo, apixaban 2.5 mg, and apixaban 5 mg groups, whereas the rates of minor bleeding were 2.3%, 3.0%, and 4.2%.

Studies based on the AMPLIFY trials reported that apixaban has a good efficacy profile and superior efficacy when compared with the conventional treatment, being another drug that can be used as an anticoagulant in the initial phase of the treatment of VTE. In addition, full-dose and prophylactic dose apixaban was shown to have an excellent safety profile in the extended treatment period, preventing late VTE recurrence without increasing the bleeding rates.

The dosing schedule of apixaban for VTE treatment is 10 mg every 12 h for 7 days. Thereafter, a dose of 5 mg every 12 h is used for 6 months (as per the AMPLIFY algorithm). If the patient has two of these three characteristics—age > 80 years, weight < 60 kg, and serum creatinine < 1.5 mg/dL—the dose should be reduced to 2.5 mg every 12 h after the first week of treatment with the full dose. After the 6 months of treatment, during the extended period, the dose used as prophylaxis against VTE recurrence is 2.5 mg every 12 h.

EDOXABAN

Edoxaban is a factor Xa antagonist. It is an oral drug that is administered in its active form. The bioavailability of edoxaban is 62%, and its absorption is increased by 6-22% when it is administered with food. However, there is no recommendation that edoxaban be administered concomitantly with food. No significant dyspeptic effects or reduction in edoxaban absorption are observed with concomitant use of proton pump inhibitors. Approximately 50% of edoxaban is excreted by the kidneys, and its half-life is 9-11 h. There is minimal interaction with drugs that are metabolized by (hepatic) cytochrome CYP3A4, and less than 4% of edoxaban is eliminated by the liver.[18]

In 2013, a study called the Hokusai-VTE trial was published.[25] Unlike the literature trend for factor Xa antagonists, the authors chose to test the drug only in the extended period of the treatment of VTE and not in the initial phase. Therefore, 4,921 patients with DVT and 3,319 patients with PTE were randomized, after being treated with either unfractionated heparin or enoxaparin for at least 5 days, to receive either edoxaban (60 mg/day or 30 mg/day in patients with a body weight < 60 kg or a creatinine clearance of 30-50 mL/min) or warfarin, for a period ranging from 3 to 12 months. Edoxaban was as effective as warfarin for the prevention of VTE recurrence (recurrence rate: 3.2% in the edoxaban group vs. 3.5% in the warfarin group; $p < 0.001$ for non-inferiority). Edoxaban was superior to warfarin for clinically relevant bleeding (8.5% vs. 10.3%; $p = 0.004$) and similar with regard to major bleeding (1.4% vs. 1.6%; 95% CI: 0.59-1.21). A peculiarity of the Hokusai-VTE trial was the inclusion of a greater number of patients with PTE and some evidence of right ventricular dysfunction (as assessed by measurement of N-terminal pro-brain natriuretic peptide levels and CT measurement of right ventricular dimensions); therefore, those patients were potentially more severely ill. Among those 938 patients, the use of edoxaban resulted in a lower rate of VTE recurrence than did the use of warfarin (3.3% vs. 6.2%; RR = 0.52; 95% CI: 0.28-0.98).[25]

The Hokusai-VTE study[25] proved to be quite robust in acute VTE, showing that edoxaban is not inferior to warfarin, with it possibly being superior to warfarin for patients with PTE and right ventricular dysfunction and potentially being beneficial in terms of bleeding. However, despite the convenient dosing schedule (once daily), the study design does not allow for the use of edoxaban as a single drug, and its administration should be preceded by at least 5 days of some type of intravenous or subcutaneous anticoagulation.

The recommended dose of edoxaban is the same as that used in the Hokusai-VTE study[25]: 60 mg/day. In patients with a body weight < 60 kg or a creatinine clearance of 15-50 mL/min, a dose of 30 mg/day is recommended. The dosing schedule is also convenient in this case, and this can influence patient adherence to treatment, improving its results. The limitation that

edoxaban cannot be used in the initial treatment of VTE should be emphasized.

SPECIAL SITUATIONS FOR USE OF THE NEW ANTICOAGULANTS

Renal failure and advanced age

Chronic renal failure is a well-known risk factor for the development of VTE as well as for bleeding, with or without anticoagulant therapy.[26] Likewise, age is a known risk factor for the development of VTE. The risk of VTE is known to be 4 to 6 times higher in patients > 70 years of age and to double every decade of life.[27,28] In addition, age alone is a determinant of outcome in pulmonary embolism, with the risk of death from a thromboembolic event being 2.3 times higher in patients > 75 years of age than in the younger population.[29] However, elderly patients and patients with renal failure are both at an increased risk of bleeding while taking anticoagulants.[30,31] In addition, patients who are elderly or have renal failure tend to have a larger number of comorbidities, which makes it difficult to manage the anticoagulant therapy.

Elderly patients and patients with renal failure were both analyzed in the aforementioned large-scale studies of new anticoagulants.[19-25] A recent meta-analysis[32] evaluated these subgroups of patients and showed that the new anticoagulants have a better safety and efficacy profile in elderly patients, as well as having a safety and efficacy profile comparable to that of the conventional treatment in patients with renal failure. In fact, this so-called fragile population (those who are elderly and/or have renal failure and/or are at extreme levels of body weight) is the population that most benefits from the use of the new drugs, whether in terms of efficacy or, especially, in terms of safety.

Cancer

Cancer patients are at an increased risk both for thromboembolic events in general and for disease manifestations of greater severity.[33] Approximately 10-20% of VTE patients have a history of or have active cancer.[34] In contrast, cancer patients are at a 4- to 7-times higher risk of developing VTE.[35] The likelihood of thromboembolic events of greater severity is also associated with the presence of cancer.

Cancer patients have been included in all of the randomized studies on the use of new anticoagulants and VTE, and the results in favor of the new drugs persisted in the subgroup analyses. However, the therapies were not compared with the currently recommended gold standard, but rather with warfarin. According to the ACCP, the current therapy of choice for patients with cancer-related VTE is based on the use of low-molecular-weight heparins.[9] That recommendation is based on studies showing the efficacy of this type of treatment in the maintenance phase of VTE treatment in the cancer population, when compared with that of warfarin.[36] There has been no direct comparison between the new anticoagulants and low-molecular-weight heparins, in terms of their effects in the medium term, for VTE treatment in cancer patients. Such studies are in progress and, until their results are available, the new anticoagulants should still be used with caution in this population, it being preferable that low-molecular-weight heparins be used.

MANAGEMENT OF COMPLICATIONS OF VTE TREATMENT WITH THE NEW ANTICOAGULANTS

Bleeding

A major concern of inexperienced physicians with regard to the new anticoagulants is management of bleeding, especially major bleeding. The fear of this complication with regard to prescribing warfarin has been mitigated by 50 years of experience and clinical practice. In fact, hemorrhagic complications should be borne in mind by anyone prescribing an anticoagulant medication. In this case, prevention is essential; some simple measures can reduce an individual's patient risk of bleeding, regardless of the selected anticoagulant. Avoiding concomitant use of nonsteroidal anti-inflammatory drugs or antiplatelet agents, controlling systemic blood pressure, assessing the need for prophylaxis of upper gastrointestinal tract bleeding with the use of a proton pump inhibitor, assessing renal and hepatic function periodically, and educating patients are measures that contribute to the prevention of such complications.

Serum activity levels of the new anticoagulants cannot be accurately monitored with current coagulation tests. Even for factor Xa antagonists, anti-factor Xa test results do not have a linear correlation with anticoagulant activity, because they are calibrated to measure activity of low-molecular-weight heparins.

In addition to prevention, data from recent registries are quite reassuring with regard to the bleeding rates with the new anticoagulants[37]: rates of major bleeding reach 3-4 per 100 patients per year, with a mortality rate of 6% in these cases. The same registries show a rate of severe bleeding of 8 per 100 patients per year, with a mortality rate of 15% with the use of warfarin.[38] Another peculiarity of the use of the new anticoagulants is that the pattern of hemorrhagic complications seems to be different from that usually found with the use of warfarin. With the new anticoagulants, hemorrhages tend to be more common in the digestive tract, the approach to which is less complex than is that required when hemorrhage affects the central nervous system (more common with the use of warfarin).[39]

The management of bleeding with the use of the new anticoagulants is similar to the management of warfarin-related hemorrhages[40]: in the event of minor local bleeding, it is suggested that the following dose be discontinued and that mechanical compression or local measures, such as nasal packing for a nosebleed, be used. In the event of major hemorrhage, in addition

to local measures and clinical support measures (such as fluid replacement, red blood cell transfusion, and platelet transfusion if platelet count is below 60,000), administration of prothrombin complex (25-50 U/kg) or activated prothrombin complex (50-200 U/kg) can be considered. Prothrombin complex has high levels of vitamin K-dependent coagulation factor. Therefore, because it antagonizes the action of warfarin, prothrombin complex can also antagonize the action of the new anticoagulants, given that its formulation contains a large amount of factor II (for dabigatran) or factor X (for rivaroxaban, apixaban, and edoxaban). Therefore, in theory, for the treatment of potentially fatal hemorrhage in patients receiving one of the new anticoagulants, the use of prothrombin complex is preferred over the traditional use of fresh frozen plasma. In plasma, the blocked factors (II or X) are diluted among all other serum proteins, therefore being present in smaller amounts and consequently less effective. However, the validity of this strategy has not been systematically evaluated, having been investigated only in experimental models.[41] Likewise, one can consider administering activated factor VII (at a dose of 90 μg/kg), which, when given at high doses such as the one suggested, is able to induce propagation of the coagulation cascade, even if this cascade is blocked at some point below, whether in factor II or factor X. If the drug in question is dabigatran, another alternative can be hemodialysis, given that dabigatran can thus be removed.

Recently, antidotes for dabigatran—idarucizumab[42]—and for factor Xa antagonists—andexanet alfa[43]—have become available. Neither antidote has been widely used. It is likely that they will not become widely available and that they will rarely actually be required. However, the existence of these antidotes should encourage the use of the new anticoagulants and reduce the level of concern on the part of the medical community regarding the management of bleeding.

Another situation that may raise questions is perioperative management when the patient is taking one of the drugs in this new class. For elective surgery, it will suffice to consider the half-life of the drugs and discontinue their use for a period of not less than 24 h. For emergency surgery in patients who haven taken a new anticoagulant within a period less than that of its half-life, the use of the aforementioned antidotes (idarucizumab for dabigatran or andexanet alfa for factor Xa antagonists) can be considered for acute reversal of anticoagulation so that the surgical procedure can be performed with increased safety. The timing of the reinitiation of anticoagulant therapy should be individualized on the basis of the potential postoperative risk of hemorrhage as well as the risk of another thromboembolic event, which is increased postoperatively. It is recommended that the new anticoagulants be restarted as early as possible. If, for surgical reasons, fasting is required, one can consider the use of low-molecular-weight heparins for a transitional period until re-establishment of proper gastrointestinal transit and reinitiation of the new anticoagulants.[18]

Recurrence

As previously mentioned, even if the new anticoagulants are used appropriately, there may be recurrence of VTE, especially in the acute phase but also in the long-term and extended periods. In such cases, the ACCP recommendation is that, in addition to confirming that it truly is a new episode of VTE and checking patient adherence to treatment (remembering that, given the shorter half-life of the drugs, missing even a single dose is sufficient to leave patients susceptible to a new event), the drug being used be temporarily replaced with a low-molecular-weight heparin for at least 30 days.[9]

CURRENT RECOMMENDATION FOR VTE TREATMENT

On the basis of the aforementioned studies, phase IV studies, and large epidemiologic registries that confirmed the data from phase III studies in real life,[44,45] the most recent guidelines of the European Society of Cardiology/European Respiratory Society assign treatment with the new anticoagulants the same grade of recommendation and level of evidence as those assigned to the conventional treatment of heparins followed by warfarin, without hierarchization.[46] However, in the most recent ACCP guidelines, the new anticoagulants, mainly because of their favorable safety profile, are placed as the first choice for the treatment of VTE unrelated to cancer.[9] This emphasizes the relevance of this class of drugs and the need for knowledge of their pharmacological properties and side effect profiles. Safety in prescribing the new drugs, as well as confidence in managing their complications, especially hemorrhagic complications, will come with the experience of using them and with clinical practice.

REFERENCES

1. Heit JA. The epidemiology of venous thromboembolism in the community. Arterioscler Thromb Vasc Biol. 2008;28(3):370-2. http://dx.doi.org/10.1161/ATVBAHA.108.162545
2. Cohen AT, Agnelli G, Anderson FA, Arcelus JI, Bergqvist D, Brecht JG, et al. Venous thromboembolism (VTE) in Europe. The number of VTE events and associated morbidity and mortality. Thromb Haemost. 2007;98(4):756-64. http://dx.doi.org/10.1160/th07-03-0212
3. Andrade Ede O, Bindá FA, Silva AM, Costa TD, Fernandes MC, Fernandes MC. Risk factors and prophylaxis for venous thromboembolism in hospitals in the city of Manaus, Brazil. J Bras Pneumol. 2009;35(2):114-21.
4. Biss TT, Brandão LR, Kahr WH, Chan AK, Williams S. Clinical features and outcome of pulmonary embolism in children. Br J Haematol. 2008;142(5):808-18. http://dx.doi.org/10.1111/j.1365-2141.2008.07243.x
5. Konstantinides S, Torbicki A. Management of venous thromboembolism: an update. Eur Heart J. 2014;35(41):2855-63. http://dx.doi.org/10.1093/eurheartj/ehu243
6. Kernohan RJ, Todd C. Heparin therapy in thromboembolic disease. Lancet. 1966;1(7438):621-3. http://dx.doi.org/10.1016/S0140-

6736(66)90822-1

7. BARRITT DW, JORDAN SC. Anticoagulant drugs in the treatment of pulmonary embolism. A controlled trial. Lancet. 1960;1(7138):1309-12.
8. Hull R, Delmore T, Genton E, Hirsh J, Gent M, Sackett D, et al. Warfarin sodium versus low-dose heparin in the long-term treatment of venous thrombosis. N Engl J Med. 1979;301(16):855-8. http://dx.doi.org/10.1056/NEJM197910183011602
9. Kearon C, Akl EA, Ornelas J, Blaivas A, Jimenez D, Bounameaux H, et al. Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report. Chest. 2016;149(2):315-52. http://dx.doi.org/10.1016/j.chest.2015.11.026
10. Hull R, Delmore T, Carter C, Hirsh J, Genton E, Gent M, et al. Adjusted subcutaneous heparin versus warfarin sodium in the long-term treatment of venous thrombosis. N Engl J Med. 1982;306(4):189-94. http://dx.doi.org/10.1056/NEJM198201283060401
11. Ridker PM, Goldhaber SZ, Danielson E, Rosenberg Y, Eby CS, Deitcher SR, et al. Long-term, low-intensity warfarin therapy for the prevention of recurrent venous thromboembolism. N Engl J Med. 2003;348(15):1425-34. http://dx.doi.org/10.1056/NEJMoa035029
12. Hutten BA, Prins MH. Duration of treatment with vitamin K antagonists in symptomatic venous thromboembolism. Cochrane Database Syst Rev. 2006;(1):CD001367. http://dx.doi.org/10.1002/14651858.cd001367.pub2
13. Phillips KW, Ansell J. The clinical implications of new oral anticoagulants: will the potential advantages be achieved? Thromb Haemost. 2010;103(1):34-9. http://dx.doi.org/10.1160/TH09-06-0361
14. Kakkar AK, Mueller I, Bassand JP, Fitzmaurice DA, Goldhaber SZ, Goto S, et al. Risk profiles and antithrombotic treatment of patients newly diagnosed with atrial fibrillation at risk of stroke: perspectives from the international, observational, prospective GARFIELD registry. PloS One. 2013;8(5):e63479. http://dx.doi.org/10.1371/journal.pone.0063479
15. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009;361(12):1139-51. http://dx.doi.org/10.1056/NEJMoa0905561
16. Holbrook AM, Pereira JA, Labiris R, McDonald H, Douketis JD, Crowther M, et al. Systematic overview of warfarin and its drug and food interactions. Arch Intern Med. 2005;165(10):1095-106. http://dx.doi.org/10.1001/archinte.165.10.1095
17. Amin A, Deitelzweig S, Jing Y, Makenbaeva D, Wiederkehr D, Lin J, et al. Estimation of the impact of warfarin's time-in-therapeutic range on stroke and major bleeding rates and its influence on the medical cost avoidance associated with novel oral anticoagulant use-learnings from ARISTOTLE, ROCKET-AF, and RE-LY trials. J Thromb Thrombolysis. 2014;38(2):150-9. http://dx.doi.org/10.1007/s11239-013-1048-z
18. Heidbuchel H, Verhamme P, Alings M, Antz M, Hacke W, Oldgren J, et al. EHRA practical guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation: executive summary. Eur Heart J. 2013;34(27):2094-106. http://dx.doi.org/10.1093/eurheartj/eht134
19. Schulman S, Kearon C, Kakkar AK, Mismetti P, Schellong S, Eriksson H, et al. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. N Engl J Med. 2009;361(24):2342-52. http://dx.doi.org/10.1056/NEJMoa0906598
20. Schulman S, Kearon C, Kakkar AK, Schellong S, Eriksson H, Baanstra D, et al. Extended use of dabigatran, warfarin, or placebo in venous thromboembolism. N Engl J Med. 2013;368(8):709-18. http://dx.doi.org/10.1056/NEJMoa1113697
21. EINSTEIN Investigators E, Bauersachs R, Berkowitz SD, Brenner B, Buller HR, Decousus H, et al. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med. 2010;363(26):2499-510. http://dx.doi.org/10.1056/NEJMoa1007903
22. EINSTEIN-PE Investigators, Büller HR, Prins MH, Lensin AW, Decousus H, Jacobson BF, et al. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. N Engl J Med. 2012;366(14):1287-97. http://dx.doi.org/10.1056/NEJMoa1113572
23. Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, et al. Oral apixaban for the treatment of acute venous thromboembolism. N Engl J Med. 2013;369(9):799-808. http://dx.doi.org/10.1056/NEJMoa1302507
24. Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, et al. Apixaban for extended treatment of venous thromboembolism. N Engl J Med. 2013;368(8):699-708. http://dx.doi.org/10.1056/NEJMoa1207541
25. Hokusai-VTE Investigators, Büller HR, Décousus H, Grosso MA, Mercuri M, Middeldorp S, et al. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. N Engl J Med. 2013;369(15):1406-15. http://dx.doi.org/10.1056/NEJMoa1306638
26. Ocak G, Lijfering WM, Verduijn M, Dekker FW, Rosendaal FR, Cannegieter SC, et al. Risk of venous thrombosis in patients with chronic kidney disease: identification of high-risk groups. J Thromb Haemost. 2013;11(4):627-33. http://dx.doi.org/10.1111/jth.12141
27. Anderson FA Jr, Wheeler HB, Goldberg RJ, Hosmer DW, Patwardhan NA, Jovanovic B, et al. A population-based perspective of the hospital incidence and case-fatality rates of deep vein thrombosis and pulmonary embolism. The Worcester DVT Study. Arch Intern Med. 1991;151(5):933-8. http://dx.doi.org/10.1001/archinte.1991.00400050081016
28. Stein PD, Hull RD, Kayali F, Ghali WA, Alshab AK, Olson RE. Venous thromboembolism according to age: the impact of an aging population. Arch Intern Med. 2004;164(20):2260-5. http://dx.doi.org/10.1001/archinte.164.20.2260
29. Laporte S, Mismetti P, Décousus H, Uresandi F, Otero R, Lobo JL, et al. Clinical predictors for fatal pulmonary embolism in 15,520 patients with venous thromboembolism: findings from the Registro Informatizado de la Enfermedad TromboEmbolica venosa (RIETE) Registry. Circulation. 2008;117(13):1711-6. http://dx.doi.org/10.1161/CIRCULATIONAHA.107.726232
30. Nieto JA, Solano R, Ruiz-Ribó MD, Ruiz-Gimenez N, Prandoni P, Kearon C, et al. Fatal bleeding in patients receiving anticoagulant therapy for venous thromboembolism: findings from the RIETE registry. J Thromb Haemost. 2010;8(6):1216-22. http://dx.doi.org/10.1111/j.1538-7836.2010.03852.x
31. Prandoni P, Trujillo-Santos J, Sanchez-Cantalejo E, Dalla Valle F, Piovella C, Pesavento R, et al. Major bleeding as a predictor of mortality in patients with venous thromboembolism: findings from the RIETE Registry. J Thromb Haemost. 2010;8(11):2575-7. http://dx.doi.org/10.1111/j.1538-7836.2010.04039.x
32. Geldhof V, Vandenbriele C, Verhamme P, Vanassche T. Venous thromboembolism in the elderly: efficacy and safety of non-VKA oral anticoagulants. Thromb J. 2014;12:21. http://dx.doi.org/10.1186/1477-9560-12-21
33. Marinho FC, Takagaki TY. Hypercoagulability and lung cancer. J Bras Pneumol. 2008;34(5):312-22. http://dx.doi.org/10.1590/S1806-37132008000500011
34. Büller HR, Davidson BL, Decousus H, Gallus A, Gent M, Piovella F, et al. Fondaparinux or enoxaparin for the initial treatment of symptomatic deep venous thrombosis: a randomized trial. Ann Intern Med. 2004;140(11):867-73. http://dx.doi.org/10.7326/0003-4819-140-11-200406010-00007
35. Blom JW, Doggen CJ, Osanto S, Rosendaal FR. Malignancies, prothrombotic mutations, and the risk of venous thrombosis. JAMA. 2005;293(6):715-22. http://dx.doi.org/10.1001/jama.293.6.715
36. Lee AY, Levine MN, Baker RI, Bowden C, Kakkar AK, Prins M, et al. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. N Engl J Med. 2003;349(2):146-53. http://dx.doi.org/10.1056/NEJMoa025313
37. Majeed A, Hwang HG, Connolly SJ, Eikelboom JW, Ezekowitz MD, Wallentin L, et al. Management and outcomes of major bleeding during treatment with dabigatran or warfarin. Circulation. 2013;128(21):2325-32. http://dx.doi.org/10.1161/CIRCULATIONAHA.113.002332
38. Beyer-Westendorf J, Förster K, Pannach S, Ebertz F, Gelbricht V, Thieme C, et al. Rates, management, and outcome of rivaroxaban bleeding in daily care: results from the Dresden NOAC registry. Blood. 2014;124(6):955-62. http://dx.doi.org/10.1182/blood-2014-03-563577
39. Chan NC, Paikin JS, Hirsh J, Lauw MN, Eikelboom JW, Ginsberg JS. New oral anticoagulants for stroke prevention in atrial fibrillation: impact of study design, double counting and unexpected findings on interpretation of study results and conclusions. Thromb Haemost. 2014;111(5):798-807. http://dx.doi.org/10.1160/TH13-11-0918
40. Siegal DM, Crowther MA. Acute management of bleeding in patients on novel oral anticoagulants. Eur Heart J. 2013;34(7):489-498b. http://dx.doi.org/10.1093/eurheartj/ehs408
41. Lazo-Langner A, Lang ES, Douketis J. Clinical review: Clinical management of new oral anticoagulants: a structured review with emphasis on the reversal of bleeding complications. Crit Care. 2013;17(3):230. http://dx.doi.org/10.1186/cc12592

42. Pollack CV Jr, Reilly PA, Eikelboom J, Glund S, Verhamme P, Bernstein RA, et al. Idarucizumab for Dabigatran Reversal. N Engl J Med. 2015;373(6):511-20. http://dx.doi.org/10.1056/NEJMoa1502000
43. Siegal DM, Curnutte JT, Connolly SJ, Lu G, Conley PB, Wiens BL, et al. Andexanet Alfa for the Reversal of Factor Xa Inhibitor Activity. N Engl J Med. 2015;373(25):2413-24. http://dx.doi.org/10.1056/NEJMoa1510991
44. Schulman S, Kakkar AK, Goldhaber SZ, Schellong S, Eriksson H, Mismetti P, et al. Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis. Circulation. 2014;129(7):764-72. http://dx.doi.org/10.1161/CIRCULATIONAHA.113.004450
45. Ageno W, Mantovani LG, Haas S, Kreutz R, Monje D, Schneider J, et al. Safety and effectiveness of oral rivaroxaban versus standard anticoagulation for the treatment of symptomatic deep-vein thrombosis (XALIA): an international, prospective, non-interventional study. Lancet Haematol. 2016;3(1):e12-21. http://dx.doi.org/10.1016/S2352-3026(15)00257-4
46. Konstantinides SV, Torbicki A, Agnelli G, Danchin N, Fitzmaurice D, Galie N, et al. 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. Eur Heart J. 2014;35(43):3033-69, 3069a-3069k.
47. Schulman S, Kakkar AK, Goldhaber SZ, Schellong S, Eriksson H, Mismetti P, et al. Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis. Circulation. 2014;129(7):764-72. http://dx.doi.org/ 10.1161/CIRCULATIONAHA.113.004450

J Bras Pneumol. 2016;42(2):155-156
http://dx.doi.org/10.1590/S1806-37562015000000044

Bronchial thermoplasty in a patient with difficult-to-control asthma

Adalberto Rubin[1,2], Suzana Zelmanovitz[1], Manuela Cavalcanti[1], Fernanda Spilimbergo[1], Paulo Goldenfum[1], José Felicetti[3], Paulo Cardoso[4]

TO THE EDITOR:

A small but significant proportion of asthma patients have persistent symptoms, lung function changes, and frequent exacerbations, despite appropriate management.[1,2] This subset of patients, who are classified as having difficult-to-control asthma (DTCA), have high morbidity and mortality rates, as well as consuming a large part of the health resources allocated to the disease. Bronchial thermoplasty (BT)[3] is the first nonpharmacological treatment for patients with DTCA and is currently available in several countries, including Brazil.

A 46-year-old female patient with DTCA receiving continuous treatment with salmeterol/fluticasone (50/500 µg twice daily) and omalizumab (200 mg every two weeks) for the past 2 years presented to our facility. Despite the aforementioned treatment, she had had three episodes of exacerbation in the previous year and was unable to tolerate physical activity, often using inhaled albuterol for symptom relief. Although she had preserved lung function, her FEV_1 being 2.5 L (85% of predicted), she had poorly controlled asthma. In June of 2014, her Asthma Control Test (ACT) score was 10. Patients with an ACT score of less than 20 are considered to have uncontrolled asthma. On August 19, 2014, the patient underwent BT for the first time, the right lower lobe being treated (Figure 1). She underwent another two BT procedures, three weeks apart, the left lower lobe and upper lobes being treated. A total of 152 activations were performed. All procedures were performed with the patient under general anesthesia. There were no significant complications, and the patient was discharged 4 h after each procedure. Clinical and functional evaluation performed at 60 days after the last procedure revealed stable lung function, her FEV_1 being 2.58 L (88% of predicted), and significantly improved disease control, her ACT score being 23 (Table 1). In addition to increased exercise tolerance, the patient reported virtually no rescue albuterol use.

The objective of BT is to reduce the thickness of segmental and subsegmental bronchial smooth muscle through the delivery of radiofrequency energy to the airways.[3] The resulting anatomical change is intended to provide clinical benefits to asthma patients, reducing airway smooth muscle contractility and possibly reducing bronchoconstriction and asthma exacerbation.

Preliminary studies of BT use showed improved morning and evening PEF, as well as reduced rescue bronchodilator use,[4] together with improved quality of life. The first multicenter study of BT use[3] showed better disease control in asthma patients treated with BT than in controls. In a subsequent study involving patients with severe asthma, the aforementioned results were confirmed.[5] The aforementioned studies provided the basis for the largest study to date,[6] in which nearly 300 asthma patients were randomized to receive BT + conventional treatment or conventional treatment alone (the latter constituting the control group). The study was a double-blind trial and showed that the asthma patients who were treated with BT had a significant reduction in severe exacerbations and emergency room visits for asthma. On the basis of the aforementioned results, the US Food and Drug Administration approved the clinical use of BT in 2010. A 5-year follow-up evaluation showed a maintained reduction in exacerbations and emergency room visits, no BT-related adverse effects or anatomical abnormalities being observed.[7]

In the case reported here, treatment with BT was effective (as evidenced by the ACT score) and well tolerated, results that are consistent with those of previous studies.[5] Similar results have been reported in Brazil.[8] BT is a new treatment modality that is aimed at patients with severe asthma in whom the disease remains uncontrolled despite the use of all available drugs, including omalizumab.

In Brazil, this is the first case report of a patient treated with BT after the use of BT was approved by national

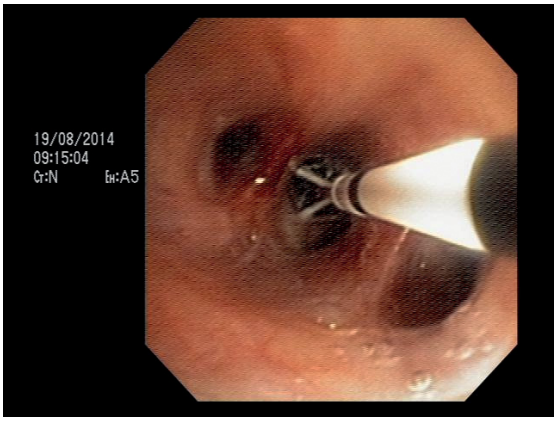

Figure 1. Photograph showing the use of bronchial thermoplasty.

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Table 1. Clinical and functional evaluation performed at baseline and after treatment with bronchial thermoplasty.

Variable	Baseline	After treatment
FVC, L	3.53	3.57
FVC, % of predicted	97.9	99.1
FEV_1, L	2.5	2.58
FEV_1, % of predicted	85.0	88.0
ACT score	10	23

ACT: Asthma Control Test.

regulatory agencies. The results of previous studies and those of the present study show that BT is a promising treatment option for the management of moderate to severe asthma. BT has been approved for clinical use in several countries and has recently been included in the Global Initiative for Asthma guidelines as a treatment option for patients with severe asthma.[1] In the near future, BT is expected to become a treatment option for DTCA patients nationwide.

REFERENCES

1. Global Initiative for Asthma – GINA [homepage on the Internet]. Bethesda: GINA [updated 2014; cited 2015 Jan 21]. Global Strategy for Asthma Management and Prevention. Available from : http://www.ginasthma.org/
2. Wenzel SE. Severe asthma in adults. Am J Respir Crit Care Med. 2005;172(2):149-60. http://dx.doi.org/10.1164/rccm.200409-1181PP
3. Cox G, Miller JD, McWilliams A, Fitzgerald JM, Lam S. Bronchial thermoplasty for asthma. Am J Respir Crit Care Med. 2006;173(9):965-9. http://dx.doi.org/10.1164/rccm.200507-1162OC
4. Cox G, Thomson NC, Rubin AS, Niven RM, Corris PA, Siersted HC, et al. Asthma control during the year after bronchial thermoplasty. New Engl J Med. 2007;356(13):1327-37. http://dx.doi.org/10.1056/NEJMoa064707
5. Pavord ID, Cox G, Thomson NC, Rubin AS, Corris PA, Niven RM, et al. Safety and efficacy of bronchial thermoplasty in symptomatic, severe asthma. Am J Respir Crit Care Med. 2007;176(12):1185-91. http://dx.doi.org/10.1164/rccm.200704-571OC
6. Castro M, Rubin AS, Laviolette M, Fiterman J, De Andrade Lima M, Shah PL, et al. Effectiveness and safety of bronchial thermoplasty in the treatment of severe asthma: a multicenter, randomized, double-blind, sham-controlled clinical trial. Am J Respir Crit Care Med. 2010;181(2):116-24. http://dx.doi.org/10.1164/rccm.200903-0354OC
7. Wechsler ME, Laviolette M, Rubin AS, Fiterman J, Lapa e Silva JR, Shah PL, et al. Bronchial thermoplasty: Long-term safety and effectiveness in patients with severe persistent asthma. J Allergy Clin Immunol. 2013;132(6):1295-302. http://dx.doi.org/10.1016/j.jaci.2013.08.009
8. Rubin AS, Cardoso PF. Bronchial thermoplasty: report on the first endoscopic treatment for asthma in Latin America. J Bras Pneumol. 2008;34(1):59-62. http://dx.doi.org/10.1590/S1806-37132008000100011

J Bras Pneumol. 2016;42(2):157-157
http://dx.doi.org/10.1590/S1806-37562015000000328

HRCT in smoking-related interstitial lung diseases: a kaleidoscopic overlap of patterns

Gaetano Rea[1], Tullio Valente[1], Edson Marchiori[2,3]

A 39-year-old male patient, a leather trader by profession, presented with a 6-month history of dyspnea, hypoxemia, and digital clubbing. He had a 30-pack-year smoking history. Laboratory test results were unremarkable. Pulmonary function tests showed a severe decrease in DLCO (49% of predicted) and FVC (64% of predicted), suggestive of restriction. An HRCT scan (Figure 1) showed poorly defined micronodules with subtle pseudocystic airway changes, and mild patchy septal thickening in the upper lobes. Other findings were centrilobular and paraseptal emphysema and bronchial wall thickening. Patchy ground-glass opacities (GGOs), with fine reticular elements and containing small areas of bronchiectasis, were observed in the lower lobes. A coronal reconstruction clearly showed the coexistence of smoking-related findings: centrilobular nodules in the upper lobes, typical of respiratory bronchiolitis (RB); interlobular septal thickening, characteristic of RB-associated interstitial lung disease (RB-ILD); centrilobular and paraseptal areas of attenuation, as seen in emphysema; and patchy GGOs and cysts in the lower lobes, suggestive of desquamative interstitial pneumonia (DIP)-like elements. Bronchoalveolar lavage, performed in the right upper lobe, revealed 82% pigment-laden macrophages (although RB-ILD overlaps with DIP, they differ in their extent/distribution). As reported in the most recent American Thoracic Society/European Respiratory Society statements,[1,2] multiple patterns on HRCT can be observed in the same smoking patient. Therefore, the radiologist can truly make a difference in the final diagnosis.

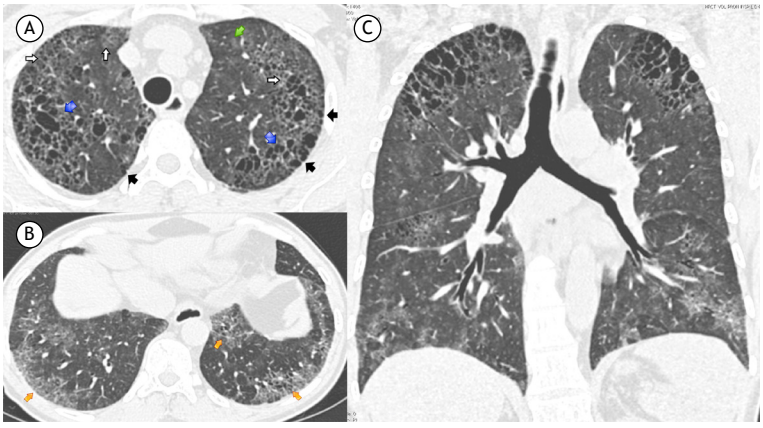

Figure 1. HRCT scan of the upper lobes (A), showing poorly defined micronodules (green arrow), with subtle pseudocystic airway changes (blue arrows) and mild patchy septal thickening in the upper lobes (white arrows). Ancillary findings were rare centrilobular and paraseptal emphysema (black arrows) and bronchial wall thickening. HRCT scan of the lower lobes (B), showing patchy ground-glass opacities with fine reticular elements and containing very small areas of bronchiolectasis (orange arrows). Coronal reconstruction (C) better demonstrates the coexisting patterns described in the HRCT axial scans.

RECOMMENDED READING

1. Travis WD, Costabel U, Hansell DM, King TE Jr, Lynch DA, Nicholson AG, et al. An official American Thoracic Society/European Respiratory Society statement: Update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med. 2013;188(6):733-48. http://dx.doi.org/10.1164/rccm.201308-1483ST

2. Sverzellati N, Lynch DA, Hansell DM, Johkoh T, King TE Jr, Travis WD. American Thoracic Society-European Respiratory Society Classification of the Idiopathic Interstitial Pneumonias: Advances in Knowledge since 2002. Radiographics. 2015;35(7):1849-71. http://dx.doi.org/10.1148/rg.2015140334

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J Bras Pneumol. 2016;42(2):158-159
http://dx.doi.org/10.1590/S1806-37562016000000006

Pre-operative evaluation in obstructive sleep apnea patients undergoing bariatric surgery: sleep laboratory limitations

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Obesity[1,2] is a proven risk factor for obstructive sleep apnea (OSA), and it is predictable that various patients who will undergo bariatric surgery (BS) might have the disease.

However, most frequently, patients are not diagnosed with the disease whether they are symptomatic or not. Surgeons[2] usually examine those patients in order to evaluate the risk of OSA before performing BS and might refer such patients for proper study and treatment.

Duarte and Magalhães-da-Silveira[1] conducted a retrospective study aiming to evaluate and identify which parameters could predict a higher chance of OSA in that specific population. They also developed a 6-item score that had good accuracy for the diagnosis of moderate and severe OSA.

We understand the limitations of the study; however, we would like to consider some key aspects that need to be taken into account for a proper clinical extrapolation.

First, hypertension[3] is known to be an important factor in the development of OSA.[4] There are widely available data revealing the benefits of BS in blood pressure control. In that study,[1] we found that hypertension was not considered a predictive factor in their group of patients. This might have been due to the fact that patients being treated for hypertension or not were grouped together, which might have influenced the results.

Second, the authors referred that they were not able to address all known comorbidities or other sleep complaints. Considering that the article is about OSA patients awaiting BS, we think that there is a potentially relevant predictive factor that was not fully explored: metabolic syndrome,[4] which is consistently associated with both OSA and BS. We believe that, even if we exclude hypertension, cholesterol levels, and other comorbidities, such as diabetes, the metabolic syndrome might predict OSA and must be taken into account in future studies.

Finally, we know that it is necessary to perform OSA screening in all patients who will undergo this type of surgery, regardless of any score. We do not want to undermine the value or the clinical importance of the NO-OSAS score; however, we question whether there is any advantage to its routine application. Would it change our behavior?

In our opinion, that article[1] demonstrates that it is possible to perceive which subgroups of this specific population are at a higher risk in order to direct our attention to them. However, other important clinical parameters need to be assessed so that its predictive power can be enhanced.

REFERENCES

1. Duarte RL, Magalhães-da-Silveira FJ. Factors predictive of obstructive sleep apnea in patients undergoing pre-operative evaluation for bariatric surgery and referred to a sleep laboratory for polysomnography. J Bras Pneumol. 2015;41(5):440-8. http://dx.doi.org/10.1590/S1806-37132015000000027
2. Selim BJ, Surani SR, Ramar K. Role of preoperative screening for adult patients for obstructive sleep apnea. Hosp Pract (1995). 2014;42(5):100-7. http://dx.doi.org/10.3810/hp.2014.12.1163
3. Torres G, Sánchez-de-la-Torre M, Barbé F. Relationship Between OSA and Hypertension. Chest. 2015;148(3):824-32. http://dx.doi.org/10.1378/chest.15-0136
4. Bonsignore MR, Borel AL, Machan E, Grunstein R. Sleep apnoea and metabolic dysfunction. Eur Respir Rev. 2013;22(129):353-64. http://dx.doi.org/10.1183/09059180.00003413

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ISSN 1806-3713

Authors' reply

Ricardo Luiz de Menezes Duarte[1,2], Flavio José Magalhães-da-Silveira[1]

In response to questions raised about our study,[1] we would like to make some comments. The literature indicates that there is a bidirectional association between obstructive sleep apnea (OSA) and systemic arterial hypertension (SAH).[2] With regard to the role of SAH and OSA as risk factors for the development of OSA and SAH, respectively, some data merit special attention: OSA as a causal risk factor for the development of SAH has been more extensively studied than has the reverse; in addition, the treatment of OSA with continuous positive airway pressure usually improves blood pressure levels in patients with hypertension.[2] In contrast, the treatment of SAH with antihypertensives in order to improve OSA yields conflicting results; except, perhaps, for the treatment of SAH with diuretics, especially spironolactone, because it reduces parapharyngeal edema and secondary airway obstruction.[2]

With regard to whether or not patients were being treated, we do not believe that this would have influenced the magnitude of association between SAH and OSA, because the main clinical questionnaires that use the variable SAH do not discriminate between patients who are on antihypertensive treatment and those who are not.[3] In our study,[1] SAH was found to be a prognostic factor in the univariate analysis at three different cut-off points—apnea-hypopnea index (AHI) ≥ 5 events/h; AHI ≥ 15 events/h; and AHI ≥ 30 events/h—however, when used in the multivariate analysis, SAH was found to be an independent prognostic factor only at the cut-off point of AHI ≥ 5 events/h, showing that, in the more severe forms of OSA, SAH acts as a confounding factor, which is why it was not used in our questionnaire.

Metabolic syndrome is defined as the presence of three or more of the following five factors: 1) waist circumference > 80 cm in women and > 94 cm in men; 2) serum triglycerides ≥ 150 mg/dL (or on drug treatment for elevated triglycerides); 3) HDL cholesterol < 40 mg/dL in men and < 50 mg/dL in women (or on drug treatment for reduced HDL cholesterol); 4) SAH (or on antihypertensive drug treatment); and 5) fasting glucose ≥ 100 mg/dL (or on drug treatment for elevated glucose).[4] Metabolic syndrome was not used in our questionnaire because its confirmation requires serum level determinations, which would make it impossible to produce an easy-to-administer questionnaire for physicians and patients.

The aim in designing a clinical questionnaire is not to replace polysomnography (PSG). The aim of a questionnaire is to screen patients, selecting those at high risk and enabling faster and cheaper diagnosis with portable monitoring devices.[3] Type I PSG, despite being the gold standard for the diagnosis of OSA, has its inherent costs and is associated with long waiting lists. Since the use of portable methods has been validated in the bariatric population,[5] our questionnaire, specifically developed for this population, can indeed change practice, selecting high-risk patients for home diagnosis, limiting costs, decreasing the waiting time for surgery, and decreasing the waiting time for laboratory PSG.

REFERENCES

1. Duarte RL, Magalhães-da-Silveira FJ. Factors predictive of obstructive sleep apnea in patients undergoing pre-operative evaluation for bariatric surgery and referred to a sleep laboratory for polysomnography. J Bras Pneumol. 2015;41(5):440-8. http://dx.doi.org/10.1590/S1806-37132015000000027
2. Torres G, Sánchez-de-la-Torre M, Barbé F. Relationship between OSA and hypertension. Chest. 2015;148(3):824-32. http://dx.doi.org/10.1378/chest.15-0136
3. Abrishami A, Khajehdehi A, Chung F. A systematic review of screening questionnaires for obstructive sleep apnea. Can J Anesth. 2010;57(5):423-38. http://dx.doi.org/10.1007/s12630-010-9280-x
4. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation. 2009;120(16):1640-5. http://dx.doi.org/10.1161/CIRCULATIONAHA.109.192644
5. Oliveira MG, Treptow EC, Fukuda C, Nery LE, Valadares RM, Tufik S, et al. Diagnostic accuracy of home-based monitoring system in morbidly obese patients with high risk for sleep apnea. Obes Surg. 2015;25(5):845-51. http://dx.doi.org/10.1007/s11695-014-1469-6

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J Bras Pneumol. 2016;42(2):160-160
http://dx.doi.org/10.1590/S1806-37562016000000037

Open letter to city, state, and federal health authorities, to State Health Councils, and to the National Council of Municipal Health Secretaries in Brazil

The World Health Organization estimates that chronic respiratory diseases (CRDs) are responsible for approximately 12 million deaths annually. Of the five leading causes of death worldwide, three are lung diseases. In Brazil, estimates indicate that approximately 15% of the population has a CRD, and CRDs are therefore the cause of approximately 200,000 hospitalizations. In the state of Minas Gerais, CRDs as a group are the third leading contributor to the disability burden. One example is COPD, which was projected to rank third among the leading causes of death only in 2030 and was already ranked as such in 2014. In Brazil, COPD affects nearly 16% of the population over 40 years of age.

The Brazilian *Sistema Único de Saúde* (SUS, Unified Health Care System) has introduced a series of public policies and initiatives aimed at addressing CRDs as a group, including the following: primary care booklets; clinical protocols and therapeutic guidelines for asthma; programs for the management and control of tuberculosis and smoking; the Popular Pharmacy program, which distributes essential medications and high-cost drugs at no charge, with support from state and federal funding; and the prevention, diagnosis, and treatment of bronchopulmonary neoplasms.

CRDs are not explicitly part of the program that has recently been launched by the Brazilian National Ministry of Health, called "*Programa Mais Especialidades*" (More Specialties Program). This shows the lack of coordination among such initiatives, which is why they have not produced the necessary response to the multifaceted epidemiological context involving them. Therefore, it is imperative that strategies for organically promoting their integration be proposed.

The strategy that has been implemented in the city of Belo Horizonte and its metropolitan area, which was presented and discussed in a workshop held on November 27, 2015 and attended by professionals from the four corners of Brazil who have extensive experience in the management of CRDs at the level of SUS, was based on the recommendations of the World Health Organization Practical Approach to Lung Health program and led to the publication, on July 1, 2014, of Resolution No. 1,861 of the *Comissão Intergestores Bipartite de Minas Gerais* (Bipartite Liaison Committee of Minas Gerais)-SUS/MG, approving the establishment of a management program specifically aimed at CRDs as a group. That resolution, which would allow the implementation of a comprehensive health care model that would bring together primary health care facilities, specialty centers, hospitals (including those affiliated with universities), and other existing resources, highlighting the complexity, severity, and level of resolution of CRDs at the various levels of health care, has yet to be put into practice. We emphasize the previous successful experience in care provision to patients with CRDs in the city of Ribeirão das Neves, located in the state of Minas Gerais, which was based on the recommendations of the aforementioned Practical Approach to Lung Health program and led to effective care, as well as increasing the feasibility of the activities. It is of note that, in the other Brazilian states (including the Federal District of Brasília), there is no formalized proposal with this level of comprehensiveness, a fact that underscores the urgent need to develop a strategy to be implemented nationwide.

The professionals working in civil society organizations, medical societies, the legislature, universities, and city/state administration who met in Belo Horizonte draw attention to the lack of articulation among the current public policies aimed at CRDs and demand that public health managers urgently adopt integrating strategies that are based on existing experiences—the focus of the event held on that date—and, at the same time, make themselves available to city, state, and federal health authorities to develop and implement a comprehensive line of care for treatment of CRDs. That line of treatment should be given the same priority as that now given to other diseases of equal epidemiological importance that affect the Brazilian population.

Belo Horizonte, February 1, 2016.

Board of Representatives for the Global Initiative for Chronic Obstructive Lung Disease in Brazil

Board of Representatives for the Global Initiative for Asthma in Brazil

Board of Representatives for the World Health Organization Global Alliance against Chronic Respiratory Diseases in Brazil

Medical Association of Minas Gerais

Minas Gerais Society of Pulmonology and Thoracic Surgery

Federal University of Minas Gerais *Hospital das Clínicas*

Health Committee of the Legislative Assembly of Minas Gerais

ISSN 1806-3713

J Bras Pneumol. 2016;42(2):161-161
http://dx.doi.org/10.1590/S1806-37562015000000294

Interlobular septal thickening

Edson Marchiori[1,2], Gláucia Zanetti[2,3], Bruno Hochhegger[4,5]

A 52-year-old female patient presented with progressive dyspnea. One year prior, she had undergone gastrectomy for gastric cancer. An HRCT scan of the chest revealed nodular interlobular septal thickening (ILST) at the right lung base (Figure 1).

Although ILST is often seen in association with other CT findings, such as consolidation and ground-glass opacities, it can be the predominant (or sole) finding, as was the case here.

ILST can be smooth, irregular (spiculated), or nodular. Smooth ILST is the most common and least specific of the three and can be found in a large number of venous, lymphatic, and infiltrative diseases, especially pulmonary edema. Irregular ILST is basically indicative of interstitial fibrosis and is seen in patients with fibrotic lung disease; rather than being the predominant finding, it is generally found in association with other fibrotic patterns.

Nodular ILST (which was found in our patient) is a finding that is associated with a very specific group of diseases. Although it can be found in cases of amyloidosis, sarcoidosis, lymphoproliferative disorders (lymphomas and lymphocytic interstitial pneumonia), and silicosis, it is an uncommon finding in such cases. It is primarily seen in patients with lymphangitic carcinomatosis (LC).

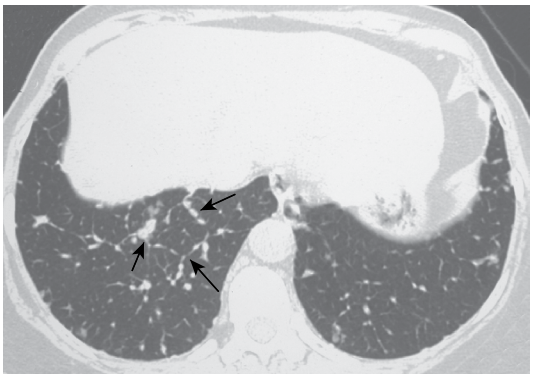

Figure 1. HRCT scan of the chest showing nodular interlobular septal thickening at the lung bases, particularly at the right lung base (arrows).

In patients with dyspnea and a history of malignancy, CT findings that are typical of LC (such as those observed in our patient) are diagnostic of the disease; that is, there is no need to perform a lung biopsy. In the case reported here, the final diagnosis was LC.

Pulmonary LC is the spread of the tumor to the pulmonary lymphatic system. Among the tumors that most commonly spread to the pulmonary lymphatic system are carcinomas of the breast, lung, stomach, colon, prostate, and pancreas, as well as metastatic adenocarcinoma of unknown primary site.

Pulmonary lymphatic vessels are found along the veins and bronchovascular sheaths, as well as in the interlobular septa and pleura. CT findings include peribronchovascular interstitial thickening, ILST, and smooth or nodular ("beaded") thickening of the subpleural interstitium, with normal lung architecture at the lobular level.

Because the peribronchial lymphatic vessels are affected, LC is, together with sarcoidosis, one of the few interstitial diseases that can often be diagnosed by transbronchial biopsy. The key histological findings are ILST and peribronchovascular interstitial thickening caused by infiltration of neoplastic cells in the lymphatic vessels. Given that LC is not always diffuse, CT is also useful in determining the best sites for transbronchial biopsy in patients with suggestive findings and no known tumor.

RECOMMENDED READING

1. Webb WR, Muller NL, Naidich DP, editors. High-resolution CT of the lung. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2008.

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J Bras Pneumol. 2016;42(2):162-162
http://dx.doi.org/10.1590/S1806-37562016000000114

What is the importance of calculating sample size?

Cecilia Maria Patino[1,2], Juliana Carvalho Ferreira[1,3]

PRACTICAL SCENARIO

In a controlled, randomized clinical trial on the management of asthma in pregnant women, researchers evaluated the effect of implementing a program in which a portable device was used for asthma control, as assessed by the Asthma Control Questionnaire (ACQ). In clinical research, our goal is to make an inference regarding something about a population by studying a sample of that population. This sample has to be representative of the target population, and the number of participants must be appropriate. It should be large enough that the probability of finding differences between groups by mere chance is low and that of detecting true, clinically significant differences is high. However, the number of participants should not be so large that resources are wasted or participants are exposed to unnecessary risk. Therefore, in the study design phase, it is essential to perform sample size calculation. To perform this calculation, one must define the key characteristics of the study, such as the study design, the primary endpoint, the expected variability, the degree of certainty desired, and the predicted number of participants who will drop out of the study. To define these parameters and calculate the ideal sample size, we need to obtain deep knowledge of the field of research in question by reviewing the literature and biostatistics.

In our example, the researchers tested the effect that using a new device had on asthma control (the primary outcome) compared with the usual treatment. They estimated that the difference between the groups would be 0.55 points on the ACQ, with a standard deviation of 0.66 points, a power of 80%, and a level of significance of 5%. In addition, they estimated that 25% of the participants could be lost to follow-up. Using those data, the authors calculated that they needed to include 72 participants. At the end of the study, the researchers analyzed the results of 69 participants and showed that the new intervention improved asthma control in pregnant women.

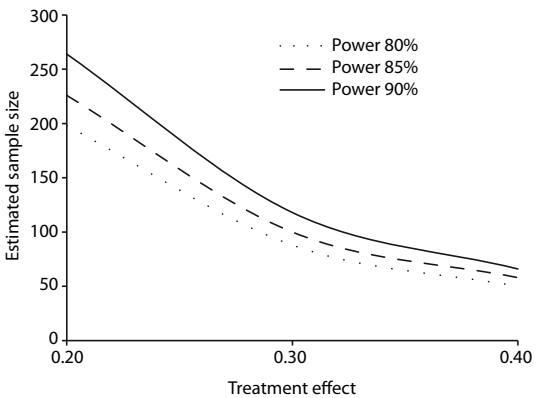

Figure 1. Relationship between the size of the treatment effect and the estimated sample size. On the x axis, we show hypothetical values for the size of the treatment effect, expressed as scores on the asthma symptoms questionnaire. We considered a fixed degree of variability (standard deviation) of 0.5 points and a level of significance of 5%. As the size of the treatment effect increases, the estimated size of the sample decreases. It is also clear that for the same effect size, choosing a higher power to detect the effect of the treatment causes an increase in the sample size.

BASIC CONCEPTS

Power

In biostatistics, power is defined as the probability of obtaining a statistically significant result when there is a real difference between treatments. In general, a power of at least 80% is needed in order to ensure a high probability of observing the effect, if any, of the intervention. To increase the power to detect differences, it is necessary to increase the sample size (Figure 1).

Critical level of significance

The critical level of significance is usually ≤ 5%. If we want greater certainty that a difference observed in the study population is not coincidental, we need to increase the sample size.

Effect size and variability

The greater the effect of the new intervention on the outcome is, the smaller is the sample size needed in order to prove it. Conversely, to show smaller effects, it is necessary to increase the sample size. If there is great variability of the effect in the population, we will also need a larger sample size (Figure 1).

It should be borne in mind that the sample size calculation is based on estimates and assumptions that can be inaccurate and is therefore subject to error. It is also important to be realistic when choosing the estimates employed in calculating the sample size. Highly optimistic choices about the effect size increase the risk of calculating an insufficient number of participants for the sample, whereas highly pessimistic choices can make the study unviable by resulting in a sample size that is too large to be practical.

RECOMMENDED READING

1. Zairina E, Abramson MJ, McDonald CF, Li J, Dharmasiri T, Stewart K, et al. Telehealth to improve asthma control in pregnancy: a randomized controlled trial. Respirology. 2016 Mar 31. doi: 10.1111/resp.12773 [Epub ahead of print]
2. Hulley SB, Cummings SR; Browner WS; Grady DG. Delineando a Pesquisa Clínica. 3rd ed. Porto Alegre: Artmed; 2008.
3. Ferreira JC, Patino CM. What does the p value really mean? J Bras Pneumol. 2015;41(5):485. http://dx.doi.org/10.1590/S1806-37132015000000215

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ISSN 1806-3713

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Abstracts

2. Singer M, Lefort J, Lapa e Silva JR, Vargaftig BB. Failure of granulocyte depletion to suppress mucin production in a murine model of allergy [abstract]. Am J Respir Crit Care Med. 2000;161:A863.

Chapter in a Book

3. Queluz T, Andres G. Goodpasture's syndrome. In: Roitt IM, Delves PJ, editors. Encyclopedia of Immunology. 1st ed. London: Academic Press; 1992. p. 621-3.

Official Publications

4. World Health Organization. Guidelines for surveillance of drug resistance in tuberculosis. WHO/Tb, 1994;178:1-24.

Theses

5. Martinez TY. Impacto da dispnéia e parâmetros funcionais respiratórios em medidas de qualidade de vida relacionada a saúde de pacientes com fibrose pulmonar idiopática [thesis]. São Paulo: Universidade Federal de São Paulo; 1998.

Electronic publications

6. Abood S. Quality improvement initiative in nursing homes: the ANA acts in an advisory role. Am J Nurs [serial on the Internet]. 2002 Jun [cited 2002 Aug 12]; 102(6): [about 3 p.]. Available from: http://www.nursingworld.org/AJN/2002/june/Wawatch.htm

Homepages/URLs

7. Cancer-Pain.org [homepage on the Internet]. New York: Association of Cancer Online Resources, Inc.; c2000-01 [updated 2002 May 16; cited 2002 Jul 9]. Available from: http://www.cancer-pain.org/

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Data: 03 a 07 de setembro de 2016
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Informações: www.ersnet.org

7 PESSOAS MORREM DE ASMA POR DIA, NO BRASIL.[2]

Clenil® HFA

dipropionato de beclometasona

O tratamento da asma ao alcance de todos[1]

- Reduz os sintomas e controla a inflamação[3]
- Pode ser usado em combinação com broncodilatadores de curta ação, conforme o GINA preconiza[4]

COMODIDADE POSOLÓGICA:[5]

ADULTOS:

200 mcg - 1 dose, 2-4 X ao dia

250 mcg - 2 doses, 2-4 X ao dia

250 mcg Jet® - 2 doses, 2-4 X ao dia

CRIANÇAS:

50 mcg - 2 doses, 2-4 X ao dia

NOVIDADE

AQUI TEM FARMÁCIA POPULAR

Custo Zero para seu paciente[1]

Referências Bibliográficas: 1- Ministério da Saúde. Gabinete do Ministro. Portaria nº 1.146, de 1 de junho de 2012. Altera e acresce dispositivos à Portaria nº 971/GM/MS, de 17 de maio de 2012, para ampliar a cobertura da gratuidade no âmbito do Programa Farmácia Popular do Brasil. DOU, Brasília, DF, 4 de junho de 2012,. P72-73. **2-** http://portaldasaude.saude.gov.br/index.php/cidadao/principal/agencia-saude/noticias-anteriores-agencia-saude/2740. **3-** Diretrizes da Sociedade Brasileira de Pneumologia e Tisiologia para o manejo da asma - 2012. J. Bras Pneumo. 2012; 38 (supl. 1) S1-S46. **4-** Global Strategy for asthma management and prevention. GINA 2014. **5-** Bula do medicamento Clenil® HFA.

Clenil® HFA dipropionato de beclometasona. **USO ADULTO E PEDIÁTRICO** (somente a apresentação de 50 mcg). **COMPOSIÇÃO, FORMA FARMACÊUTICA E APRESENTAÇÕES:** Solução pressurizada para inalação (aerossol). Clenil® HFA Spray 50, 200 e 250 mcg: aerossol com 200 doses. Clenil® HFA Jet® 250 mcg: aerossol com 200 doses. **INDICAÇÕES:** tratamento e prevenção da asma brônquica e bronquite, bem como nos processos inflamatórios das vias aéreas superiores. **CONTRAINDICAÇÕES:** hipersensibilidade individual aos derivados corticosteroides, hipersensibilidade ao álcool ou a qualquer outro constituinte desta formulação, tuberculose pulmonar, herpes simples ou crises asmáticas. **CUIDADOS E ADVERTÊNCIAS:** como todo corticoide inalatório, Clenil® HFA deve ser utilizado com cautela em pacientes com tuberculose ativa ou latente e infecção fúngica, bacteriana ou viral das vias aéreas. Também utilizar com cautela em pacientes portadores de anormalidades pulmonares como bronquiecstasia e pneumoconiose, uma vez que as mesmas estão relacionadas com maior susceptibilidade à infecções fúngicas. **Uso em idosos, crianças e outros grupos de risco:** como qualquer outro medicamento recomenda-se atenção especial na administração em pacientes idosos. O tratamento de pacientes com anomalias pulmonares como bronquiectasia e pneumoconiose, com a possibilidade de infecções fúngicas, deve ser restrito. **Administração durante a gravidez ou aleitamento:** em mulheres grávidas, o medicamento deve ser utilizado no caso de efetiva necessidade e sob supervisão médica. O uso do dipropionato de beclometasona em mães amamentando requer que os benefícios da terapêutica sejam levados em consideração frente aos riscos para mãe e lactente. **Interações medicamentosas:** os pacientes devem ser avisados que o medicamento contém pequena porcentagem de álcool e glicerol. Em doses normais, não há risco para os pacientes. Há um potencial teórico de interação particularmente em pacientes sensíveis a álcool utilizando dissulfiram ou metronidazol. **Reações adversas/Efeitos colaterais:** candidíase na boca e garganta, rouquidão e irritação na garganta, rash cutâneo, urticária, prurido, eritema, efeitos colaterais sistêmicos (supressão da adrenal, retardo no crescimento de crianças e adolescentes, diminuição da densidade mineral óssea, catarata, glaucoma), edema de olhos, faces, lábios e garganta, broncoespasmo paradoxal, chiado, dispneia, tosse, hiperatividade psicomotora, distúrbios do sono, ansiedade, depressão, agressividade, mudanças comportamentais (predominantemente em crianças), dor de cabeça, náusea. **POSOLOGIA: Clenil® HFA 50 mcg: Crianças:** a dose usual inicial é de 100 mcg a 400 mcg, de 12 em 12 horas. Dependendo da severidade da condição asmática, a dose diária pode ser fracionada de 8 em 8 horas ou ainda de 6 em 6 horas. **Adultos (incluindo os idosos):** A dose inicial usual é de 200 mcg a 800 mcg, (4 jatos) de 12 em 12 horas. A dose total diária pode ser dividida em tomadas de 8 em 8 horas ou ainda tomadas de 6 em 6 horas. **Clenil® HFA 200 mcg: Crianças:** NÃO DEVE SER UTILIZADO POR CRIANÇAS. **Adultos (incluindo os idosos):** A dose inicial do produto é de 200 mcg (um jato), de 12 em 12 horas. De acordo com a necessidade do paciente, pode-se prescrever doses mais altas (até 4 jatos por dia). A dose total diária deve ser dividida em tomadas de 12 em 12 horas, tomadas de 8 em 8 horas ou ainda tomadas de 6 em 6 horas. **Clenil® HFA 250 mcg: Crianças:** NÃO DEVE SER UTILIZADO POR CRIANÇAS. **Adultos (incluindo os idosos):** A dose inicial do produto é de 2 jatos (500 mcg), de 12 em 12 horas. Dependendo da severidade da doença, doses mais altas (até 8 jatos por dia) podem ser divididas em tomadas de 12 em 12 horas ou tomadas de 8 em 8 horas ou ainda tomadas de 6 em 6 horas. **Pacientes com insuficiência renal ou hepática:** Nenhum ajuste de dose é necessário. **VENDA SOB PRESCRIÇÃO MÉDICA. SE PERSISTIREM OS SINTOMAS, O MÉDICO DEVERÁ SER CONSULTADO.** Reg. M.S.: 1.0058.0111. SAC: 0800-114 525. www.chiesi.com.br

INTERAÇÕES MEDICAMENTOSAS: Há um potencial teórico de interação particularmente em pacientes sensíveis a álcool utilizando dissulfiram ou metronidazol. **CONTRAINDICAÇÕES:** hipersensibilidade individual aos derivados corticosteroides, hipersensibilidade ao álcool ou a qualquer outro constituinte desta formulação, tuberculose pulmonar, herpes simples ou crises asmáticas.

Material destinado exclusivamente à classe médica

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Fevereiro/2016