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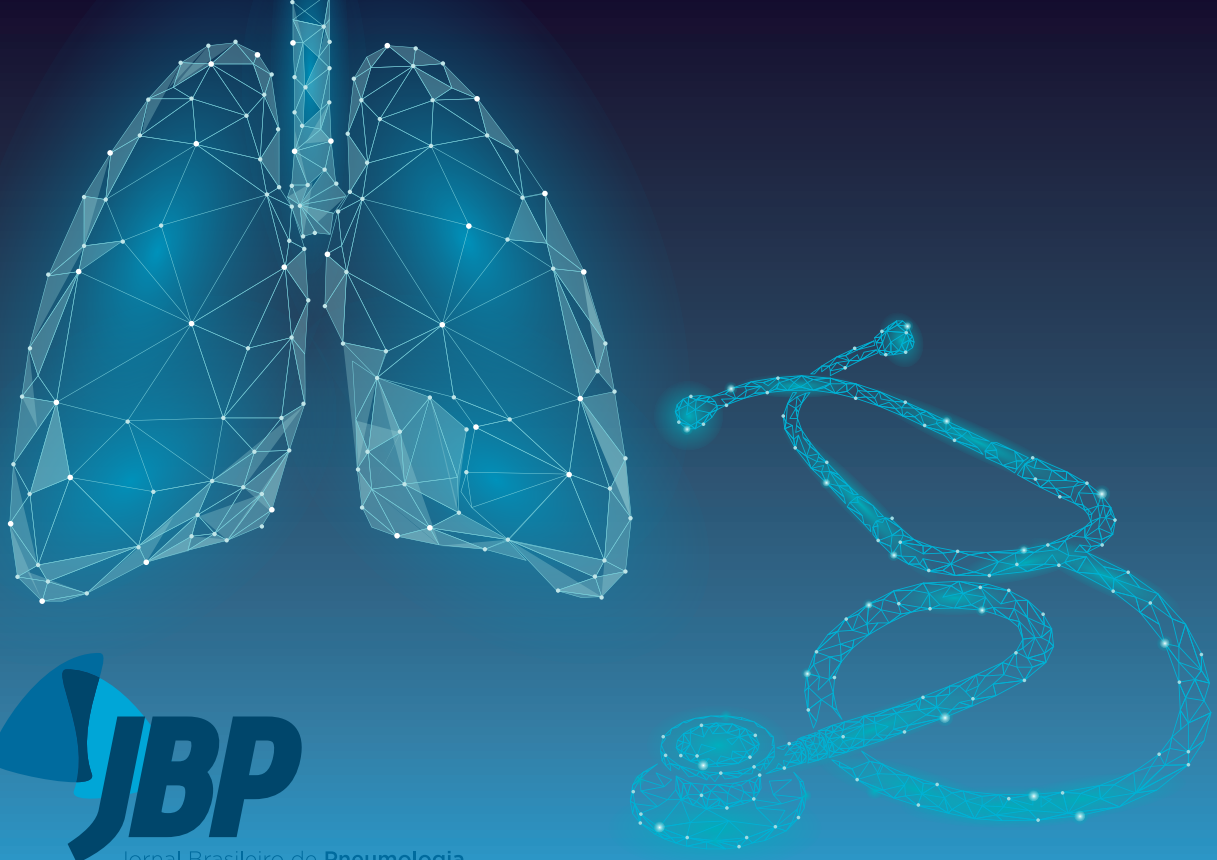
HIGHLIGHT

Weight loss and mortality in lung cancer

Obesity hypoventilation syndrome

Tuberculosis in renal transplant recipients



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Office: 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. Website: www.sbpt.org.br.
E-mail: sbpt@sbpt.org.br

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The need for a balance between highly prevalent diseases and neglected diseases

Rogério Souza[1,2,a]

Some topics can be considered as being highly represented in the JBP, in particular those related to mycobacterial diseases and obstructive airway diseases. That could not be otherwise, given that those are major public health problems and, as such, deserve to be emphasized, as well as because intervention policies targeting such diseases have an impact on a significant number of patients.

Among mycobacterial diseases, tuberculosis undoubtedly garners the most attention. In recent years, the JBP has published dozens of articles providing details on the epidemiology, diagnosis, and treatment of tuberculosis.[1-3] Likewise, the various aspects of COPD and asthma have been widely debated in our Journal.[4,5] If the intention of an official organ of dissemination of a scientific society is to keep its constituents up to date on the main aspects of the field in question, these data suggest a way forward.

There are numerous highly prevalent conditions that are underrepresented in our Journal. Perhaps the most striking examples are sleep-related breathing disorders and venous thromboembolism. Despite the epidemiological importance of both, the JBP has published an insignificant number of articles on those topics in the last decade. That raises the following question: is this low representativeness a reflection of the current state of research on those topics in our country, or (worse) does it reflect a progressive loss of interest or reduced participation of the members of our scientific society in these areas of activity? If the first hypothesis can be refuted on the basis of articles published in the international literature by highly cited Brazilian researchers, the second should be the subject of reflection and ongoing efforts by all of the parties involved. There is also a third, intermediate, hypothesis that could explain the low representativeness of those topics in the JBP: it is possible that cutting-edge research on those topics is being conducted but that the scope of that research is still too limited to prompt submission for publication in high-impact journals or in those with a more regional readership.

Despite the fact that it is not possible to provide a direct, objective answer to the question posed above, we have sought to increase the exposure of highly prevalent conditions that were previously underrepresented, in order to provide the reader with a reliable means of remaining up to date, as well as to raise awareness of the research groups existing in Brazil, particularly those working in the areas of interest. Therefore, diagnostic and therapeutic guidelines have both been discussed in depth.[6-8] In the near future, it might be worthwhile to utilize the JBP as a forum for discussion regarding the true role of the members of our scientific society in such areas, as well as to understand the need to create continuing education sections that contemplate those topics. In addition, it is important to analyze publications in these areas over time as a way of determining whether their exposure in recent years has had any significant impact.

In the JBP, not only has there been an increase in the publication of articles related to clinical conditions that are more rare or poorly investigated but such articles have also become some of the most widely cited JBP articles.[9,10] Nevertheless, the approach chosen was to seek to discuss the rarer situations through review articles. The aim was to make knowledge of poorly explored topics more accessible. Interstitial lung diseases and the evaluation of respiratory muscle function are clear examples of the demand for using the JBP as a resource for continuing education, an approach that could be translated directly to clinical practice.[11,12]

Maintaining a balance between the unequivocal interest in the most prevalent diseases and the need to explore incipient areas, including the exposure of conditions that are more rare, as well as the need to increase the representativeness of our Journal, is not a simple task and was the object of reflection in another editorial published previously in the JBP.[13] However, it is more than necessary in an environment such as ours, in which there is considerable heterogeneity in terms of the availability of resources and access to knowledge. The fruits of this attempt, initiated four years ago, will be known only in the (not too distant) future [14]. Nevertheless, it was undoubtedly a journey of absolute learning and exchange with the most distinguished researchers in Brazil, a significant number of whom are on the editorial board of our Journal, having been active participants in this journey. All of those researchers have our unequivocal, eternal gratitude. It is also certain that this path is as broad as the interest aroused in the reader—that is perhaps the key to growth: to generate interest in the most robust aspects of the field of pulmonology in Brazil, which has been consistently growing. Everyone involved has worked to see that growth reflected in our Journal, which now passes into the hands of its new Editor-in-Chief, Bruno Baldi, who has long been a member of its editorial board. I trust that his editorship will be well received and that he will enjoy the collaboration of all parties, in order to continue to expand the dissemination of the best of what is produced in respiratory medicine in Brazil.

1. Disciplina de Pneumologia, Instituto do Coração, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.
2. Editor-Chefe do Jornal Brasileiro de Pneumologia – JBP – Brasília (DF) Brasil.
a. http://orcid.org/0000-0003-2789-9143

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Pleural calcifications

Edson Marchiori[1,a], Bruno Hochhegger[2,b], Gláucia Zanetti[1,c]

An 87-year-old male diagnosed with prostate cancer, with no respiratory complaints, underwent a CT scan of the chest as part of an outpatient assessment. The scan showed pleural calcifications (calcified pleural plaques), with involvement of the diaphragmatic pleura (Figure 1).

Pleural calcifications usually result from fibrothorax, secondary to hemothorax, thoracic empyema, tuberculous pleural effusion, or even exposure to asbestos fibers. However, pleural calcifications are not always indicative of benign disease. Metastases of osteosarcoma can first appear as small foci of calcification and progress to extensive calcifications, leading to trapped lung. Talc pleurodesis can also mimic pleural calcification. Pleurodesis is currently considered the management of choice to control recurrent malignant pleural effusion. The most frequently used agent is talc, which, because of its high density, can be mistaken for calcifications in the pleural cavity.[1,2]

Our patient presented with a specific pattern of pleural calcification: calcified pleural plaques. Pleural plaques are highly suggestive of asbestos-related pleural disease. Although the use of asbestos has recently been banned in Brazil, its complications will still be seen for decades to come, as there is usually a long interval between the initial exposure to asbestos and the development of asbestos-related diseases. Individuals who are susceptible to developing asbestos-related diseases include not only those who are directly exposed to asbestos (people working with mining or other activities related to the many industrial uses of the substance, especially the fiber cement industry in Brazil) but also those who live in proximity to the mines.

Asbestos exposure can result in asbestosis, mesothelioma, and lung cancer. Asbestosis is a fibrosing interstitial pneumonitis caused by long-term exposure to asbestos through inhalation of asbestos fibers, which deposit in the lungs. The main HRCT findings of asbestosis are small subpleural nodular opacities, subpleural lines, ground-glass opacities, parenchymal bands, bronchiectasis and traction bronchiolectasis, architectural distortion, and honeycombing.[1,2]

Pleural plaques are usually asymptomatic but are a marker of asbestos exposure, indicating greater risk of developing pulmonary fibrosis or asbestos-related malignancies. They are composed of dense and relatively acellular connective tissue. They often have a rectangular shape and may be calcified or not. The involvement of the diaphragmatic pleura is highly suggestive of asbestos-related disease, which is almost always bilateral, although unilateral plaques can occur. In the case presented here, anamnesis revealed that the patient had lived near an asbestos mine for many decades and had actually worked in it for a few years. That fact, together with the imaging findings, was conclusive for the final diagnosis of asbestos-related pleural plaques.

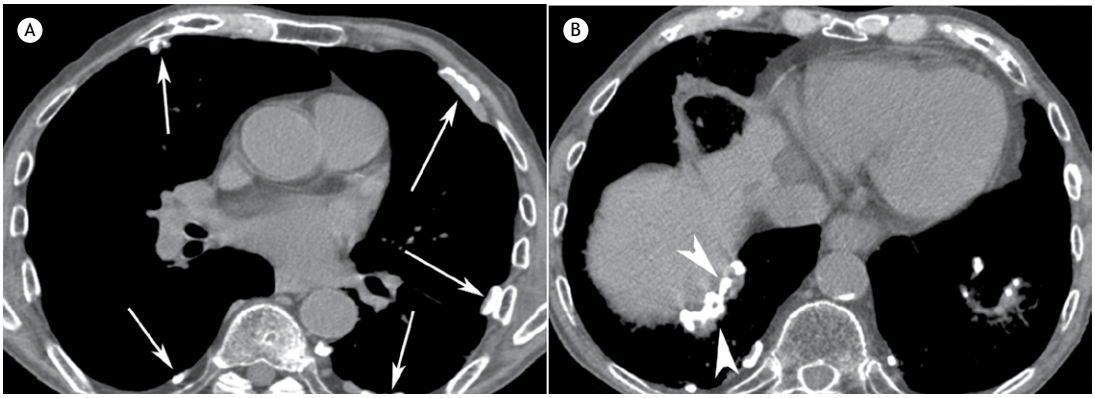

Figure 1. Axial CT scan of the chest, in mediastinal windows at the level of the middle lung regions (A) and lung bases (B), showing multiple pleural plaques, several of them partially calcified (arrows). In B, note the calcified plaques in relation to the diaphragmatic pleura, which are virtually pathognomonic of exposure to asbestos.

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1. Universidade Federal do Rio de Janeiro, Rio de Janeiro (RJ) Brasil.
2. Universidade Federal de Ciências da Saúde de Porto Alegre, Porto Alegre (RS) Brasil.
a. http://orcid.org/0000-0001-8797-7380; b. http://orcid.org/0000-0003-1984-4636; c. http://orcid.org/0000-0003-0261-1860

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Critical appraisal of the literature. Why do we care?

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

PRACTICAL SCENARIO

Investigators conducted a noninferiority, double-blind clinical trial involving 4,215 patients with mild asthma, randomly assigned to receive twice-daily placebo plus budesonide-formoterol used as needed vs. maintenance therapy with twice-daily budesonide plus terbutaline as needed. They found that budesonide-formoterol used as needed was noninferior to twice-daily budesonide concerning the rate of severe asthma exacerbations but was inferior in controlling symptoms.[1]

HOW TO CRITICALLY APPRAISE THE MEDICAL LITERATURE

As clinicians, when we read a paper reporting the benefit of a given intervention, we make a judgment regarding whether we should use those results to inform how we care for our patients. In our example, after reading the paper, we ask ourselves: should a clinician working in a public hospital in Brazil start prescribing budesonide-formoterol as needed rather than maintenance budesonide for her patients with mild asthma? What criteria should guide her decision to adopt a new intervention? One may think that if a study is published in a high-impact, peer-reviewed journal, it is of high quality and should therefore be used to guide clinical decision making. However, if the population included in the study or the context is different from her population, that may not be the case. Therefore, examining the external validity of a study is critical to informing local practice.

Other commonly used criteria are related to evaluating the quality of the evidence by evaluating the type of study design used. The pyramid of evidence puts meta-analyses at the top (as providing the highest quality of evidence), followed by systematic reviews and randomized controlled trials; then come observational studies (cohort, case-control, and cross-sectional studies); whereas case reports and case series are categorized as offering the lowest quality of evidence. Although those criteria may be helpful, making a detailed appraisal of a paper, taking into account aspects other than the study design, is a skill that researchers and clinicians can learn and apply when reading the literature.

Critical appraisal is the **systematic** evaluation of clinical research papers that helps us establish if the results are valid and if they could be used to inform medical decision in a given local population and context. There are several published guidelines for critically appraising the scientific literature, most of which are structured as checklists and address specific study designs.[2] Although different appraisal tools may vary, the general structure is shown in Table 1.

The items in Table 1 are a guide to appraising the content of a research article. There are also guidelines for appraising the quality of reporting of health research which focus on the reporting accuracy and completeness of research studies.[3] These two types of appraisal (content and reporting) are complementary and should both be used, because it is possible that a research paper has high reporting quality but is not relevant to the context in question.

KEY MESSAGE

Critical appraisal of the literature is an essential skill for researchers and clinicians, and there are easy-to-use guidelines. Clinicians have the responsibility to help patients make health-related decisions, which should be based on high-quality, valid research that is applicable in their context.

Table 1. How to appraise medical literature.

QUESTION	WHAT TO LOOK FOR
Does this study address a clearly focused, important question?	The research question should be clearly stated, and the scope of the study should be focused
Was the study design appropriate for the research question?	The chosen design should be suited to answering the research question
Did the study use valid methods to address this question?	Adequate participant allocation, intervention administration, and outcome assessments
Was systematic bias avoided or minimized?	The groups being compared should be as similar as possible except for the intervention/exposure being studied
Was the primary outcome adequately evaluated?	Assessments should be blinded when possible, measured objectively, and performed for all (or most) participants
Are these valid, significant results applicable to my patient or population?	The study intervention should be available, affordable, and acceptable in your clinical context

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1. Methods in Epidemiologic, Clinical, and Operations Research–MECOR–program, American Thoracic Society/*Asociación Latinoamericana del Tórax*, Montevideo, Uruguay.
2. Divisão de Pneumologia, Instituto do Coração, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.
3. Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA.
a. http://orcid.org/0000-0001-5742-2157; b. http://orcid.org/0000-0001-6548-1384

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ORIGINAL ARTICLE

Spirometry reference values for Black adults in Brazil

Tarciane Aline Prata[1,a], Eliane Mancuzo[2,3,b], Carlos Alberto de Castro Pereira[4,c], Silvana Spíndola de Miranda[2,d], Larissa Voss Sadigursky[5,e], Camila Hirotsu[6,f], Sérgio Tufik[6,g]

1. Programa de Pós-Graduação das Ciências Aplicadas à Saúde do Adulto, Universidade Federal de Minas Gerais – UFMG – Belo Horizonte (MG) Brasil.
2. Departamento de Clínica Médica, Faculdade de Medicina, Universidade Federal de Minas Gerais – UFMG – Belo Horizonte (MG) Brasil.
3. Laboratório de Função Pulmonar, Hospital das Clínicas, Universidade Federal de Minas Gerais – UFMG – Belo Horizonte (MG) Brasil.
4. Centro Médico Brasil, Guarulhos (SP) Brasil.
5. Laboratório de Função Pulmonar, Hospital Cárdio Pulmonar, Salvador (BA) Brasil.
6. Departamento de Psicobiologia, Universidade Federal de São Paulo – UNIFESP – São Paulo (SP) Brasil.

a. http://orcid.org/0000-0002-4765-2685
b. http://orcid.org/0000-0003-3891-875X
c. http://orcid.org/0000-0002-0352-9589
d. http://orcid.org/0000-0001-7245-4472
e. http://orcid.org/0000-0002-5561-8794
f. http://orcid.org/0000-0002-6760-0663
g. http://orcid.org/0000-0002-4012-4951

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ABSTRACT

Objective: To derive reference equations for spirometry in healthy Black adult never smokers in Brazil, comparing them with those published in 2007 for White adults in the country. **Methods:** The examinations followed the standards recommended by the Brazilian Thoracic Association, and the spirometers employed met the technical requirements set forth in the guidelines of the American Thoracic Society/European Respiratory Society. The lower limits were defined as the 5th percentile of the residuals. **Results:** Reference equations and limits were derived from a sample of 120 men and 124 women, inhabitants of eight Brazilian cities, all of whom were evaluated with a flow spirometer. The predicted values for FVC, FEV_1, FEV_1/FVC ratio, and PEF were better described by linear equations, whereas the flows were better described by logarithmic equations. The FEV_1 and FVC reference values derived for Black adults were significantly lower than were those previously derived for White adults, regardless of gender. **Conclusions:** The fact that the predicted spirometry values derived for the population of Black adults in Brazil were lower than those previously derived for White adults in the country justifies the use of an equation specific to the former population.

Keywords: Spirometry; Reference values; African continental ancestry group.

INTRODUCTION

Spirometry plays an essential role in the diagnosis and follow-up of respiratory diseases. The values obtained by spirometry should be compared with those predicted for nonsmokers without cardiopulmonary disease.[1-3]

Reference equations for spirometry in White adults in Brazil were derived in 2007.[4] The reference values obtained by using those equations were found to differ significantly from those obtained by using other equations.[5-7]

Several studies have shown that reference spirometric values (corrected for anthropometric characteristics) are lower in Black individuals than in White individuals, and this has led to the recommendation that race-specific equations be used.[3,7,8] Before spirometric reference equations were available for use in Black individuals, reference values originally derived for White individuals were used for Black individuals by applying an adjustment factor whereby the values for White individuals were reduced by 10-15%; however, the adjustment was found to be inadequate.[9]

According to the 2015 Brazilian National Household Sample Survey, 45.11% of Brazilians described themselves as White (Caucasian); 45.06% described themselves as Brown (biracial); 8.86% described themselves as Black (African); 0.47% described themselves as Yellow (Asian); and 0.38% described themselves as Red (Indigenous).[10]

In two studies conducted in Brazil, Black adults were studied in an attempt to obtain reference spirometric values, which were found to be similar to those for White adults in the country.[11,12] All spirometry tests were performed with spirometers that are currently obsolete.[4,13] Race can be determined by genetic ancestry or self-report. In a large study conducted in the USA and

Correspondence to:
Tarciane Aline Prata. Rua Piumí, 66/301, Cruzeiro, CEP 30310-080, Belo Horizonte, MG, Brasil.
Tel.: 55 31 98797-5978 or 55 31 2510-8859. E-mail: tarcipr@yahoo.com.br
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involving individuals who identified themselves as African American, spirometric values (corrected for age, sex, and height) were found to be lower in those with a higher percentage of African ancestry.[14] Similarly, in a study involving a large cohort of individuals in Brazil followed from birth to age 30 years (at which time they underwent pulmonary function testing), FVC and FEV_1 (corrected for height and other factors) were found to be lower in males and females with a higher percentage of African ancestry.[15] Regardless of genetic ancestry, anthropometric characteristics (in particular, a lower ratio of trunk length to standing height in Black individuals) and environmental factors (such as nutrition and socioeconomic status) can contribute to these differences.[15-17]

The objective of the present study was to derive reference equations for spirometry in Black adults in Brazil and compare them with those published in 2007 for White adults in the country.[4]

METHODS

All data were collected under the auspices of the *Respire e Viva* (Breathe and Live) program in the cities of São Paulo, Rio de Janeiro, Belo Horizonte, Porto Alegre, Curitiba, Santos, Brasília, and Recife, Brazil, in 2004 and in Salvador, Belo Horizonte, and a *quilombo* (a community established by escaped or freed slaves) in the state of Minas Gerais, Brazil, in the 2015-2017 period.[4] All of the participants volunteered for the study, in response to a verbal invitation or to advertisements placed in various locations. Initially, all participants completed an American Thoracic Society (ATS) Division of Lung Diseases respiratory questionnaire previously translated into Portuguese and validated for use in Brazil.[18,19] Subsequently, they underwent testing at designated facilities. The study project was approved by the local research ethics committee (Protocol no. CAAE 60844316.0.0000.5149).

The inclusion criteria were as follows:

- being over 20 years of age (for females) or over 25 years of age (for males), ages at which peak FVC is achieved[20]
- having a body mass index (BMI) of 18-30 kg/m^2
- having no significant respiratory symptoms, as determined by the aforementioned questionnaire[19]
- having had no lung disease (including the flu) in the last seven days
- having no history of respiratory disease potentially resulting in permanent pulmonary dysfunction, including tuberculosis, asthma, and thoracic surgery, with asthma being defined as a lifetime history of two or more episodes of wheezing relieved by bronchodilators
- having no history of physician-diagnosed heart disease
- not having been diagnosed with uncontrolled hypertension
- not having worked (for 1 year or more) in environments in which the concentration of dust was high and therefore posed a risk of lung disease
- having never smoked
- having identified themselves as Black (African) and showing phenotypic characteristics (as determined by the investigators) such as skin color, eye color, hair color, hair texture, nose shape, and lip shape[21]

The exclusion criteria were as follows: a history of pneumonia and hospitalization in the previous year; exposure to smoke from wood-burning stoves; exposure to cigarette smoke in the bedroom; and divergence between self-reported race and individual phenotypic characteristics (as determined by the investigators).

Weight and height were measured with participants standing barefoot and wearing light clothing. Spirometry was performed with participants in a sitting position and wearing a nose clip, Multispiro spirometers (Creative Biomedics, San Clemente, CA, USA) being used in 2004 and Koko spirometers (Pulmonary Data Service Inc., Louisville, CO, USA) being used in the 2015-2017 period. All spirometers met the technical requirements set forth in the ATS guidelines.[2] All spirometry tests were performed in accordance with the standards and acceptability and reproducibility criteria proposed by the Brazilian Thoracic Association (BTA)[1] and the ATS/European Respiratory Society.[22] A back-extrapolated volume of < 0.15 L or 5% of FVC (whichever was greater) was accepted. Peak flow was used in order to assess the initial effort.[1] Debris, condensed water vapor, or mucus deposition on the sensor can increase the pressure gradient and result in high flows and volumes after integration (resistance error). Tests with peak flows above 14 L/s in males and 11 L/s in females were excluded,[4] as were those in which peak flow was low in comparison with FEV_1, indicating inadequate effort, i.e., an FEV_1 (mL)/PEF (L/min) ratio > 8.5 in males and > 8.8 in females. The aforementioned values are above the 99th percentile found in the *Respire e Viva* (Breath and Live) study, which was conducted in 2004 and included Black and White participants, 413 of whom were male and 447 of whom were female (unpublished data). In that study, in addition to the standard reproducibility criteria for FEV_1 and FVC (0.15 L), at least two peak flow values lower than the highest value by 10% or less were required.[4]

After the acceptability and reproducibility criteria were met, the highest FVC, FEV_1, and PEF values were recorded. Expiratory flows were derived from maneuvers with the highest sums of FVC and FEV_1.[1,22]

All tests were performed by the investigators themselves or by technicians certified by the BTA. Calibrations were performed before each session of testing with the use of 3-L syringes. All tests were reviewed after the three best curves had been printed.

Sample size was calculated on the basis of a recommendation from the European Respiratory Society, which suggested that studies aimed at establishing

lung function reference values should include more than 100 males and 100 females.[23]

Statistical analysis was performed with the IBM SPSS Statistics software package, version 22.0 (IBM Corporation, Armonk, NY, USA). All calculations were performed in accordance with Pereira et al.[4] The lower limits of the regressions were estimated by the 5th percentile of the nonstandardized residuals. The spirometric and anthropometric data obtained in São Paulo, Belo Horizonte, and Rio de Janeiro were compared by ANOVA, and the influence of location (if any) on spirometric variables was determined by analysis of covariance.

The differences between the predicted spirometry values derived for White adults in Brazil in 2007 and those derived for Black adults in the present study were plotted against the former values. The paired Student's t-test was used in order to compare the means. Given the multiple comparisons, the level of significance was set at $\alpha < 0.01$.

RESULTS

Of the 264 Black adults who underwent spirometry, 244 (124 women and 120 men) were included in the final analysis. A total of 11 women and 9 men were excluded because of discrepant FVC/height^2 values or because of submaximal initial efforts. Data on the study participants were collected in the following locations: São Paulo (n = 88); Belo Horizonte plus a *quilombo* in the state of Minas Gerais (n = 83); Rio de Janeiro (n = 52); Salvador (n = 10); other cities in Brazil (n = 11). Table 1 shows anthropometric data for the study participants, by sex. Males ranged in age from 26 years to 82 years, whereas females ranged in age from 20 years to 83 years. The median height was 171 cm (range, 151-187 cm) in males and 158 cm (range, 145-175 cm) in females.

Table 2 shows spirometric data (means ± standard deviations) for the study participants, by sex. ANOVA showed that FVC in females was lower in Belo Horizonte than in São Paulo and Rio de Janeiro. However, analysis of covariance (with age and height as covariates) showed that the difference was not significant. The mean age of females was highest in Belo Horizonte (56 ± 17 years vs. 43 ± 14 years; $p < 0.01$).

The predicted values for FEV_1, FVC, FEV_1/FVC, and PEF were better described by linear equations, whereas the flows were better described by logarithmic equations. Prediction equations for males and females are shown in Table 3 and Table 4, respectively. Weight played no relevant role in any of the reference equations.

The coefficients of determination (r^2) were generally similar between males and females, being higher for FVC and FEV_1 than for expiratory flows. With regard to the flows, r^2 values were highest for $FEF_{75\%}$. With regard to age, FEV_1 decreased on average 24 mL per year in males and 17 mL per year in females.

The lower limit for the FEV_1/FVC ratio in Black adults in Brazil was determined by subtracting 9 from the predicted value for males (Table 3) and 8 from the predicted value for females (Table 4).[24,25] Values below 70% were observed among males over 60 years of age and females over 65 years of age.

Figure 1 shows a comparison of the FVC and FEV_1 values derived for White adults in Brazil in 2007[4] with those derived for Black adults in Brazil in the present study. The predicted values for FVC and FEV_1 were consistently lower in Black individuals than in White individuals, regardless of sex. In males, FVC was on average 0.30 L lower in Black individuals than in White individuals, FEV_1 being 0.28 L lower in the former than in the latter ($p < 0.001$ for both). In females, FVC was on average 0.14 L lower in Black individuals than in White individuals, FEV_1 being 0.11 L lower in the former than in the latter ($p < 0.001$ for both). The differences between the predicted values for White individuals and those for Black individuals were

Table 1. Anthropometric data (age, height, and body mass index) for the study participants, by sex.

Variable	Males (n = 120)		Females (n = 124)	
	n	%	n	%
Age, years				
20-24	-	-	7	5.6
25-34	33	27.5	31	25.0
35-44	31	25.8	18	14.5
45-54	23	19.2	23	18.5
55-64	16	13.3	24	19.4
65-74	8	6.7	13	10.5
≥ 75	9	7.5	8	6.5
Height, cm				
145-154	1	0.8	29	23.3
155-164	25	20.8	74	59.7
165-174	55	45.8	20	16.1
175-184	34	28.3	1	0.8
≥ 185	5	4.2	-	
BMI, kg/m^2				
18-24	38	31.7	43	34.7
25-30	82	68.3	81	65.3

BMI: body mass index.

Table 2. Spirometric data for the study participants, by sex.[a]

Variable	Males (n = 120)	Females (n = 124)
FVC, L	4.42 ± 0.78	3.10 ± 0.52
FEV_1, L	3.55 ± 0.69	2.55 ± 0.48
FEV_1/FVC, %	80.3 ± 5.4	82.0 ± 5.4
$FEF_{25-75\%}$, L/s[b]	3.54 ± 1.17	2.77 ± 0.93
$FEF_{50\%}$, L/s[b]	4.39 ± 1.36	3.54 ± 1.06
$FEF_{75\%}$, L/s[b]	1.43 ± 0.63	1.11 ± 0.52
PEF, L/s	9.77 ± 2.07	6.73 ± 1.28

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

found to increase as the predicted values increased. A significant positive correlation was found between height and FVC in males and females (r = 0.93 and r = 8.88, respectively; p < 0.001 for both).

The paired Student's t-test showed that the FEV_1/FVC ratio was higher in White males than in Black males, albeit only 1.0% higher on average (p = 0.021). In females, the FEV_1/FVC ratio was similar between White

Table 3. Regression equations, coefficient of determination (r^2), and lower limits for spirometric variables in Black males.

Type of equation	Height coefficient	Age coefficient	Constant	r^2	Lower limit
Linear					
FVC, l	0.048	−0.019	−2.931	0.52	P − 0.78
FEV_1, l	0.033	−0.024	−0.989	0.57	P − 0.76
FEV_1/FVC, %	−0.134	−0.189	112.0	0.26	P − 8.70
PEF, L/s	0.059	−0.048	1.903	0.24	P − 2.67
Logarithmic					
$FEF_{25-75\%}$, L/s	−	−0.670	3.735	0.42	P × 0.62
$FEF_{50\%}$, L/s	−	−0.517	3.383	0.30	P × 0.62
$FEF_{75\%}$, L/s	−	−0.956	3.872	0.50	P × 0.57

P: predicted. Linear equations: height × coefficient − age × coefficient ± constant. Example: FVC = height × 0.048 − age × 0.019 − 2.931 Logarithmic equations: natural log $^{(\log \text{height} \times \text{coefficient} - \log \text{age} \times \text{coefficient} \pm \text{constant})}$. Example: $FEF_{25-75\%} = 2.7183^{(-\log n \text{ age} \times 0.670 + 3.735)}$.

Table 4. Regression equations, coefficient of determination (r^2), and lower limits for spirometric variables in Black females.

Type of equation	Height coefficient	Age coefficient	Constant	r^2	Lower limit
Linear					
FVC, L	0.035	−0.013	−1.83	0.47	P − 0.66
FEV_1, L	0.025	−0.017	−0.69	0.56	P − 0.55
FEV_1/FVC, %	−0.074	−0.200	103.2	0.33	P − 7.8
PEF, L/s	−	−0.029	8.134	0.14	P− 1.77
Logarithmic					
$FEF_{25-75\%}$, L/s	−	−0.625	3.32	0.37	P × 0.63
$FEF_{50\%}$, L/s	−	−0.436	2.862	0.23	P × 0.61
$FEF_{75\%}$, L/s	−	−1.01	3.805	0.50	P × 0.54

P: predicted. Linear equations: height × coefficient − age × coefficient ± constant.
Logarithmic equations: natural log$^{(\log \text{height} \times \text{coefficient} - \log \text{age} \times \text{coefficient} \pm \text{constant})}$.

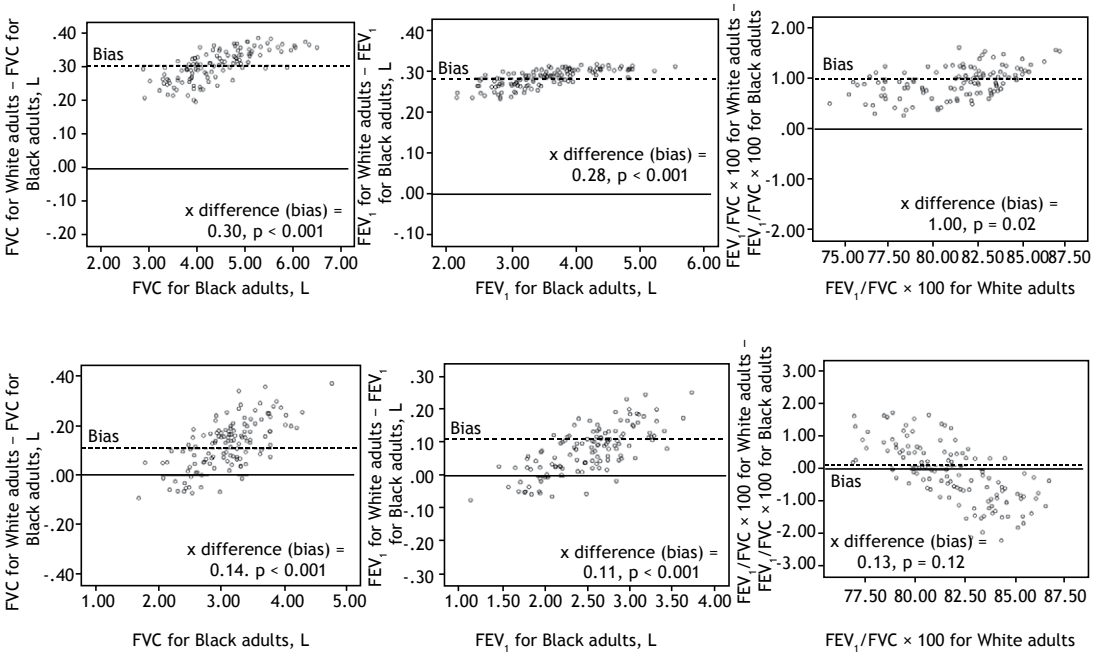

Figure 1. Differences between the FVC, FEV_1, and FEV_1/FVC% values predicted for White adults by Pereira et al.[4] and those predicted for Black males (above) and females (below).

individuals and Black individuals (p = 0.12). There was no significant correlation between the difference in FEV_1/FVC between White and Black individuals and age in males or females.

When the predicted values for White and Black individuals were plotted, the percentage difference was found to be proportional for FVC and FEV_1 (~6.5%; p < 0.01) in males but not in females (Figure 2).

DISCUSSION

To our knowledge, the present study is the first multicenter study in Brazil to derive reference equations for spirometry in Black adults by including a representative sample of volunteers and using spirometers meeting the ATS criteria.[2] A comparison between the equations derived for Black adults in the present study and those derived for White adults in 2007[4] showed a disproportionate difference between the two regarding FVC and FEV_1 in females, indicating the need for an equation specific to the former population and the inappropriateness of applying a correction factor to values originally derived for White individuals.[9] Although the differences between the two groups of equations regarding FVC and FEV_1 in males were proportional, they were lower than reported in the literature.[9]

Studies aimed at deriving lung function reference values should include only nonsmokers without respiratory symptoms or cardiopulmonary disease. To that end, a previously validated respiratory epidemiology questionnaire should be used. If all of the aforementioned criteria are met, it is valid to use volunteers to establish reference values.[18,26,27]

Reference values should not be extrapolated to age groups or patient heights other than those included in the regression equations.[1] Our study sample was representative of Black adults in Brazil because males and females of varying heights and ages were included in the study. The oldest males and females meeting the criteria for inclusion in the present study were 82 years old and 83 years old, respectively.

The number of participants over 65 years of age was low in the present study because it is difficult to find healthy 65-year-old individuals meeting the inclusion criteria.[4] With regard to participant height, there was no difference between the present study and the study published in 2007.[4] The median height of the individuals who participated in the present study was found to be similar to that of those in the Brazilian population: 170.5 cm vs. 171 cm in males and 158 cm vs. 159 cm in females.[28] The negative correlation between the FEV_1/FVC ratio and height in the present study was due to increased expiratory muscle strength

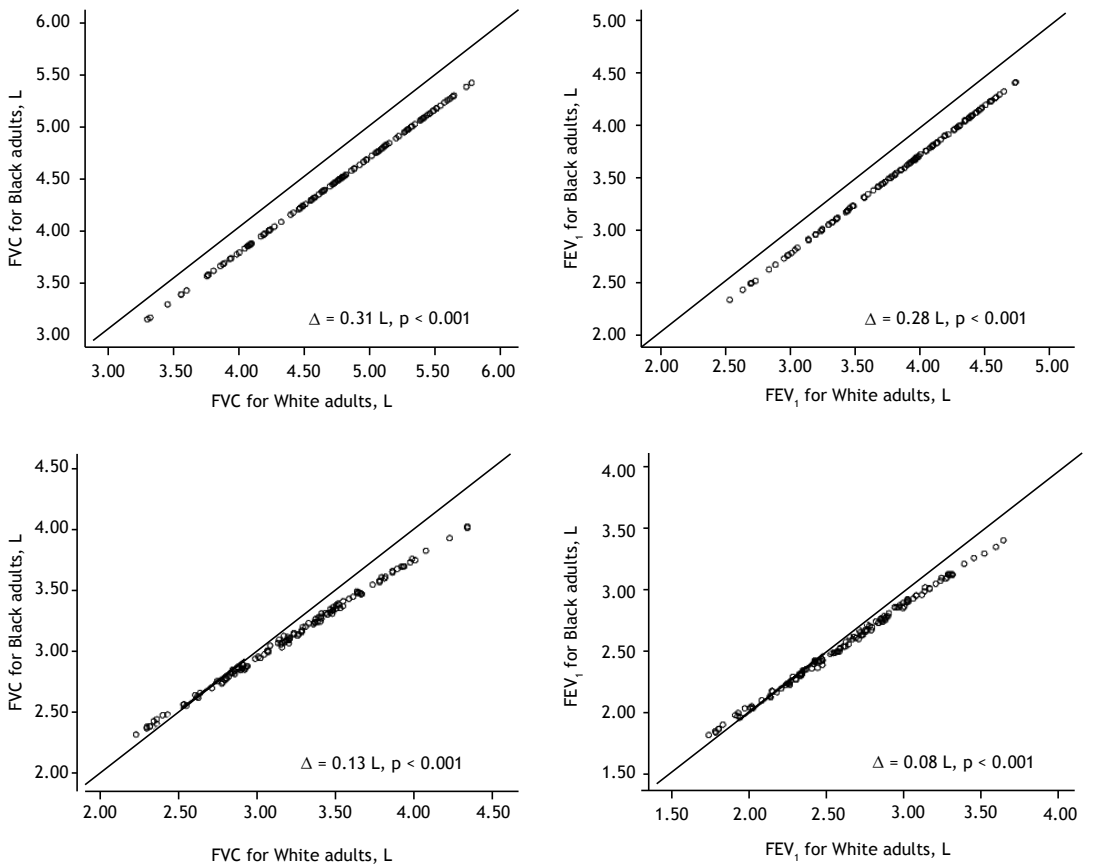

Figure 2. Comparisons between the FVC and FEV_1 values predicted for White adults by Pereira et al.[4] and those predicted for Black males (above) and females (below).

and, consequently, airway compression.[1] Individuals with a BMI > 30 kg/m^2 were not included, the effect of obesity on lung volumes therefore being excluded.[29]

The process of building a regression model involves several steps, and, because of their simplicity, linear equations should be preferred whenever the adjustment is similar to other models. As occurred in the study in which reference equations were derived for White adults in Brazil,[4] the flow equations derived in the present study followed a logarithmic curve, the lower limit therefore being a fixed percentage of the predicted value, with sensitivity for detecting airflow obstruction.[4] In the present study, $FEF_{75\%}$ was found to have the highest coefficient of determination with anthropometric data, a finding that is of particular interest and is consistent with those of the aforementioned study.[4]

Approximately 10% of the White individuals included in the aforementioned study[4] were obese; nevertheless, FVC and FEV_1 were lower in the present study than in that study.[4]

It has long been recognized that lung function values are lower in Black adults than in White adults, although the FEV_1/FVC ratio is similar.[7,8,16,30-32] These findings have been confirmed in studies employing genetic ancestry to determine race.[14,15]

Studies conducted in Brazil and establishing a relationship between self-reported skin color and genetic ancestry have shown conflicting results. In a study conducted by Menezes et al.,[15] a good correlation was found between self-reported skin color and genetic ancestry. Similar results were obtained in an unpublished study involving 137 individuals recruited in São Paulo. However, in another study conducted in Brazil, no correlation was found between self-reported race and genetic ancestry.[33] In individual cases, the apparent race and genetically determined race can be widely divergent. In addition, genetic ancestry testing is not without limitations.[34]

The difference in lung function across races has been attributed in part to anthropometric factors, including a lower ratio of trunk length to standing height (Cormic index) in Black individuals.[15,16,32,35] The aforementioned ratio decreases as height increases, thus explaining why the difference in lung function between Black and White individuals increases as height increases.[36] Other explanations include socioeconomic and environmental factors, which are closely related to race in several countries, including Brazil.[35,37] However, in a study conducted in the USA and in the study by Menezes et al.,[5,15] socioeconomic and environmental factors were found to have only a minor influence on lung function. Anthropometric factors, socioeconomic conditions, and other indicators explain in part the difference in spirometric values across races.[17] Lung function is determined by several genes, and extensive genetic mapping combined with determination of race (ancestry) might refine predicted lung function values beyond anthropometric measures.[38]

Unlike our study, two studies involving Black adults in Brazil found no differences between the predicted spirometry values derived for Black adults and those derived for White adults.[11,12] Scalambrini et al.[11] studied 139 Black men and 56 Black women and compared the obtained values with those obtained in a parallel study involving White individuals (334 men and 141 women),[37] both studies having been conducted in the 1990s and having employed a Vitalograph spirometer (Vitalograph, Buckingham, UK). Race was determined by the investigators. In an unpublished review of the data from the two aforementioned studies,[11,37] FVC was found to be significantly lower in Black males and females.

Rufino et al.[12] derived predicted values from a sample of 146 male volunteers and 242 female volunteers in the state of Rio de Janeiro, Brazil. Race was self-reported. Although there were no apparent differences between Black and White individuals regarding FVC or FEV_1, the data were raw and not corrected for age or height. The fact that a single bellows spirometer (Vitalograph) was used during the 4-year study period explains why FVC values were on average 0.5 L lower than those found by Pereira et al.[4] Because of accumulation of debris and humidity (and because cleaning is impossible), the compliance of the spirometer bellows decreases with repeated use, and this can lead to an underestimation of the parameter values.[4,13]

The present study has some limitations that should be noted. Sitting height and socioeconomic status were not assessed. Had they been assessed, the differences in FVC and FEV_1 between Black and White individuals might have been less dramatic.[16] The number of individuals over 80 years of age was small. Women taller than 175 cm were not represented.

In conclusion, the predicted spirometry values obtained in the present study were derived from a large sample of Black adults in Brazil. The fact that the predicted spirometry values derived for the population of Black adults in Brazil were lower than those previously derived for White adults in the country[4] justifies the use of equations specific to the former population.

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ORIGINAL ARTICLE

Longitudinal follow-up of cardiac vagal activity in individuals undergoing endoscopic thoracic sympathectomy

Ana Paula Ferreira[1,2,3,a], Plinio dos Santos Ramos[1,2,3,b], Jorge Montessi[2,3,4,c], Flávia Duarte Montessi[2,3,d], Eveline Montessi Nicolini[3,4,e], Edmilton Pereira de Almeida[4,f], Djalma Rabelo Ricardo[1,2,3,g]

1. Programa de Pós-Graduação Strictu Sensu, Universidade do Estado do Rio de Janeiro – UERJ – Rio de Janeiro (RJ) Brasil.
2. Faculdade de Ciências Médicas e da Saúde de Juiz de Fora – FCMS/JF – Juiz de Fora (MG) Brasil.
3. Hospital e Maternidade Therezinha de Jesus – HMTJ – Juiz de Fora (MG) Brasil.
4. Hospital Monte Sinai, Juiz de Fora (MG) Brasil.

a. http://orcid.org/0000-0002-5761-798X
b. http://orcid.org/0000-0003-4035-3890
c. http://orcid.org/0000-0002-0143-8384
d. http://orcid.org/0000-0001-7736-3094
e. http://orcid.org/0000-0002-4973-2398
f. http://orcid.org/0000-0001-5510-0015
g. http://orcid.org/0000-0003-2456-1470

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Study carried out at the Faculdade de Ciências Médicas e da Saúde de Juiz de Fora – FCMS/JF – Juiz de Fora (MG) Brasil.

ABSTRACT

Objective: To conduct a longitudinal investigation of cardiac vagal activity (CVA) by measuring resting HR and calculating the cardiac vagal index (CVI) in individuals undergoing sympathectomy for the treatment of primary hyperhidrosis. **Methods:** This was a descriptive longitudinal study involving 22 patients, 13 of whom were female. The mean age was 22.5 ± 8.8 years. The palms, soles, and axillae were the most commonly affected sites. Resting HR was measured by an electrocardiogram performed 20 min before the 4-second exercise test (4sET), which was used in order to evaluate CVA at three different time points: before surgery, one month after surgery, and four years after surgery. **Results:** Resting HR (expressed as mean ± SE) was found to have decreased significantly at 1 month after surgery (73.1 ± 1.6 bpm before surgery vs. 69.7 ± 1.2 bpm at one month after surgery; p = 0.01). However, the HR values obtained at four years after surgery tended to be similar to those obtained before surgery (p = 0.31). The CVI (expressed as mean ± SE) was found to have increased significantly at one month after surgery (1.44 ± 0.04 before surgery vs. 1.53 ± 0.03 at one month after surgery; p = 0.02). However, the CVI obtained at four years after surgery tended to be similar to that obtained before surgery (p = 0.10). **Conclusions:** At one month after sympathectomy for primary hyperhidrosis, patients present with changes in resting HR and CVA, both of which tend to return to baseline at four years after surgery.

Keywords: Hyperhidrosis; Sympathectomy; Autonomic nervous system; Exercise test; Electrocardiography.

INTRODUCTION

Primary or essential hyperhidrosis is a disorder that is characterized by uncontrollable excessive sweating of unknown cause.[1] It primarily affects the axillae, palms, soles, and face, causing intense discomfort and having a negative effect on social, emotional, and professional functioning.[2]

The clinical treatment of hyperhidrosis can be topical, electrical, or systemic; however, in most cases, surgery is the only effective treatment option. The increasing availability of video-assisted thoracic surgery plays a decisive role in establishing sympathectomy as the gold standard for definitive treatment of severe hyperhidrosis.[3,4]

It is well described in the literature that the sympathetic and parasympathetic nervous systems are involved in autonomic cardiovascular control,[5-7] and that T2, T3, and T4 sympathetic ganglia are responsible for cardiac control.[8] Several studies have investigated the effects of sympathectomy on the autonomic nervous system, having found changes in autonomic cardiac function after surgical intervention.[8-11] However, in the aforementioned studies, assessment of heart rate variability (HRV) was the only method used in order to assess cardiovascular autonomic function. Although HRV assessment is a widely used method, it is poorly reproducible.

Cardiovascular autonomic dysfunction is associated with an increased risk of mortality, which is primarily due to reduced vagal activity.[12-14] Therefore, an investigation of the parasympathetic nervous system in patients with hyperhidrosis appears to be useful from a clinical standpoint, contributing to future therapeutic strategies for heart disease patients. The objective of the present study was to conduct a longitudinal investigation of cardiac vagal activity (CVA) by measuring resting HR and calculating the cardiac vagal index (CVI) in individuals undergoing sympathectomy for the treatment of primary hyperhidrosis.

METHODS

Sample

This was a descriptive longitudinal study involving 22 patients, 13 of whom were female. The mean age

Correspondence to:
Djalma Rabelo Ricardo. Faculdade de Ciências Médicas e da Saúde de Juiz de Fora, SUPREMA, Alameda Salvaterra, 200, Salvaterra, CEP 36033-003, Juiz de Fora, MG, Brasil.
Tel.: 55 32 98886-2891. E-mail: djalmaricardo@suprema.edu.br
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was 22.5 ± 8.8 years (range, 12-45 years). All of the study participants sought surgical treatment (sympathectomy) for hyperhidrosis, and none had a history of cardiovascular disease. All of the study participants had primary hyperhidrosis of varying severity. The palms and soles were the most commonly affected sites, followed by the axillae and face. The exclusion criteria were as follows: being a smoker; being unable to perform the 4-second exercise test (4sET); being obese (i.e., having a body mass index > 30 kg/m^2); and using medications potentially affecting the autonomic nervous system. Smokers were defined as those who had smoked one or more cigarettes in the 30 days preceding the study.

The study participants were evaluated at a teaching hospital in the city of Juiz de Fora, Brazil, between January of 2010 and December of 2014, at three different time points: before surgery, 1 month after surgery, and 4 years after surgery. The present study was approved by the local research ethics committee (Ruling no. 1,324,807). All of the study participants gave written informed consent.

Height (in cm) was measured to the nearest 0.1 cm with a stadiometer (Sanny; American Medical do Brasil Ltda., São Bernardo do Campo, Brazil), and body weight (in kg) was measured to the nearest 0,1 kg with a digital scale (Welmy, São Paulo, Brazil). Blood pressure was measured at rest.[15] At the three time points, participants underwent assessment of CVA by analysis of resting HR and the 4sET, which was performed on a cycle ergometer.

Sympathectomy

Sympathectomy was performed with patients in the supine position, with both arms extended laterally at a 70° angle to the ipsilateral hemithorax and resting comfortably on a customized armrest. Patients subsequently underwent total intravenous anesthesia and endotracheal intubation, patient weight being taken into account in order to adjust mechanical ventilation settings. Throughout the procedure, patients received ventilatory support at a tidal volume of 7 mL/kg of body weight, a respiratory rate of 12 breaths/min, and an FiO_2 of 100%. For standardization purposes, all surgical procedures were on the right side, sympathectomy being performed at T4, T5, and T6. Apnea duration was assessed by capnography and expressed as disconnection time, which was used as a proxy for surgical time (i.e., the time elapsed between insertion and removal of the trocar through which a video camera and electrocautery device were inserted). The surgical procedure was discontinued if pulse oximetry showed an SpO_2 of < 90% on room air, patients being ventilated until pulse oximetry showed an SpO_2 > 98% on room air.

Resting HR

Resting HR was obtained by a continuous recording of a single electrocardiographic lead (CC5 or CM5) with the PowerLab system (PowerLab 4/26T and Lab Chart Pro 7 software; ADInstruments Pty Ltd, Bella Vista, Australia), with an accuracy of 1 ms.

4sET

The 4sET is performed in order to evaluate the parasympathetic nervous system alone over the course of 4 s of exercise performed during a 12-s breath hold following a maximal inspiratory maneuver. The 4sET is performed on a cycle ergometer and consists of pedaling as fast as possible without load from the 5th to the 9th second of a 12-s breath hold following a maximal inspiratory maneuver. The 4sET quantifies CVA through the CVI, which represents HR acceleration triggered reflexively by cardiac vagal inhibition. Individuals performing the 4sET are required to follow four consecutive commands: first, a maximal inspiratory maneuver performed rapidly through the mouth; second, pedaling as fast as possible; third, an abrupt stop; and fourth, an expiratory maneuver.[16,17]

The CVI is a dimensionless index obtained by the 4sET, being the ratio between the RR interval immediately before exercise (or the first RR interval during exercise, whichever is longer) and the shortest RR interval during exercise (which is typically the last RR interval).

The 4sET allows evaluation of the integrity of the parasympathetic nervous system alone and was used in the present study because it would have been impossible to measure CVA accurately and noninvasively by other methods for cardiovascular autonomic function assessment. In addition, the 4sET is reliable[16] and has been pharmacologically validated.[18] The system that was used for measuring resting HR was also used for electrocardiographic recordings.

Statistical analysis

The Shapiro-Wilk test was used in order to determine the distribution of the data, which was found to be normal. For all autonomic function variables, the paired Student's t-test and one-way ANOVA were used. The level of significance was set at 5%. Statistical analysis was performed with the GraphPad software, version 5.01 (GraphPad Inc., San Diego, CA, USA).

RESULTS

A total of 22 patients, 13 of whom were female, underwent sympathectomy for the treatment of primary hyperhidrosis, their mean age being 22.5 ± 8.8 years (range, 12-45 years). Of those 22 patients, only 12 (7 of whom were female) returned for a follow-up evaluation 4 years after surgery, their mean age being 25.6 ± 8.2 years. The demographic characteristics of the study sample are shown in Table 1.

Resting HR (expressed as mean ± SE) was measured by an electrocardiogram performed 20 min before the 4sET and was found to have decreased significantly at 1 month after surgery (73.1 ± 1.6 bpm before surgery vs. 69.7 ± 1.2 bpm at 1 month after surgery; p =

0.01). At 4 years after surgery, resting HR was found to be 72.1 ± 1.7 bpm (p = 0.31), meaning that the HR values obtained at 4 years after surgery tended to be similar to those obtained before surgery. These results are shown in Figure 1.

The CVI (as assessed by the 4sET and expressed as mean ± SE) reflects the magnitude of parasympathetic modulation of HR, a significant difference being found between the CVI obtained before surgery and the CVI obtained at 1 month after surgery (1.44 ± 0.04 vs. 1.53 ± 0.03; p = 0.02). As can be seen in Figure 2, the CVI obtained at 4 years after surgery tended to be similar to that obtained before surgery (p = 0.10).

DISCUSSION

Hyperhidrosis severely affects the social life, quality of life, self-confidence, and character of patients. The surgical treatment of primary hyperhidrosis is aimed at improving all of the above by means of ablation of thoracic sympathetic ganglia.[19] However, surgical complications such as compensatory sweating are common and not always preventable. Therefore, in the present study, ablation was performed at T4, T5, and T6 because compensatory sweating rates are known to be lower when sympathectomy is performed at those levels.[4]

The sympathetic fibers that innervate the heart, lungs, and other thoracic viscera can also be affected because they lie along the surgical path. Therefore, autonomic changes (particularly sympathetic nervous system changes) resulting from such surgical procedures are theoretically unavoidable.[20]

Although sympathetic cardiac changes are expected to occur after sympathectomy,[21] little is known about the effect of sympathectomy on CVA. In the present study, significant differences were found between the preoperative and postoperative period regarding resting HR and the CVI, CVA having increased at 1 month after surgery. This finding is consistent with those of Cruz et al.,[22] who analyzed HRV through 24-h Holter monitoring after T2-T3 sympathectomy and found an increase in high-frequency (HF) power in normalized units, a reduction in low-frequency (LF) power in normalized units, and a reduction in the LF/HF ratio 2 weeks after surgery.

Schmidt et al.[23] longitudinally followed individuals undergoing sympathectomy for hyperhidrosis and compared them with matched controls, calculating HRV and sequential baroreflex sensitivity at three different time points (before surgery, 6 months after surgery, and 12 months after surgery). At 12 months after surgery, significant differences were found between patients and controls regarding HRV, which subsequently returned to relatively normal values. These findings suggest that sympathectomy resulted in reduced sympathetic activity and increased cardiac parasympathetic activity. However, there were no significant changes in sequential baroreflex sensitivity.

Our findings suggest a significant increase in parasympathetic activity at 1 month after surgery. In

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

Characteristic	Before surgery (N = 22)	One month after surgery (N = 22)	Four years after surgery (n = 12)
Age	22.5 ± 8.8	22.5 ± 8.8	25.6 ± 8.2
Weight, kg	62.7 ± 13.2	62.6 ± 13.3	65.0 ± 11.5
Height, m	1.7 ± 0.1	1.7 ± 0.1	1.7 ± 0.1
BMI, kg/m^2	22.4 ± 2.9	22.4 ± 2.9	22.8 ± 2.6
SBP, mmHg	113.5 ± 12.4	111.8 ± 10.2	117.0 ± 9.2
DBP, mmHg	74.6 ± 9.9	75.4 ± 9.2	75.5 ± 8.5

BMI: body mass index; SBP: systolic blood pressure; and DBP: diastolic blood pressure. [a]Values expressed as mean ± SD.

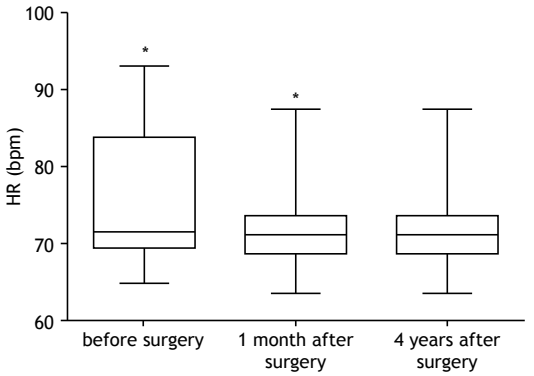

Figure 1. Resting HR before surgery, one month after surgery, and four years after surgery. *p = 0.01.

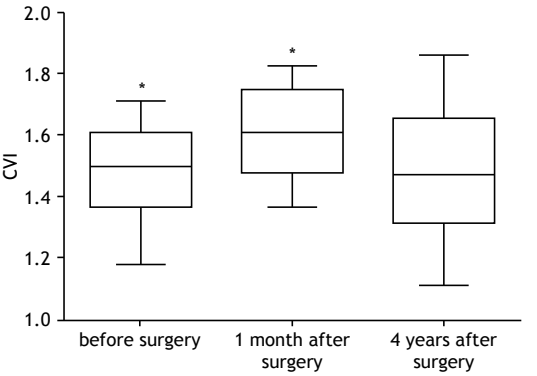

Figure 2. Cardiac vagal index (CVI) before surgery, one month after surgery, and four years after surgery. *p = 0.02.

contrast, Wiklund et al.[8] measured HRV and found a reduction in LF power after sympathectomy, with no significant increase in HF power; after 6 months of follow-up, LF power remained at a lower level, whereas HF power decreased, returning to baseline values. The authors concluded that sympathectomy results in an initial sympathovagal imbalance, with a parasympathetic predominance, which is restored in the long term.

Senard et al.[24] investigated 19 patients with hyperhidrosis and 20 age-matched healthy controls and found no significant differences between the two groups regarding LF or HF power in normalized units during HRV assessment, a finding that is consistent with those of another study comparing hyperhidrosis patients and healthy controls.[10,24] The fact that the aforementioned findings are inconsistent with those of the present study is probably due to the physiological nature of the tests employed, the 4sET being used in the present study in order to evaluate the parasympathetic nervous system.

In the present study, cardiac parasympathetic activity was found to have increased after surgery, a finding that might be due to the fact that the 4sET is a test that is reliable[16] and has been validated[18] for assessment of CVA by means of the CVI, a dimensionless index that reflects vagal withdrawal induced by rapid exercise. Assessment of HRV is used in most such studies; although HRV assessment is widely used in order to assess cardiac autonomic modulation, it has low reproducibility.[17,25-27] Given that our study focused on assessing the cardiac parasympathetic nervous system, HRV assessment[28] was not used.

In summary, parasympathetic nervous system activity was found to have increased at 1 month after sympathectomy for the treatment of primary hyperhidrosis. However, in the long term, mean resting HR values returned to baseline, suggesting a physiological adaptation 4 years after surgery.

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Prevalence of latent *Mycobacterium tuberculosis* infection in renal transplant recipients

Mônica Maria Moreira Delgado Maciel[1,2,a], Maria das Graças Ceccato[3,b], Wânia da Silva Carvalho[3,c], Pedro Daibert de Navarro[1,d], Kátia de Paula Farah[1,e], Silvana Spindola de Miranda[1,f]

1. Faculdade de Medicina, Universidade Federal de Minas Gerais, Belo Horizonte (MG) Brasil.
2. Grupo de Transplante Renal, Hospital de Clínicas, Universidade Federal de Minas Gerais, Belo Horizonte (MG) Brasil.
3. Faculdade de Farmácia, Universidade Federal de Minas Gerais, Faculdade de Farmácia

a. http://orcid.org/0000-0002-3884-9507
b. http://orcid.org/0000-0002-4340-0659
c. http://orcid.org/0000-0002-2575-6352
d. http://orcid.org/0000-0003-3267-4985
e. http://orcid.org/0000-0002-8978-4512
f. http://orcid.org/0000-0001-7245-4472

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Study carried out at the Hospital das Clínicas, Universidade Federal de Minas Gerais, Belo Horizonte (MG) Brasil.

ABSTRACT

Objective: To estimate the prevalence of latent *Mycobacterium tuberculosis* infection (LTBI) in renal transplant recipients and to assess sociodemographic, behavioral, and clinical associations with positive tuberculin skin test (TST) results. **Methods:** This was a cross-sectional study of patients aged ≥ 18 years who underwent renal transplantation at the Renal Transplant Center of the Federal University of Minas Gerais *Hospital das Clínicas*, located in the city of Belo Horizonte, Brazil. We included renal transplant recipients who underwent the TST between January 2011 and July 2013. If the result of the first TST was negative, a second TST was administered. Bivariate and multivariate analyses using logistic regression were used to determine factors associated with positive TST results. **Results:** The sample included 216 patients. The prevalence of LTBI was 18.5%. In the multivariate analysis, history of contact with a tuberculosis case and preserved graft function (estimated glomerular filtration rate ≥ 60 mL/min/1.73 m^2) were associated with positive TST results. TST induration increased by 5.8% from the first to the second test, which was considered significant ($p = 0.012$). **Conclusions:** The prevalence of LTBI was low in this sample of renal transplant recipients. The TST should be administered if renal graft function is preserved. A second TST should be administered if the first TST is negative.

Keywords: Tuberculosis; Tuberculin test; Immunocompromised host.

INTRODUCTION

According to the Brazilian Transplant Registry, the absolute number of renal transplantations from January to December 2016 was 5,492 in Brazil, 563 of which occurred in the state of Minas Gerais. There are 21,264 renal transplant candidates on the waiting list nationwide, 2,297 of whom are from the state of Minas Gerais.[1]

The incidence of tuberculosis in renal transplant recipients compared with that in the general population is approximately 20 to 74 times higher (0.5-15% among kidney recipients)[2] and varies according to the geographical area (0.5% to 1% in North America).[3]

Current immunosuppressive drugs have more specific and potent pharmacological activity to prevent graft rejection, especially in deceased donor recipients at high immunological risk, who require antibody therapy to prevent early humoral rejection.[4] However, these drugs may cause toxicity effects[5] and predispose patients to increased risk of infections,[6] such as tuberculosis and neoplasia.

The most common form of tuberculosis infection after transplantation is reactivation of latent *Mycobacterium tuberculosis* infection (LTBI). Disease development is favored by immunosuppression, and most cases of tuberculosis occur in the first year after transplantation.[2,6,7]

In most countries, the tuberculin skin test (TST) is used for diagnosing LTBI, having a sensitivity of approximately 70%, despite various factors that affect its result, such as immunosuppressant pharmacokinetics, induction therapy, previous therapy for cellular or humoral rejection, cytomegalovirus (CMV) infection, time elapsed since transplantation, retransplantation, chronic renal disease (CRD) stage after transplantation, diabetes mellitus (DM), etc.[8]

The TST for detection of LTBI is relevant as a diagnostic assessment test and, consequently, for the prescription of preventive therapy in positive cases, being able to contribute to reducing the rate of tuberculosis in renal transplant recipients.[9,10] However, the TST is not performed rigorously at transplant centers in Brazil.[11,12] It is of note that there are few published studies on this topic in the country.

Therefore, the objective of the present study was to estimate the prevalence of LTBI in renal transplant recipients and to assess sociodemographic, behavioral, and clinical associations with positive TST results.

Correspondence to:
Silvana Miranda. Avenida Alfredo Balena, 190, Santa Efigênia, CEP 30130-100, Belo Horizonte, MG, Brasil.
Tel.: 55 31 9882-17282. E-mail: silvanaspindola@gmail.com
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METHODS

This was a cross-sectional study conducted at the Renal Transplant Center of the *Universidade Federal de Minas Gerais* (UFMG, Federal University of Minas Gerais) *Hospital das Clínicas*, located in the city of Belo Horizonte, Brazil. All renal transplant recipients were screened for LTBI between January 2011 and July 2013 by using the TST. The study was approved by the UFMG Research Ethics Committee (Protocol no. 132/10).

Study population

For sample size calculation, we considered as potentially eligible 324 patients at the Renal Transplant Outpatient Clinic of the hospital. Assuming a confidence interval of 95%, an error of 5%, and an LTBI prevalence of 15% (according to a previous study),[6] we estimated the required sample size to be 160 patients. After adding a refusal rate of 30%, we determined that the minimum sample size was 208 patients. The inclusion criteria were as follows: being ≥ 18 years of age and having undergone transplantation at least three months previously. The exclusion criteria were as follows: 1) history of tuberculosis treated before or after transplantation; 2) preventive treatment with isoniazid before transplantation; 3) renal graft loss and return to dialysis therapy before the first TST (TST_1) or second TST (TST_2); 4) death; 5) nonadherence to immunosuppressive therapy; 6) having made fewer than two annual visits to the transplant outpatient clinic; or 7) not having given written informed consent (Figure 1).

Screening for LTBI

Participants were screened for LTBI by using the TST with purified protein derivative RT23 (PPD RT23; Statens Serum Institute, Copenhagen, Denmark). The TST was performed by the Mantoux method, which consists of intradermal administration of 0.1 mL (2 tuberculin units) of PPD RT23 on the volar aspect of the forearm. Test results were read within 72-96 h of administration and were recorded in millimeters of induration. TST_1 was administered after three months following renal transplantation, and TST_2 was administered three weeks later if TST_1 was negative, in order to assess reactivation of the immune response. All patients with a TST_1 induration ≥ 5 mm were considered to have a positive result; those with a negative result were referred for TST_2, which was considered positive if there was a > 10-mm increase in induration compared with the TST_1 reading.[13-15] The cumulative frequency of LTBI was also calculated (N = 216).

Variables and definitions

We investigated the following variables: (i) sociodemographic variables (gender, age, individual income, place of residence, and history of contact with tuberculosis); (ii) behavioral variables (smoking, alcoholism, and marital status); (iii) clinical variables (BCG vaccination scar, body mass index [BMI], DM, autoimmune disease, hepatitis B, hepatitis C, and neoplasms); (iv) transplant-related variables (living/deceased donor, double transplantation, retransplantation, immunosuppressive regimen, time

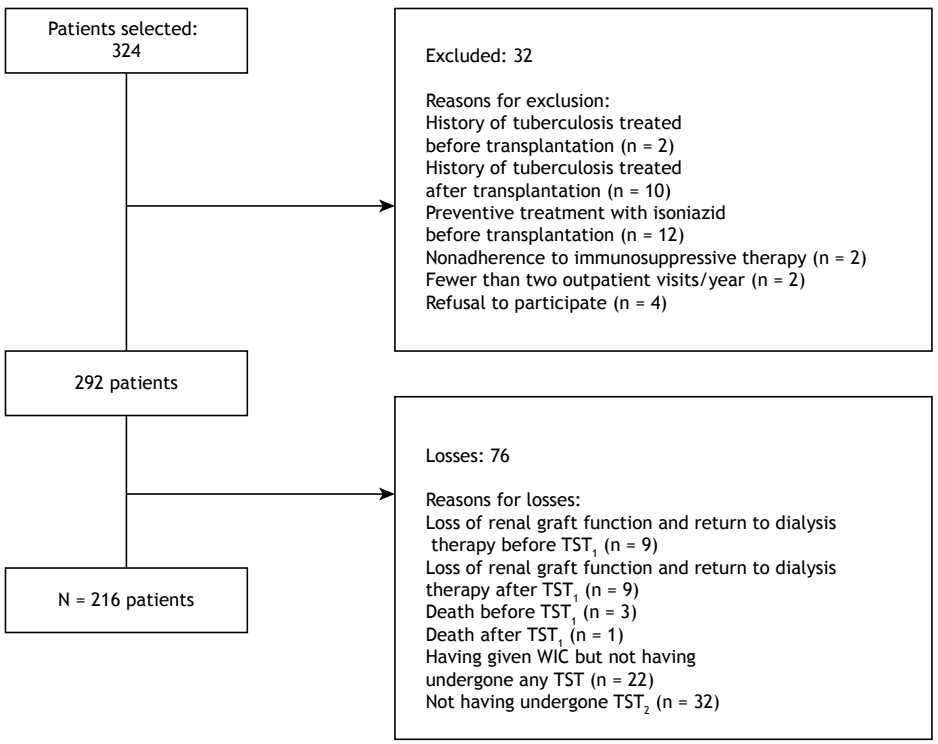

Figure 1. Study flow chart of renal transplant patient selection. TST_1: first tuberculin skin test; TST_2: second tuberculin skin test; and WIC: written informed consent.

interval between transplantation and TST, and renal graft function based on the glomerular filtration rate).

Patients were classified as "having individual income" (employed, retired, or away from work/medical leave) or as "having no income" (unemployed or never worked). Patients were screened for alcoholism with the Cut down, Annoyed, Guilty, and Eye-opener questionnaire, which was incorporated into the patient interview.[16] Patients were classified as "smokers" or "nonsmokers" (people who had never smoked or people who had quit smoking one year prior to the study).[17] BCG vaccination status was determined using the presence or absence of a BCG scar on the right arm. Renal transplant recipient age was categorized on the basis of the median age of the study population. BMI was calculated as recommended by the World Health Organization.[18] Patients were categorized as obese (BMI > 30 kg/m^2) or non-obese (18.5 < BMI ≤ 29.9 kg/m^2). A diagnosis of DM was made in accordance with the classification proposed by the American Diabetes Association[19] and the Brazilian Diabetes Society.[20] Renal graft function was assessed by means of the estimated glomerular filtration rate (eGFR), as calculated by the Modification of Diet in Renal Disease equation.[21] Renal graft function was categorized as "preserved renal function" (eGFR values ≥ 60 mL/min/1.73 m^2) or as "impaired renal function" (eGFR values < 59 mL/min/1.73 m^2).

Statistical analysis

Descriptive statistics (frequency distribution and measures of central tendency and dispersion) were used to analyze the characteristics of the study population. The mean differences for continuous variables were compared by using the Student's t-test for independent samples, and the proportions of categorical variables were compared by using Pearson's chi-square test or Fisher's exact test. For all tests, p values ≤ 0.05 were considered significant. The measure of association in the bivariate analysis was OR and 95% CI.

Explanatory variables with p values ≤ 0.20 in the bivariate analysis were selected for multivariate analysis via a logistic regression model. The level of significance required for inclusion in the final model was 0.05, with adjustment for confounding factors. The goodness of fit of the final model was assessed by using the Hosmer-Lemeshow test.

The data collected were entered into Microsoft® Excel spreadsheets. All statistical analyses were performed with the IBM SPSS Statistics software package, version 21.0 (IBM Corporation, Armonk, NY, USA), and the R software, version 2.15.1 (The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

The characteristics of the study population (N = 216) and the causes of CRD are shown in Table 1. Age at the time of the test ranged from 18 to 75 years, with a median of 48 years and a mean of 46.5 ± 12.3 years. History of contact with tuberculosis was positive in 38 patients (17.6%), negative in 168 (77.8%), and unknown in 10 (4.6%). Obesity was present in 23 patients (10.6%), and 54 patients (25%) had diabetes, of whom 13 were diagnosed with type I DM before transplantation and 41 were diagnosed with type II DM or drug-induced diabetes after transplantation. Seven patients (3.2%) had a previous diagnosis of autoimmune disease. Post-transplant neoplasia, including skin cancer, was present in 23 (10.6%) of the patients.

Of the 216 patients included in the study, 167 (77.3%) reported having income from employment, retirement pension, or medical leave. A total of 152 (70.4%) resided in the greater metropolitan area of Belo Horizonte, close to the transplant center, 63 (29.2%) resided in other areas of the state of Minas Gerais, and 1 (0.4%) resided in the state of Amapá.

The time interval between renal transplantation and TST_1 ranged from 3.0 to 360.4 months, with a mean of 86.8 ± 75.6 months and a median of 68.2 months. The time interval between renal transplantation and TST_2 ranged from 3.5 to 376.1 months, with a mean of 99.0 ± 78.3 months and a median of 79 months.

The prevalence of LTBI was 18.5%, and 40 individuals had positive TST results. Twenty-nine patients (13.4%) had positive TST_1 results, and 11 (5.1%) had positive TST_2 results. TST induration increased by 5.8% from the first to the second test, which was significant (p = 0.012).

The cumulative frequency of LTBI in the study population (baseline, TST_1, and TST_2) was 42.5%, because, of the 216 patients included in the study, 40 had previous positive TST results (18.5%); of the remaining 176 patients, 29 had positive TST_1 results (16.5%); therefore, there remained 147 patients to undergo TST_2, 11 of whom tested positive (7.5%).

In the bivariate analysis (p ≤ 0.20), the following factors were associated with a diagnosis of LTBI: having a history of contact with a tuberculosis case; alcoholism; presence of a BCG vaccination scar; eGFR ≥ 60 mL/min/1.73 m^2; double organ transplantation; and preemptive transplantation (transplantation performed before the initiation of dialysis therapy). In the final logistic regression model, the following variables were statistically significantly associated (p ≤ 0.05) with a diagnosis of LTBI: having a history of contact with a tuberculosis case; presence of a BCG vaccination scar; and eGFR ≥ 60 mL/min/1.73 m^2 (Table 2).

DISCUSSION

Various studies have shown a higher prevalence of tuberculosis in patients undergoing renal transplantation in countries with a low, medium, or high prevalence of the disease if these patients are infected with *M. tuberculosis*.[4,12,22] Therefore, there is a need to diagnose LTBI, and prescribing preventive therapy is relevant to preventing the development of the disease,[13] although this is not routinely done in clinical practice in Brazil.

Table 1. Sociodemographic, clinical, and behavioral characteristics, immunosuppressive regimen, and transplant-related variables in renal transplant recipients (N = 216).

Characteristic	n (%)	N
Sociodemographic variables		
Male gender	134 (62.0)	216
History of contact with a tuberculosis case	38 (17.6)	206
Cause of chronic renal disease		
Unknown	108 (50)	216
Chronic glomerulopathy	48 (22.2)	216
Diabetic nephropathy	20 (9.3)	216
Adult polycystic kidney	13 (6.0)	216
Other	27 (12.5)	216
Clinical variables		
BCG vaccination scar	165 (76.4)	216
BMI from 18.5-29.9 kg/m^2	193 (89.4)	216
Diabetes mellitus	54 (25.0)	216
Type I	13 (24.1)	
Type II/NODAT	41 (75.9)	
Autoimmune disease	7 (3.2)	216
Hepatitis B	7 (3.2)	216
Hepatitis C	4 (1.9)	216
Neoplasms	23 (10.6)	216
Behavioral variables		
Smoking	55 (25.5)	216
Alcoholism	66 (30.6)	216
Immunosuppressants		
Induction therapy	62 (28.7)	216
Monoclonal antibody	50 (80.6)	62
Polyclonal antibody	10 (16.2)	
Monoclonal + polyclonal antibody	2 (3.2)	
Triple immunosuppressive regimen	179 (83.0)	216
CNI + antiproliferative agent + prednisone	119 (66.5)	
mTORi + antiproliferative agent + prednisone	43 (24.0)	
CNI + mTORi + prednisone	17 (9.5)	
Double immunosuppressive regimen	36 (16.5)	216
mTORi + antiproliferative agent	2 (5.6)	
Antiproliferative agent + prednisone	12 (33.3)	
mTORi + prednisone	6 (16.7)	
CNI + prednisone	11 (30.5)	
CNI + antiproliferative agent	5 (13.9)	
Single immunosuppressive regimen	1 (0.5)	216
mTORi	1 (100)	1
Transplantation		
Deceased donor	108 (50.0)	216
Living donor	108 (50.0)	216
Simultaneous double transplantation	14 (6.5)	216
Pancreas + kidney	13 (6.0)	
Liver + kidney	1 (0.5)	
Preemptive transplantation	8 (3.7)	216
Retransplantation	11 (5.1)	216

BMI: body mass index; NODAT: new-onset diabetes after transplantation; CNI: calcineurin inhibitor; and mTORi: mammalian target of rapamycin inhibitor.

Although it is recommended that transplant candidates be referred for TST,[13] there have been no studies on this practice. In the present study, the frequency of LTBI in our population was found to be high (42.5%). To our knowledge, this is the first time that LTBI and its associations with sociodemographic, behavioral, and clinical characteristics have been assessed in renal transplant recipients at a transplant center in Brazil.

Table 2. Bivariate and multivariate analysis of factors associated with tuberculin skin test results (N= 216)

Variables	Tuberculin skin test result[a]		Analysis			
	Positive (n = 40)	Negative (n = 176)	Bivariate OR	p*	Multivariate OR	p*
Sociodemographic						
Age > 46 years	21 (19.4)	87 (80.6)	1.13 (0.57-2.25)	0.73		
Male gender	30 (22.4)	104 (77.6)	2.08 (0.96-4.5.1)	0.60		
History of contact with tuberculosis	18 (47.4)	20 (52.6)	6.66 (0.07-0.33)	0.001	7.16 (3.11-16.49)	0.001
Clinical						
BCG vaccination scar	34 (20.6)	131 (79.4)	1.95 (0.77-4.94)	0.16	3.07 (1.03-9.19)	0.45
BMI from 18.5-29.9 kg/m^2	35 (18.1)	158 (81.9)	1.25 (0.44-3.61)	0.67		
Diabetes mellitus	12 (22.2)	042 (77.8)	1.37 (0.64-2.92)	0.42		
Autoimmune disease	1 (14.3)	6 (85.7)	0.73 (0.85-6.21)	0.77		
Hepatitis B	1.40(0.0)	7 (100.0)	1.04 (1.00-1.01)	0.35*		
Hepatitis C	1 (25.0)	3 (75.0)	0.74 (0.15-14.6)	0.74		
Neoplasms	3 (13.0)	20 (87.0)	0.63 (0.18-2.24)	0.48		
Behavioral						
Smoking	11 (20.0)	44(80.0)	1.14 (0.53-2.47)	0.74		
Alcoholism	16 (24.2)	50 (75.8)	1.68 (0.82-3.43)	0.15		
Immunosuppressants						
Induction therapy	13 (21.0)	49 (79.0)	0.80 (0.38-1.68)	0.56		
CNI + antiproliferative agent + prednisone	21 (17.6)	98 (82.4)	1.14 (0.57-2.26)	0.72		
CNI + mTORi + prednisone	5 (29.4)	12 (70.6)	0.51 (0.17-1.55)	0.23		
mTORi + antiproliferative agent + prednisone	1 (50.0)	1 (50.0)	0.22 (0.01-3.64)	0.25		
Antiproliferative agent + prednisone	1 (8.3)	11 (91.7)	2.60 (0.33-20.7)	0.35		
CNI + prednisone	2 (18.2)	9 (81.8)	1.02 (0.21-4.93)	0.97		
mTORi+ prednisone	0 (0.00)	6 (100.0)	0.81 (0.76-0.86)	0.24*		
Renal graft function (MDRD) at the time of TST_1 (N = 216)						
≥ 60 mL/min/1.73 m^2	19 (18.6)	83 (81.4)	2.14 (1.06-4.34)	0.03	2.14 (0.98 - 4.69)	0.056
< 60 mL/min/1.73 m^2	10 (8.8)	104 (91.2)	1			
Renal graft function (MDRD) at the time of TST_2 (N = 187)						
≥ 60 mL/min/1.73 m^2	5 (18.6)	78 (94.0)	1.05 (0.31-3.56)	0.94		
< 60 mL/min/1.73 m^2	19 (18.6)	83 (81.4)	1			
Transplantation						
Deceased donor	17 (15.7)	91 (84.3)	0.70 (0.35-1.38)	0.29		
Simultaneous double transplantation	5 (35.7)	9 (64.3)	2.65 (0.84-8.40)	0.09		
Preemptive transplantation	3 (37.5)	5 (62.5)	2.77 (0.08-1.58)	0.18		
Retransplantation	1 (9.1)	10 (90.9)	0.43 (0.05-3.42)	0.41		
Time interval between renal transplantation and TST_1						
3-68 months	13 (12.0)	95 (88.0)	1.27 (0.58-2.79)	0.55		
> 68 months	16 (14.8)	92 (85.2)	1			
Time interval between renal transplantation and TST_2						
3,5-79 months	6 (6.4)	88 (93.6)	0.83 (0.25-2.83)	0.77		
> 79 months	5 (5.4)	88 (94.6)	1			

BMI: body mass index; CNI: calcineurin inhibitor; mTORi: mammalian target of rapamycin inhibitor; MDRD: Modification of Diet in Renal Disease (equation); TST_1: first tuberculin skin test; TST_2: second tuberculin skin test. Values expressed as n (%). *Fisher's exact test.

The use of the TST to detect LTBI in pre-renal transplant evaluation is recommended in various countries,[4] including Brazil, where interferon-gamma release assays (IGRAs) have not been validated for routine use.[13,14] Some factors, such as DM, immunosuppressant pharmacokinetics, induction therapy, previous therapy for humoral rejection, CMV infection, etc., may cause false-negative TST results.[10,13] In 2015, the World Health Organization stated that the IGRAs or the TST can be used to detect LTBI, their use being strongly recommended, but with a low level of evidence.[14]

The predominant etiology of CRD before transplantation was indeterminate, because most patients in the present study did not undergo renal biopsy for histological confirmation of CRD. It is of note that, in the present study, glomerulopathies were important, as previously mentioned in another study.[7] Alcoholism and smoking are risk factors for LTBI and for the development of tuberculosis.[23-26] Since, in our study, most patients did not drink alcohol or smoke, there was no statistical association of alcoholism or smoking (they were not risk factors) with positive TST results.

Patients undergoing organ transplantation are more susceptible to infections because of immunosuppressant use. However, in our study, we found no such association with immunosuppressant use. Therefore, the best strategy is to screen for LTBI before organ transplantation. The World Health Organization recommends that high- and medium-income countries with a low incidence of tuberculosis (< 100 cases per 100,000 population) test for and treat LTBI in patients preparing for organ or hematologic transplantation.[14]

Use of tacrolimus and/or mycophenolate in young recipients, DM,[27] age of recipients,[8] time elapsed since transplantation,[7,12] hepatitis C,[28] CMV infection, cancer, and autoimmune diseases[8] have been reported as factors for reactivation of tuberculosis and development of severe tuberculosis, especially during the first six months after solid organ transplantation.[6] If LTBI is detected, as occurred in our study, prevention with isoniazid is recommended.[29]

Transplantation of deceased-donor kidneys with increased ischemia times and retransplantation are situations perceived as being of high immunological risk. In these situations, it is recommended that induction therapy consist of higher potency drugs, such as basiliximab, thymoglobulin, or other polyclonal antibodies, in order to prevent acute rejection and reduce the effects of delayed graft function both in the short and long term. This therapy increases the risk of developing tuberculosis after transplantation and may cause negative TST results,[4,6] thereby compromising the diagnosis of LTBI.[4,7] However, in our study, such an association with deceased-donor kidneys and retransplantation was not observed. Preemptive renal transplantation and double organ transplantation showed a trend toward higher TST positivity. Nevertheless, it should be taken into consideration that these transplant types represent a small sample, which would lead to an underestimated analysis.

We found that history of contact with a tuberculosis case, presence of a BCG vaccination scar, and preserved renal graft function were associated with positive TST results.

The likelihood of having a positive TST result is 7.16 times higher in patients reporting a history of contact with a tuberculosis case. A history of contact with tuberculosis has long been described as being associated with positive TST results and, therefore, has a direct relationship with a diagnosis of LTBI.[3,9,13] In the present study, having a history of contact with tuberculosis showed a significant association with positive TST results.

The presence of a BCG vaccination scar increases by 3.07 times the likelihood of a patient having a positive TST result. In contrast, recent BCG vaccination may cause a false-positive TST result.[30] However, studies have shown that TST results are unaffected if the TST is administered many years after vaccination,[13,31] given that the response to the TST is almost null and void 8-10 years after vaccination.[15,32] In the present study, we found a significant relationship between BCG vaccination and TST positivity. All patients in our study who had a BCG vaccination scar had been vaccinated more than 15 years previously (mean age, 46 years). A history of BCG vaccination[13,15,32] is commonly considered a confounding factor rather than a causal factor.

In our study, a six-month course of isoniazid was used to prevent tuberculosis; some studies recommend that a careful evaluation be made in order to arrive at a decision regarding the use of other drugs to prevent the disease.[2,6,8,33]

In the present study, preserved renal graft function (eGFR ≥ 60 mL/min/1.73 m^2) was the only dependent variable that was associated with positive TST results. The immunological effects resulting from uremia, such as changes in phagocytosis, bacterial lability, and lymphocyte transformation, may lead to negative TST results.[2,34] Therefore, in cases of reduced renal graft function, we observed negative TST results, as reported in another study.[28]

The prevalence of LTBI among the renal transplant recipients in our study (18.5%) was lower than that found by Sester et al.,[35] who obtained positive TST results in 52.14%, but similar to that reported in the study by Atasever et al. (13.6%).[6] This is probably due to the fact that the state of Minas Gerais has registered low tuberculosis incidence rates in recent years.[36]

The increase in induration from TST_1 to TST_2 (significant response) shows that it is advisable to administer a second test if the first one is negative, given that most patients failed to respond to TST_1 (81%). Similar results have been reported in other studies in which a TST_2 was administered,[5,13] with the administration of the second test favoring the detection of LTBI in patients receiving immunosuppressants.[8] Although the Brazilian National Tuberculosis Control Program recommends that the TST be administered to transplant recipients, we find that, given the significant increase in TST induration from the first to the second test, further studies including other populations should be conducted in order to assess reactivation of the immune response and inform the recommendation of the second test in clinical practice, because, if the second test is positive, preventive medications should be initiated, thus preventing the development of tuberculosis.

The limitation of our study is the use of the TST, which may not reflect the reality of LTBI because of lymphocyte immunodeficiency and variation in the prescribed immunosuppressive regimens. Some authors have studied the possibility of new markers for the diagnosis of LTBI and tuberculosis in order to overcome this limitation, but there is still no evidence of the use of new tests in solid organ transplantation.[37,38]

In conclusion, the risk factors observed for positive TST results in screening for LTBI in renal transplant recipients are history of contact with tuberculosis cases and preserved renal graft function. The prevalence of LTBI was low in renal transplant recipients. A TST_2 should be administered to these patients if TST_1 is negative. The TST should be administered if renal function is improved.

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ORIGINAL ARTICLE

Impact of thoracic radiotherapy on respiratory function and exercise capacity in patients with breast cancer

Milena Mako Suesada[1,a], Heloisa de Andrade Carvalho[2,b], André Luis Pereira de Albuquerque[1,c], João Marcos Salge[1,d], Silvia Radwanski Stuart[2,e], Teresa Yae Takagaki[1,f]

1. Divisão de Pneumologia, Instituto do Coração – InCor – Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.
2. Departamento de Radiologia e Oncologia / Radioterapia, Instituto de Radiologia – InRad –Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.

a. http://orcid.org/0000-0002-7665-9704
b. http://orcid.org/0000-0003-0979-7768
c. http://orcid.org/0000-0003-3486-5240
d. http://orcid.org/0000-0001-5121-0129
e. http://orcid.org/0000-0002-0504-776X
f. http://orcid.org/0000-0003-2277-2100

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ABSTRACT

Objective: To evaluate the impact of thoracic radiotherapy on respiratory function and exercise capacity in patients with breast cancer. **Methods:** Breast cancer patients in whom thoracic radiotherapy was indicated after surgical treatment and chemotherapy were submitted to HRCT, respiratory evaluation, and exercise capacity evaluation before radiotherapy and at three months after treatment completion. Respiratory muscle strength testing, measurement of chest wall mobility, and complete pulmonary function testing were performed for respiratory evaluation; cardiopulmonary exercise testing was performed to evaluate exercise capacity. The total radiotherapy dose was 50.4 Gy (1.8 Gy/fraction) to the breast or chest wall, including supraclavicular lymph nodes (SCLN) or not. Dose-volume histograms were calculated for each patient with special attention to the ipsilateral lung volume receiving 25 Gy (V_{25}), in absolute and relative values, and mean lung dose. **Results:** The study comprised 37 patients. After radiotherapy, significant decreases were observed in respiratory muscle strength, chest wall mobility, exercise capacity, and pulmonary function test results ($p < 0.05$). DLCO was unchanged. HRCT showed changes related to radiotherapy in 87% of the patients, which was more evident in the patients submitted to SCLN irradiation. V_{25}% significantly correlated with radiation pneumonitis. **Conclusions:** In our sample of patients with breast cancer, thoracic radiotherapy seemed to have caused significant losses in respiratory and exercise capacity, probably due to chest wall restriction; SCLN irradiation represented an additional risk factor for the development of radiation pneumonitis.

Keywords: Breast neoplasms; Radiotherapy; Radiation pneumonitis; Respiratory function tests; Exercise test.

INTRODUCTION

In breast cancer, postoperative thoracic radiotherapy is widely used in order to reduce the risks of loco-regional recurrence and to improve overall survival.[1,2] However, irradiation of thoracic structures involves risks, primarily to the lungs.

Radiation pneumonitis (RP) is the most significant adverse effect and generally appears between one and four months after radiotherapy completion.[3,4] The etiology and physiopathology of RP are related to a cytokine-mediated signal cascade that causes early damage of the cells in the alveolar space, progressing to an acute exudative inflammatory process. Clinical symptoms include cough, low-grade fever, dyspnea, fatigue, and pleuritic chest pain.[3-5] These symptoms can be reflected by changes on pulmonary function tests (PFTs) results, with reduced FVC, FEV_1, TLC, and DLCO.[3,4] Radiologic evaluation of the lung toxicity has usually been made by chest X-rays. However, HRCT has proven to be sensitive in detecting early changes, but it is not used as part of routine follow-up.[6,7]

Radiotherapy-induced injury may also acutely lead to systemic impairment, frequently referred to as a diminished exercise capacity and worsening of quality of life.[8-10] Those changes have been evaluated by means of specific questionnaires, but the objective quantification of such changes, to our knowledge, has not been previously performed. In breast cancer, this should be carefully considered due to improvement of prognosis and life expectancy in these patients. Therefore, it is essential to quantify and investigate exercise limitation after thoracic radiotherapy in order to identify the involved mechanisms.

The purpose of the present study, therefore, was to quantify the acute impact of thoracic radiotherapy on respiratory function and exercise capacity in patients with breast cancer at three months after irradiation.

METHODS

The study was approved by the institutional research ethics committee, and giving informed consent was mandatory for enrollment. Inclusion criteria were confirmed histological diagnosis of breast cancer, indication

Correspondence to:
Heloisa de Andrade Carvalho. InRad, Travessa da Rua Dr. Ovídio Pires de Campos, 75, Portaria 3, CEP 05403-010, São Paulo, SP, Brasil.
Tel.: 55 11 2661-6722. Fax: 55 11 3885-7036. E-mail: heloisa.carvalho@hc.fm.usp.br
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for postoperative irradiation, in accordance with the institutional routine protocol, and a period of at least four weeks with no treatment before radiotherapy was required. All of the patients had to be fully treated in the institution and were consecutively selected over a one-year period. Patients were excluded if they presented with metastatic disease, concomitant respiratory disease, neuromuscular or rheumatologic disease, or cognitive disorders hindering the completion of PFTs or exercise tests. The patients underwent HRCT of the chest, complete PFT, cardiopulmonary exercise testing (CPET), respiratory muscle strength testing, and measurement of chest wall mobility. In addition, the Medical Research Council (MRC) dyspnea scale was also applied to evaluate respiratory symptoms during activities of daily living over the study period.[11]

All of the measurements were conducted a few days (an average of 2 to 5 days) prior to the beginning of radiotherapy and at three months after the completion of treatment.

Radiotherapy

Radiotherapy was delivered using a 3D conformal technique. The whole breast or chest wall was irradiated with opposed tangential fields and, when indicated, additional irradiation of supraclavicular lymph nodes (SCLNs) was performed with a direct anterior field. Patients were treated with 6 MV photon beams and a total dose of 50.4 Gy (28 × 1.8 Gy; 5 days/week). Dose-volume histograms for the heart, lungs, and contralateral breast were calculated with no tissue heterogeneity correction (Eclipse planning system; Varian®, Palo Alto, CA, USA). The ipsilateral lung volume that received at least 50% of the dose (25 Gy = V_{25}), corresponding to the limits of the fields (or the actual irradiated lung volume) and the mean lung dose were correlated with the functional test results. V_{25} was calculated as absolute (cm^3) and relative (%) values.

Respiratory function evaluation

Complete PFTs and DLCO were performed with a body plethysmograph (Elite DX; MedGraphics Corp., Saint Paul, MN, USA). The following parameters were measured: FVC, FEV_1, inspiratory capacity (IC), TLC, RV, maximal voluntary ventilation, and DLCO. Measurements were expressed as absolute volumes and percentages of the predicted values for the Brazilian population[12-14] and performed according to the guidelines of the American Thoracic Society (ATS)/European Respiratory Society.[15]

Respiratory muscle strength was assessed by MIP and MEP in accordance with the ATS guidelines.[16] These variables were measured by using a pressure transducer (OEM Medical, Marshalltown, IA, USA).

Chest cirtometry was used in order to evaluate chest wall mobility at the level of axillary level and at the level of the xiphoid process.[17] Patients were asked to exhale up to RV and then inhale up to TLC, and the difference between the two measurements was calculated.

Exercise capacity evaluation

A maximal incremental cycle ergometer protocol was conducted in accordance with the ATS recommendations[18] using a CardiO$_2$ System® (MedGraphics). The following parameters were determined: oxygen uptake (VO_2; $mL \cdot min^{-1}$); carbon dioxide output (VCO_2; $mL \cdot min^{-1}$); respiratory exchange ratio; minute ventilation (V_E, $L \cdot min^{-1}$); tidal volume (V_T, mL); and RR (breaths/min). The mean VO_2 for the last 15 seconds of the ramp was considered as the peak oxygen uptake (VO_{2peak}). During the test, 12-lead electrocardiography, blood pressure, and pulse oximetry values were monitored. In addition, dyspnea and leg fatigue were assessed by the modified Borg scale every two minutes.[19]

Dynamic relationships were determined to evaluate metabolic ($\Delta VO_2/\Delta$workload [W]; $mL \cdot min^{-1} \cdot W^{-1}$), cardiovascular ($\Delta HR/\Delta VO_2$; $beats \cdot min^{-1} \cdot L \cdot min^{-1}$), and respiratory ($\Delta V_E/\Delta VCO_2$; $L \cdot min^{-1} \cdot L \cdot min^{-1}$) responses, as previously described.[20] Ventilatory reserve was calculated using the V_E at exercise cessation/maximal voluntary ventilation ratio as a reference.

HRCT

HRCT was performed with 1-mm slices at increments of 10 mm from the apex to the base of the lungs during maximal inspiration without the use of i.v. contrast. The scans were analyzed and scored in accordance with the Schratter-Sehn et al. scoring system.[6] Briefly, this score ranges from zero (no changes) to 5 according to the severity of radiological abnormalities. A single radiologist, specializing in lung diseases, evaluated and classified all of the scans in accordance with the protocol.

Classification of RP and radiation dermatitis

RP was graded in accordance with the toxicity criteria by Cox et al.,[21] and radiation dermatitis was classified in accordance with the criteria for skin adverse events described by Freedman et al.[22] The two systems are based on the severity of respiratory and dermatological symptoms after radiotherapy, respectively.

Statistical analysis

The analyses of variations between the respiratory and exercise test results obtained before and after radiotherapy were performed using the Student's t-test. ANOVA was used in order to analyze the variance in HRCT scan results, in severity of RP, and in severity of radiation dermatitis in relation to changes in PFT and CPET variables after radiotherapy completion. The differences in changes observed in respiratory and exercise capacity variables between the group submitted to SCLN irradiation and that submitted to chest wall/breast radiotherapy only were analyzed with the Student's t-test. The differences in chest wall mobility and inspiratory muscle strength between the patients submitted to mastectomy and those submitted to sectorectomy were analyzed by the Student's t-test

for independent samples. The significance level was set at 5% ($p \leq 0.05$). Statistical analysis of the data was performed with the IBM SPSS Statistics software package, version 20.0 (IBM Corporation, Armonk, NY, USA).

RESULTS

The study comprised 40 female patients; of those, 2 were excluded because they developed pleural metastasis, and 1 was excluded because she missed the third-month evaluation. Therefore, the final sample comprised 37 patients. The mean age of the study population was 53.5 ± 10.9 years. Seven patients (18.9%) had a smoking history, but only 1 was a current smoker during the study period. No significant changes in the mean body mass index were observed between the two time points studied, that is, before radiotherapy and at three months after radiotherapy (28.2 ± 4.4 kg/m^2 vs. 28.2 ± 4.8 kg/m^2). Table 1 presents the affected breasts and the characteristics of treatment prior to radiotherapy. The mean time between chemotherapy and radiotherapy was 107.0 ± 81.8 days. SCLNs were irradiated in 20 (54%) of the cases. At three months after radiotherapy, 29 (78%) of the patients had developed RP and 33 (89%) presented with skin toxicity according to the adopted scales (Table 2). Worsening of respiratory symptoms was also observed according to MRC scale. Before radiotherapy, 30 (81.2%) of the patients reported no symptoms (zero score), and 7 (18.9%) had a score of 1. After radiotherapy, the number of patients with no symptoms decreased to 8 (21.6%), 24 (64.9%) had a score of 1, and 5 (13.5%) had a score of 2.

Table 3 shows a comparison of mean lung dose (MLD) and V_{25} (in absolute and relative values) between patients who underwent SCLN irradiation or and those who did not. Only V_{25}% showed a significant difference between the two groups of patients.

At 3 months after radiotherapy, we found that there was a significant loss in MIP and MEP ($p < 0.0001$ for both), as well as significant decreases in all chest wall mobility at the axillary level and at the level of the xiphoid process ($p < 0.0001$). Regarding PFTs, except for DLCO, a significant decrease in FVC, FEV_1, TLC, and IC was detected after radiotherapy (Table 4).

Maximal CPET results showed that there was a significant decrease in workload and VO_{2peak} after radiotherapy ($p < 0.05$). Significant reductions were also detected in V_E, V_T, and respiratory exchange ratio but not in RR (Table 4). All of those changes were observed only at peak exercise.

The dynamic relationships showed significant changes in metabolic response, and there was a tendency toward a decrease in the respiratory response when compared with the pre-radiotherapy condition (Table 4). All of the patients used an average of 40% of ventilatory reserve at peak exercise before and after radiotherapy.

All of the respiratory parameters, as well as those obtained from exercise testing, showed to be decreased when patients submitted to SCLN irradiation were included; however, the only significant decrease was found for chest wall mobility at the level of the xiphoid process ($p = 0.03$; Table 3).

After radiotherapy, changes were identified in 87% of the HRCT scans (Figure 1), and the distribution according to the adopted scoring system[6] is presented in Table 5. Those changes were more prominent in the patients submitted to SCLN irradiation.

Higher HRCT scores were significantly correlated with greater losses of FVC ($p = 0.01$). None of the patients had grade 3 or higher radiation dermatitis, and the presence of skin symptoms was significantly correlated with reductions in chest wall mobility at the level of the xiphoid process ($p = 0.05$).

Patients submitted to mastectomy showed greater losses in chest wall mobility when compared with the other patients ($p = 0.06$). Grade 2 radiation dermatitis was more prevalent in the former group of patients (51% vs. 33% in those submitted to breast conserving surgery).

DISCUSSION

The present study reports the results of a prospective analysis of the early effects of thoracic radiotherapy on respiratory function at rest and during exercise in patients treated for breast cancer. Changes in PFT results and radiological findings after irradiation in

Table 1. Affected breast and delivered treatments prior to radiotherapy in the study sample (N = 37).

Parameter	Patient, n (%)
Side of the disease	
Right	22 (59.5)
Left	14 (37.8)
Bilateral	1 (2.7)
Surgery	
Mastectomy	22 (59.5)
Sectorectomy	15 (40.5)
Chemotherapy	30 (81.1)
AC	10 (33.3)
Taxol	3 (10.0)
AC + taxol	13 (43.3)
FAC	3 (10.0)
CMF	1 (3.3)
Hormone therapy	23 (62.1)
Tamoxifen	14 (37.8)
Other	9 (24.3)

AC: adriamycin + cyclophosphamide; FAC: fluorouracil + doxorubicin + cyclophosphamide; and CMF: cyclophosphamide + methotrexate + fluorouracil.

Table 2. Incidence of radiation pneumonitis and radiation dermatitis at three months after radiotherapy in the study sample (N = 37).

Grade	0	1	2
Radiation pneumonitis	8 (21.6%)	19 (51.3%)	10 (27.1%)
Radiation dermatitis	4 (10.8%)	16 (43.3%)	17 (45.9%)

Table 3. Comparisons of dosimetric values, as well as of respiratory and exercise test results, between patients who underwent supraclavicular lymph node irradiation and those who did not.

Variable	SCLN irradiation		p
	No	Yes	
Dosimetric value			
Mean lung dose, cGy	539.2 ± 168.1	738.5 ± 339.5	0.10
V_{25} ,cm^3	114.6 ± 53	203.9 ± 127.8	0.10
V_{25}%	6.9 ± 3.0	11.7 ± 6.4	0.04
Respiratory and exercise test			
Muscle strength, cmH_2O			
Σ MIP	25.0 ± 16.3	24.7 ± 14.6	0.98
Σ MEP	15.5 ± 15.1	22.6 ± 16.5	0.27
Chest wall mobility, cm			
Σ Axillary	1.3 ± 1.0	1.7 ± 0.8	0.21
Σ Xiphoid	1.0 ± 1.4	1.9 ± 1.2	0.03
Pulmonary function test			
Σ FVC, L	0.14 ± 0.22	0.23 ± 0.23	0.13
Σ FEV_1, L	0.11 ± 0.2	0.16 ± 0.17	0.19
Exercise test			
Σ Workload, Watts	4.2 ± 1.49	17.4 ± 22.0	0.21
VO_{2peak}, mL/kg/min	0.96 ± 3.0	0.98 ± 2.1	0.98

SCLN: supraclavicular lymph node; V_{25}: ipsilateral lung volume receiving 25 Gy; and VO_{2peak}: oxygen uptake at peak exercise.

Table 4. Variation in respiratory muscle strength, chest wall mobility, pulmonary function testing, and cardiopulmonary exercise testing before and after three months of radiotherapy.

Variable	Pre-RT	Post-RT	p
Muscle strength, cmH_2O			
Σ MIP	−95.6 ± 22.4	−71.8 ± 14.7	0.0001
Σ MEP	100.0 ± 23.0	80.9 ± 16.8	0.0001
Chest wall mobility, cm			
Σ Axillary	4.1 ± 0.9	2.5 ± 0.7	0.0001
Σ Xiphoid	3.0 ± 1.7	1.6 ± 1.4	0.0001
MVV, L/min	124.0± 33.6	111 ± 32.6	0.0001
Pulmonary function test			
Σ FVC, L	3.0 ± 0.8	2.8 ± 0.7	0.0001
Σ FEV_1, L	2.4 ± 0.6	2.2 ± 0.6	0.0001
Σ IC, L	2.3 ± 0.5	2.1 ± 0.6	0.008
Σ TLC, L	4.7 ± 1.0	4.5 ± 0.9	0.01
Σ DLCO, mL/min/mmHg	21.4 ± 4.5	21.13 ± 4.5	0.56
Cardiopulmonary exercise test			
Workload, Watts	96.5 ± 30	88.0 ± 20.8	0.04
Σ VO_{2peak}, mL/kg/min	16.8 ± 3.0	15.6 ± 3.9	0.04
Σ V_{Epeak}, L/min	51.4 ± 14.0	45.0 ± 11.9	0.01
Σ RER_{peak}	1.2 ± 0.1	1.1 ± 0.1	0.009
Σ RR_{peak}, breaths/min	35.6 ± 6.6	34.7 ± 5.9	0.46
Σ V_{Tpeak} , L	1.4 ± 0.3	1.2 ± 0.2	0.003
Dynamic relationship			
Σ Metabolic ($\Delta VO_2/\Delta W$)	9.2 ± 1.6	10.0 ± 1.5	0.02
Σ Respiratory ($\Delta V_E/\Delta VCO_2$)	33.1 ± 5.0	31.4 ± 5.5	0.07
Σ Cardiovascular ($\Delta HR/\Delta VO_2$)	73.6 ± 18.6	75.2 ± 18.2	0.50

RT: radiotherapy; MVV: maximal voluntary ventilation; IC: inspiratory capacity; VO_{2peak}: oxygen uptake at peak exercise; V_{Epeak}: minute ventilation at peak exercise; RER_{peak}: respiratory exchange ratio at peak exercise; and ΔVCO_2: carbon dioxide output.

breast cancer patients have been described in previous studies.[3,4,5,7] In our study, irradiation has led to negative effects on exercise capacity, respiratory muscle strength, and chest wall mobility. To our knowledge, these findings have never been published and reveal a physiological approach to cancer-related fatigue, present in more than 30% of breast cancer patients at the completion of therapy.[23] Those symptoms may limit activities of daily living and enhance muscle atrophy, contributing to impairment of physical performance. The reported incidence of RP in breast cancer patients submitted to radiotherapy varies from 4.5% to 80% in prospective studies,[24-29] and these results are related to the irradiated lung volumes,[25,26] MLD,[6,27] age,[4] performance status,[28] use of chemotherapy,[27] and use of tamoxifen.[29] In the present study, we observed

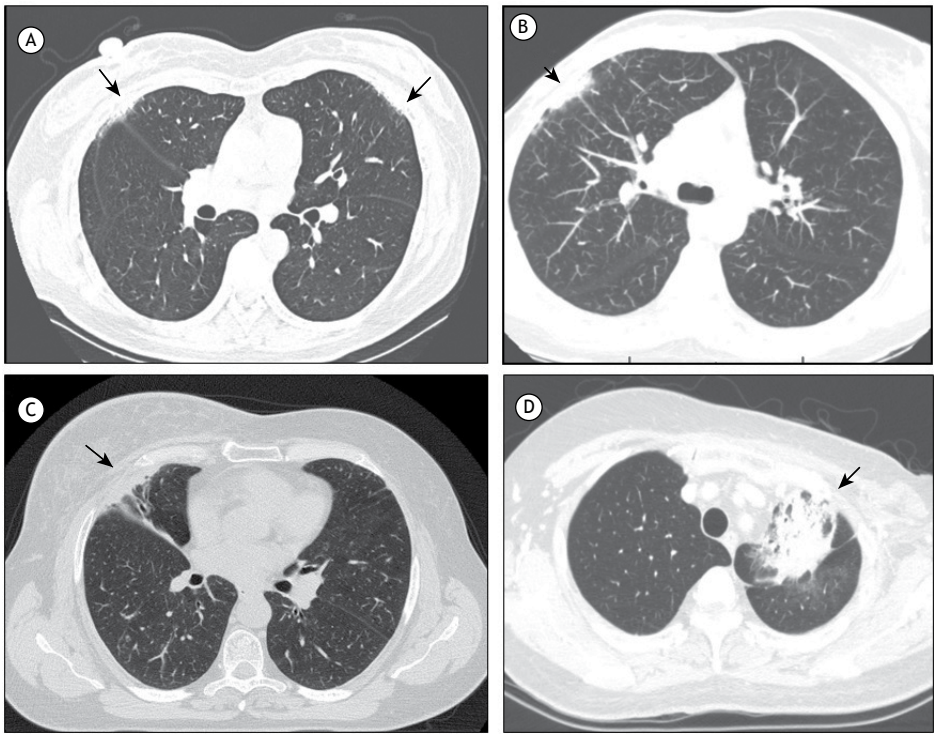

Figure 1. HRCT scans showing features of radiation pneumonitis. In A, HRCT scan scored as 1 in a patient submitted to bilateral treatment. In, B, C, and D, respectively, HRCT scans scored as 2, 3, and 5..

Table 5. Classification of HRCT scans after radiotherapy in the overall study population (N = 37), as well as in patients who underwent supraclavicular lymph node irradiation and those who did not, according to the scoring system by Schratter-Sehn et al.[6],[a]

HRCT scan score	Overall	SCLN irradiation	
		No (n = 17)	Yes (n = 20)
0	5 (13.5%)	3 (17.7%)	2 (10%)
1	17 (45.9%)	9 (52.9%)	8 (40%)
2	8 (21.6%)	3 (17.6%)	5 (25%)
3	5 (13.5%)	2 (11.8%)	3 (15%)
4	0 (0.0%)	0 (0.0%)	0 (0.0%)
5	2 (5.4%)	0 (0.0%)	2 (10%)

SCLN: supraclavicular lymph node. [a]Score: 0 = no changes; 1 = septal thickening, reticular subpleural opacities; 2 = subpleural thickening > 2 cm parallel to the chest wall; 3 = parenchymal bands ≥ 2.5 cm from the lung toward the pleural surface; 4 = honeycombing aspect, cystic areas (> 1 cm diameter), thickened walls; 5 = ground glass opacities, acute radiological changes.

a 78% incidence of RP, 51% and 27% being classified as grade 1 and grade 2, respectively. The incidence of RP in the present study correlated with the MRC scale results, reinforcing that the severity of respiratory symptoms correlated with decreased activities of daily living and exercise tolerance.

The majority of the patients (81%) included in the present study had been previously treated with chemotherapy, which prevents the analysis of differences between patients treated with chemotherapy and those who were not. Chemotherapy by itself may cause pulmonary toxicity, among other side effects. Therefore, a higher risk of RP might be present when chemotherapy is associated with radiotherapy.[30]

We found that the patients who used tamoxifen prior to radiotherapy (61%) showed more relevant losses in chest wall mobility than those who did not use it. However, changes in muscle strength and pulmonary function parameters were similar in both groups.

In the present study, the high incidence of radiation dermatitis (grade 1, in 43% of the patients; and grade 2, in 46%) corroborates other studies.[22,31] Both radiation dermatitis grades and treatment with SCLN irradiation were significantly correlated with the decrease in chest wall mobility at the level of the xiphoid process. These results strongly suggest that the loss of chest wall mobility might be associated with the severity of skin toxicity and SCLN irradiation. However, these

findings might not only be related to SCLN irradiation but also to the fact that patients with more advanced tumors had been submitted to mastectomy or to more extended axillary surgery, and, consequently, SCLN irradiation had been prescribed.

Dunlap et al.[32] suggested that chest wall toxicity might affect muscles, connective tissue, neurovascular bundle, and bones. In addition, Kinsella et al.[33] showed that doses over 60 Gy correlated with symptoms of nerve dysfunction, including paresthesia, weakness, and pain. Those studies reinforce the hypothesis that radiotherapy for breast cancer treatment might ultimately engender chest wall restriction, which would diminish the ability of muscles to contract and generate power, eventually leading to muscle weakness. Our patients had decreases in MIP and MEP, which could be also found in pulmonary function impairment. Inspiratory muscle weakness affects the maximal IC effort, causing reductions in TLC and IC. Conversely, expiratory muscle weakness affects the maximal expiratory effort, leading to an increase in RV.

A few studies[3,4,7] have demonstrated gas exchange, PFT, and radiological abnormalities due to irradiation of breast cancer. In the present study, DLCO was the only variable with no significant change, unlike in other studies in the literature. Erven et al.[34] suggested that TLC was the most affected parameter and that that reduction was probably related to decreased parenchymal elasticity in the irradiated portion of the lung, which could be due to fibrosis and could explain further reductions in DLCO. Our results indicate that the reduction in TLC was probably related to changes in respiratory muscle strength and chest wall mobility. Furthermore, the HRCT scans showed a high incidence of parenchymal changes after radiotherapy; however, they were mostly confined to the pulmonary parenchyma near the pleural surface and chest wall—HRCT scan score of 1-2 in 66% of the cases, and only 2 (5.4%) of the patients presented with a score of 5. The low incidence of severe parenchymal changes probably preserved DLCO in our patients, but this fact also limited the statistical power of the analysis of severe events.

As expected, the inclusion of the SCLN irradiation in the treatment was related to greater severity of RP and radiological changes. The loss of chest wall mobility at the level of the xiphoid process was also significantly higher in those patients. Once again, this finding might be confused with the type of surgery performed in more advanced cases.

Likewise, V_{25}% was significantly higher in patients submitted to SCLN irradiation treatment. V_{25} has been previously described as a predictor of lung toxicity in a study of radiotherapy dose escalation for lung cancer.[35] However, V_{20}% values higher than 30% were also defined as causing a higher risk of RP, resulting in radiological and functional impairment.[36] We have chosen V_{25} in order to correlate our results with lung volumes, which are included in the limits of the fields for radiotherapy in breast cancer patients. Only V_{25}% correlated with functional/radiological impairment, in agreement with the already defined constraints that are related to the proportion of the irradiated lung volume that receives a certain dose.[37] However, minimizing V_{25} to 100 cm^3 or less may also be a strategy to reduce pulmonary toxicity[4] due to breast cancer irradiation. The MLD was not related to any abnormality, probably due to the small amount of lung tissue irradiated in breast cancer patients.

Few investigations have evaluated the exercise capacity as a predictor of RP. Miller et al.[38] used the six-minute walk test in patients with lung cancer and found that good functional capacity and good PFT results prior to radiotherapy apparently reduced the risk of RP. In our study, CPET was chosen for this evaluation, because it allows a global assessment of integrative exercise responses.[18] We observed a significant decrease in workload, in VO_{2peak}, in V_E, and in V_T and respiratory exchange ratio at peak exercise.

Normally, VO_2 increases almost at the same pace as does workload, and this relationship ($\Delta VO_2/\Delta W$) reflects the efficiency of the metabolic component linked to skeletal muscles. A high $\Delta VO_2/\Delta W$ ratio after radiotherapy might reflect a great overload related to excessive work done by the ventilatory muscles, restricted chest wall mobility, and reduced expansion of V_T during exercise. Lower ventilation and V_T reinforce chest wall restriction after the intervention, which is in line with the lower cirtometry and lung volume results found in our study. Despite this possible overload of ventilatory muscles, a definitive ventilatory limitation was not found. Finally, we cannot rule out an additional component of peripheral muscle limitation, since maximal VO_2 was reduced and leg fatigue by the modified Borg scale was increased after radiotherapy.

Decreased exercise performance, with no ventilatory or cardiovascular limitation, indicates that our patients presented lower exercise tolerance at three months after radiotherapy. These findings reinforce our qualitative MRC scale results and could be part of the so-called cancer-related fatigue[39-41]; however, further studies are needed to improve the determination of the mechanisms involved.

The fact that the present study was designed to evaluate the early effects of radiation may represent a limitation, because these effects may or may not be reversible. Late reactions are expected to be present at least six months after the end of the treatment and may be reflected as fibrosis, with or without symptoms or clinical manifestations.[5,34] Therefore, a long-term follow-up period is needed to assess the outcome of these patients and the impact of our findings on their quality of life.

In conclusion, thoracic radiotherapy for breast cancer can acutely lead to significant impairment in functional capacity and exercise performance. The negative impact on the respiratory system was characterized by muscle weakness and restriction of chest wall mobility that could cause decreases in PFT results. There were significant decreases in maximal CPET results. V_{25}%

was correlated with a higher risk of RP. Finally, the inclusion of SCLN irradiation in the treatment fields represents a potential risk factor for the development of RP with functional repercussions.

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ORIGINAL ARTICLE

Self-reported smoking status and urinary cotinine levels in patients with asthma

Gabriela Pimentel Pinheiro[1,2,a], Carolina de Souza-Machado[1,3,b], Andréia Guedes Oliva Fernandes[4,c], Raquel Cristina Lins Mota[5,d], Liranei Limoeiro Lima[2,e], Diego da Silva Vasconcellos[6,f], Ives Pereira da Luz Júnior[7,g], Yvonbergues Ramon dos Santos Silva[7,h], Valmar Bião Lima[1,4,i], Sérgio Telles de Oliva[8,j], Luane Marques de Mello[9,k], Ricardo David Couto[10,l], José Miguel Chatkin[11,m], Constança Margarida Sampaio Cruz[12,13,n], Álvaro Augusto Cruz[1,14,o]

1. Programa para o Controle da Asma na Bahia – ProAR – Universidade Federal da Bahia – UFBA – Salvador (BA) Brasil.
2. Programa de Pós-Graduação em Ciências da Saúde, Universidade Federal da Bahia – UFBA – Salvador (BA) Brasil.
3. Escola de Enfermagem, Universidade Federal da Bahia – UFBA – Salvador (BA) Brasil.
4. Programa de Pós-Graduação em Medicina em Saúde, Universidade Federal da Bahia – UFBA – Salvador (BA) Brasil.
5. Hospital Heliópolis, São Paulo (SP) Brasil.
6. Programa de Pós-Graduação em Química, Universidade Federal da Bahia – UFBA – Salvador (BA) Brasil.
7. Laboratório de Química Analítica e Ambiental, Instituto de Química, Universidade Federal da Bahia – UFBA – Salvador (BA) Brasil.
8. Departamento de Química Analítica, Instituto de Química, Universidade Federal da Bahia – UFBA – Salvador (BA) Brasil.
9. Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo, Ribeirão Preto (SP) Brasil.
10. Laboratório de Bioquímica Clínica, Departamento de Análises Clínicas e Toxicológicas, Faculdade de Farmácia, Universidade Federal da Bahia – UFBA – Salvador (BA) Brasil.
11. Escola de Medicina, Pontifícia Universidade Católica do Rio Grande do Sul, Porto Alegre (RS) Brasil.
12. Programa de Pós-Graduação em Medicina e Saúde Humana, Escola Bahiana de Medicina e Saúde Pública, Salvador (BA) Brasil.
13. Obras Sociais Irmã Dulce, Hospital Santo Antônio, Salvador (BA) Brasil.
14. Faculdade de Medicina da Bahia, Universidade Federal da Bahia – UFBA – Salvador (BA) Brasil.

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ABSTRACT

Objective: To determine the frequency of active smoking among patients with asthma and individuals without asthma by self-report and urinary cotinine measurement. **Methods:** This was a cross-sectional study conducted in the city of Salvador, Brazil, and involving 1,341 individuals: 498 patients with severe asthma, 417 patients with mild-to-moderate asthma, and 426 individuals without asthma. Smoking status was determined by self-report (with the use of standardized questionnaires) and urinary cotinine measurement. The study variables were compared with the chi-square test and the Kruskal-Wallis test. **Results:** Of the sample as a whole, 55 (4.1%) reported being current smokers. Of those, 5 had severe asthma, 17 had mild-to-moderate asthma, and 33 had no asthma diagnosis. Of the 55 smokers, 32 (58.2%) were daily smokers and 23 (41.8%) were occasional smokers. Urinary cotinine levels were found to be high in self-reported nonsmokers and former smokers, especially among severe asthma patients, a finding that suggests patient nondisclosure of smoking status. Among smokers, a longer smoking history was found in patients with severe asthma when compared with those with mild-to-moderate asthma. In addition, the proportion of former smokers was higher among patients with severe asthma than among those with mild-to-moderate asthma. **Conclusions:** Former smoking is associated with severe asthma. Current smoking is observed in patients with severe asthma, and patient nondisclosure of smoking status occurs in some cases. Patients with severe asthma should be thoroughly screened for smoking, and findings should be complemented by objective testing.

Keywords: Asthma; Smoking; Cotinine.

INTRODUCTION

Smoking is recognized worldwide as a chronic disease resulting from nicotine dependence and as a risk factor for the development and worsening of chronic respiratory diseases such as asthma and COPD.[1] Smoking is a major cause of preventable death and is associated with increased health care costs, morbidity, and mortality, accounting for more than 6 million deaths per year.[2]

Asthma is a chronic disease that has a high worldwide prevalence (i.e., 1-16%).[3,4] In the city of Salvador, Brazil, 13.4% of all adolescents and 5.1% of all adults have asthma.[5,6] Smoking is directly related to uncontrolled asthma and increased asthma severity, increasing the risk of exacerbations, decreased lung function, persistent dyspnea,[7] and limited response to treatment with corticosteroids.[8] Nevertheless, smoking remains prevalent among patients with asthma. In a study conducted in the city of São Paulo, Brazil, the prevalence of self-reported smoking among asthma patients was 3%, and the prevalence of self-reported former smoking was 33%.[9]

Correspondence to:
Gabriela Pimentel Pinheiro. Programa para o Controle da Asma na Bahia (ProAR), Centro de Saúde Carlos Gomes, Rua Carlos Gomes, 270, 7º andar, CEP 40060-330, Salvador, BA, Brasil.
Tel.: 55 71 3321-8467. E-mail: pimentelgabriela@yahoo.com.br

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a. http://orcid.org/0000-0002-6088-2805; b. http://orcid.org/0000-0001-7328-9608; c. http://orcid.org//0000-0001-5584-5658;
d. http://orcid.org/0000-0001-9723-8717; e. http://orcid.org/0000-0002-6129-8221; f. http://orcid.org/0000-0003-2247-4883;
g. http://orcid.org/0000-0002-9640-0193; h. http://orcid.org/0000-0003-0297-5226; i. http://orcid.org/0000-0001-8479-3666;
j. http://orcid.org/0000-0002-8874-7736; k. http://orcid.org/0000-0002-4462-8364; l. http://orcid.org/0000-0003-2119-437X;
m. http://orcid.org/0000-0002-4343-025X; n. http://orcid.org/0000-0002-3885-4314; o. http://orcid.org/0000-0002-7403-3871

Exposure to smoking can be determined by patient self-report and measurement of biological markers such as exhaled carbon monoxide and carboxyhemoglobin, as well as thiocyanate, nicotine, and cotinine levels, which can be measured in saliva, plasma, and urine.[10] Patient self-report is commonly used because it is an easy-to-use and inexpensive method for assessing smoking; however, inaccurate self-reporting (patient nondisclosure of smoking status) constitutes a disadvantage.[11]

Cotinine is a byproduct of nicotine metabolism, and measurement of cotinine levels is the most widely recommended method for quantifying exposure to tobacco smoking because it is not influenced by other exposures.[12] The technique used in order to measure cotinine levels is reliable[12-16] and allows detection of smoking occurring 19-40 h prior to urine sample collection.[17-19] This is due to the fact that the renal excretion of cotinine is low, meaning that cotinine can be easily detected by laboratory monitoring and has the prerequisites of specificity that make it the analyte of choice for quantifying exposures.[20]

The objective of the present study was to determine the frequency of active smoking among patients with varying degrees of asthma severity and individuals without asthma in the city of Salvador by self-report (with the use of standardized questionnaires) and urinary cotinine measurement.

METHODS

Study design

This was a cross-sectional study of patients diagnosed with asthma. The study was conducted between 2013 and 2015 at the Federal University of Bahia Center of Excellence in Asthma, which is located in the city of Salvador and is a research center affiliated with the *Programa para o Controle da Asma na Bahia* (ProAR, Bahia State Program for the Control of Asthma and Allergic Rhinitis).

The present study is part of a larger study entitled "*Fatores de risco, biomarcadores e endofenótipos da asma grave*" (Severe asthma: risk factors, biomarkers, and endophenotypes), which is a case-control study investigating patients with severe asthma and involving two control groups: participants with mild-to-moderate asthma and participants without asthma.

Selection and sampling

A total of 1,341 individuals were studied. Of those, 915 had been diagnosed with asthma. Of those, 417 had mild-to-moderate asthma and 498 had severe asthma (and were followed in the ProAR). The study also included 426 individuals without asthma.

The severe asthma patients participating in the study had not been under regular treatment prior to admission to the ProAR, when they were diagnosed with severe asthma (having been followed ever since). The study participants with mild-to-moderate asthma and those without asthma were recruited through advertisements in the media, in public transportation, and in public places, as well as through peer referral. Asthma severity was determined on the basis of the 2012 Global Initiative for Asthma criteria.[21]

Individuals ≥ 18 years of age living in Salvador (or in the greater metropolitan area of Salvador) and treated via the Brazilian Unified Health Care System were included in the study. All of the severe asthma patients included in the study had been under regular treatment for at least six months. Patients presenting with comorbidities that made it difficult to evaluate asthma control (including congestive heart failure, stroke, myopathies, advanced neoplasia, psychiatric disorders, and lung diseases other than asthma) were excluded, as were those with a smoking history of more than 10 pack-years, because of the difficulty in making a differential diagnosis between asthma and COPD. At the end of the study period, some of the participants were excluded for various reasons, including problems with the urine sample, treatment abandonment, and exacerbation of comorbidities that made patient evaluation difficult (Figure 1).

Participants with severe asthma

Severe asthma was diagnosed in accordance with the Global Initiative for Asthma criteria[21] by two specialists, who reviewed patient medical records during the selection phase. Disagreements between the two specialists regarding asthma diagnosis or severity were resolved by a third specialist. At the end of this phase, 949 patients meeting the inclusion criteria were contacted by telephone and invited to visit the Federal University of Bahia Center of Excellence in Asthma. Of those, only 553 visited the Federal University of Bahia Center of Excellence in Asthma, where they underwent clinical evaluation and spirometry. A total of 55 individuals were excluded, the total sample of patients with severe asthma therefore consisting of 498 individuals (Figure 1).

Participants with mild-to-moderate asthma or without asthma

A total of 2,526 patients with mild-to-moderate asthma and individuals without asthma were contacted for prescreening. Of those, 484 patients with mild-to-moderate asthma were included in the study. However, only 417 completed all tests. For comparison purposes, 464 individuals without asthma were included in the study. However, only 426 completed all tests (Figure 1).

Study procedures and data collection

During appointment scheduling, participants were instructed to collect first morning urine samples following basic safety and hygiene procedures. After delivery, the samples were labeled and stored in a freezer at −70°C. Patients were then referred for a clinical evaluation in order to confirm the diagnosis and determine the severity of asthma. In addition, they answered questions regarding exposure to smoking

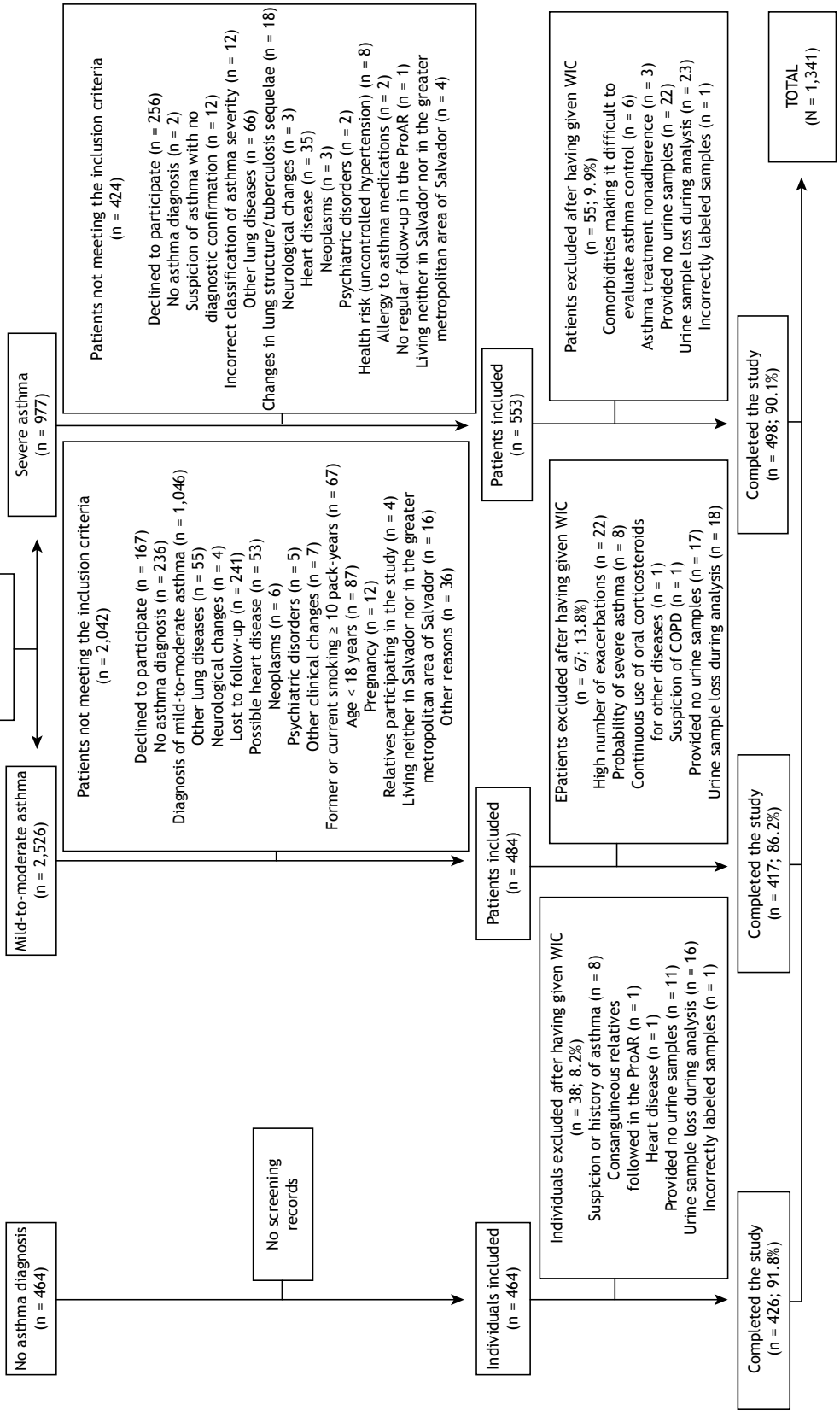

Figure 1. Flow chart of patient recruitment. ProAR: *Programa para o Controle da Asma na Bahia* (Bahia State Program for the Control of Asthma and Allergic Rhinitis); and WIC: written informed consent.

and use of medications. None of the participants were on nicotine replacement therapy.

Self-reported smoking status

The participants who reported smoking cigarettes daily or occasionally were considered to be current smokers. The participants who reported being former smokers and having quit smoking at least six months before their interview were considered to be former smokers.

Data regarding exposure to smoking were collected by asking participants questions regarding smoking history (the questions being part of the Brazilian Telephone-based System for the Surveillance of Risk and Protective Factors for Chronic Noncommunicable Diseases questionnaire)[22] and exposure to secondhand smoke at home, school, and work, as well as questions regarding exposure to smoking in public transportation and in public places (the questions being part of a questionnaire used by the Brazilian Institute of Geography and Statistics in the 2010 Census).[23]

Urinary cotinine measurement

Urinary cotinine was measured in accordance with the procedures described by Cattaneo et al.[24] A high-performance liquid chromatograph (1290 Infinity; Agilent®, Santa Clara, CA, USA) equipped with a Zorbax Eclipse XDB-C8 (4.6 mm × 150 mm × 5 μm) column and a UV-Vis (λ = 260 nm) detector (Agilent®) was used, with an injection volume of 20 μL and an isocratic mobile phase flow rate of 0.4 mL/min. The methodology was validated by using the parameters set forth in Brazilian National Health Oversight Agency Resolution no. 899.[25] Because of its sensitivity and specificity, high-performance liquid chromatography is recommended for measuring cotinine; in addition to being less expensive than other methods, high-performance liquid chromatography allows determination of low concentrations of cotinine.[26] The limits of detection and quantification were 6.46 μg/L and 19.59 μg/L, respectively.

Urinary cotinine levels are directly related to biological factors such as renal function, urine flow, and urine pH. For increased accuracy, urinary cotinine levels were adjusted for urinary creatinine levels (urinary cotinine/creatinine ratio, in μg/g).[27]

Urinary creatinine was measured with a creatinine assay kit and a spectrophotometer with a thermostated cuvette at 37°C (readings at 30 s and 90 s; wavelength, 510 ηm). An automated chemistry analyzer (BT 3000 PLUS; Wiener lab Group, Rosario, Argentina) was used.

Statistical analysis

All severe asthma patients followed in the ProAR until study initiation were included. Therefore, there was no sample size calculation. The numbers of participants with mild-to-moderate asthma and without asthma were established in order to guarantee the comparability of the groups.

The collected data were processed with the Statistical Package for the Social Sciences, version 17.0 (SPSS Inc., Chicago, IL, USA) and are presented as graphs and tables. The Shapiro-Wilk test and the Kolmogorov-Smirnov test were used in order to determine the nature of the distribution of the variables. Continuous variables were expressed as mean and standard deviation if distribution was Gaussian or as median and interquartile range (IR) if distribution was non-Gaussian. Categorical variables were expressed as absolute frequency and valid proportion. The chi-square test was used in order to compare proportions, and the Kruskal-Wallis test was used in order to compare continuous variables, given that most of the data had non-normal distribution.

Ethical considerations

The study was approved by the Research Ethics Committee of the Federal University of Bahia Climério de Oliveira Maternity Hospital (Ruling no. 099/2009; addendum no. 032/2014), as well as by the Brazilian National Health Council (Ruling no. 450/10). All of the study participants gave written informed consent.

RESULTS

A total of 1,341 patients were evaluated. Of those, 55 (4.1%) reported being current smokers, 273 (20.4%) reported being former smokers, and 1,013 (75.5%) reported being nonsmokers. The characteristics of the study participants are described in Table 1. Participants were divided into three groups on the basis of asthma status and severity: severe asthma (n = 498), mild-to-moderate asthma (n = 417), and no asthma diagnosis (n = 426).

Of the 55 participants who reported being active smokers, 32 (58.2%) reported smoking cigarettes daily and 23 (41.8%) reported smoking occasionally (Table 1). Table 2 provides detailed information on smoking in each study group. Among current smokers, smoking duration was longer in patients with severe asthma and individuals without asthma than in patients with mild-to-moderate asthma.

Smoking initiation was found to have occurred at an early age (i.e., during adolescence). Among smokers and former smokers, the mean age at smoking initiation was significantly lower in the group of patients with severe asthma (15.9 ± 5.3 years) than in that of patients with mild-to-moderate asthma (18.8 ± 5.7 years) and that of individuals without asthma (16.8 ± 4.2 years; p = 0.02).

Among current smokers, a longer smoking history was found in the group of patients with severe asthma (25.5 pack-years) when compared with that of those with mild-to-moderate asthma (1.3 pack-years) and that of those without asthma (7.7 pack-years). Among former smokers, patients with severe asthma had a smoking history of 4.4 pack-years, patients with mild-to-moderate asthma had a smoking history of 1.2 pack-years, and individuals without asthma had a smoking history of 8.0 pack-years.

Table 1. Sociodemographic characteristics of the study sample, by self-reported smoking status.[a]

Characteristic	Group		
	Smokers	Former smokers	Nonsmokers
Sample	55 (4.1)	273 (20.4)	1,013 (75.5)
Classification			
No asthma diagnosis	33 (60.0)	84 (30.8)	309 (30.5)
Mild-to-moderate asthma	17 (39.9)	56 (20.5)	344 (34.0)
Severe asthma	5 (0.1)	133 (48.7)	360 (35.5)
Female sex	40 (72.7)	199 (72.9)	862 (85.1)
Age, years	41.2 ± 13.1	51.5 ± 12.2	43.1 ± 14.4
Family income, Brazilian reals	850.00 [678.00-1,500.00]	830.00 [700.00-1,400.00]	1,000.00 [720.00-1,500.00]
Marital status			
Single	38 (69.1)	108 (39.6)	439 (43.3)
Married/SP	10 (18.2)	111 (40.7)	429 (42.3)
Divorced	6 (10.9)	37 (13.5)	79 (7.8)
Widowed	1 (1.8)	17 (6.2)	66 (6.5)
Level of education			
No schooling	3 (5.5)	16 (5.9)	25 (2.5)
5 years of schooling	6 (10.9)	71 (26.0)	110 (10.9)
9 years of schooling	15 (27.3)	67 (24.5)	189 (18.7)
High school	24 (43.6)	99 (36.3)	521 (51.4)
College	7 (12.7)	20 (7.3)	168 (16.6)
Self-reported skin color			
Black	23 (41.8)	90 (33.0)	436 (43.0)
Brown	31 (56.4)	156 (57.1)	486 (48.0)
Other[b]	1 (1.8)	27 (9.9)	91 (9.0)

SP: steady partner. [a]Values expressed as n (%), mean ± SD, or median [interquartile range]. [b]White, red, or yellow.

All of the study participants who reported smoking daily were positive for urinary cotinine. Of the study participants who reported smoking occasionally, 8 had urinary cotinine levels below the limit of detection. Median urinary cotinine levels were higher among daily smokers (758.2 µg/g; IR: 433.2-2,066.8) than among occasional smokers (97.1 µg/g; IR: 30.7-1.036.9; Table 3). Among daily and occasional smokers, urinary cotinine levels were highest in the group of patients with severe asthma.

Of the study participants who reported being nonsmokers (n = 1,286), 273 (21.3%) were former smokers. Median urinary cotinine levels were higher among former smokers (44.9 µg/g; IR: 17.4-147.9) than among individuals who reported never having smoked a cigarette (24.2 µg/g; IR: 10.9-58.5). Median urinary cotinine levels were higher among former smokers in the severe asthma group than among those in the remaining groups (Table 3). Figure 2 shows median urinary cotinine levels in smokers, former smokers, and nonsmokers, by asthma status.

Among former smokers, median urinary cotinine levels were highest in those with severe asthma. Among former smokers, median urinary cotinine levels were higher in those with severe asthma (62.5 µg/g; IR: 19.2-409.5) than in those with mild-to-moderate asthma (30.3 µg/g; IR: 13.0-110.3) and those without asthma (40.9 µg/g; IR: 9.9-129.1; $p > 0.05$).

Of the study participants who reported being nonsmokers, 440 (34.3%) reported having been exposed to secondhand smoke (at home, at work, in public transportation, in public places, or any combination of the four) in the last 24 h. Of the nonsmokers who reported having been exposed to secondhand smoke in the last 24 h, 36.7% were patients with severe asthma, 34.6% were patients with mild-to-moderate asthma, and 30.8% were individuals without asthma.

DISCUSSION

In the present study, 4.1% of the participants reported being active smokers, a proportion that is lower than the mean proportion of smokers in the Brazilian population but similar to the proportion of smokers among adults in the city of Salvador.[5]

As expected, urinary cotinine levels were higher among daily smokers than among occasional smokers, former smokers, and nonsmokers. In addition, urinary cotinine levels were found to be higher in former smokers than in nonsmokers, a finding that suggests patient nondisclosure of smoking status. Urinary cotinine levels were higher in severe asthma patients who reported being former smokers than in former smokers with mild-to-moderate asthma and no asthma diagnosis, a finding that suggests that the issue of patient nondisclosure of smoking status is even more problematic in patients with severe asthma. The proportion of former smokers was highest among patients with severe asthma and lowest among patients with mild-to-moderate asthma.

The prevalence of current smoking was found to be higher in individuals without asthma than in patients

Table 2. Exposure to smoking[a] and creatinine-corrected urinary cotinine levels (in µg/g) in the study groups.[b]

Characteristic	Group		p*
	Current smokers (n = 55)	Former smokers (n = 273)	
Age at smoking initiation, years			
Severe asthma	20.0 [13.5-23.5]	15.0 [13.0-18.0]	0.20
Mild-to-moderate asthma	18.0 [16.5-20.5]	18.0 [15.0-20.8]	0.25
No asthma diagnosis	17.0 [15.0-19.8]	16.0 [14.0-18.0]	0.20
Age at smoking cessation, years			
Severe asthma		31.5 [23.0-40.0]	
Mild-to-moderate asthma		30.0 [24.0-59.0]	
No asthma diagnosis		32.0 [25.0-40.0]	
Attempted to quit smoking			
Severe asthma	3 (60.0)		
Mild-to-moderate asthma	6 (35.3)		
No asthma diagnosis	11 (34.4)		
Duration of smoking, years			
Severe asthma	33.0 [8.5-43.5]	15.0 [5.3-24.0]	0.14
Mild-to-moderate asthma	10.0 [6.0-18.0]	11.3 [3.0-14.5]	0.07
No asthma diagnosis	27.5 [16.3-37.0]	10.2 [7.0-25.0]	< 0.01
Number of cigarettes/day			
Severe asthma	2.0 [1.5-12.5]	6.0 [3.0-20.0]	0.18
Mild-to-moderate asthma	2.0 [1.0-4.0]	5.0 [3.0-10.0]	< 0.01
No asthma diagnosis	5.0 [3.0-9.5]	10.0 [3.0-20.0]	0.03
Smoking history, pack-years			
Severe asthma	25.5 [0.4-36.9]	4.4 [1.2-16.8]	0.52
Mild-to-moderate asthma	1.3 [0.2-4.0]	1.2 [0.8-7.0]	0.25
No asthma diagnosis	7.7 [2.5-18.4]	8.0 [1.3-19.8]	0.89
Urinary cotinine, µg/g[c]			
Severe asthma	807.8 [49.1-3.239.3]	62.5 [19.2-409.5]	0.03
Mild-to-moderate asthma	41.1 [4.1-201.6]	30.3 [13.0-110.1]	0.27
No asthma diagnosis	598.3 [219.8-2.027.8]	40.9 [9.9-129.1]	< 0.01
Exposure to secondhand tobacco smoke in the last 24 h			
Severe asthma	4 (80.0)	59 (44.4)	0.12
Mild-to-moderate asthma	10 (58.8)	24 (42.9)	0.25
No asthma diagnosis	24 (72.7)	29 (34.5)	< 0.01

[a]On the basis of references 22 and 23. [b]Values expressed as n (%) or median [interquartile range]. [c]Results below the limit of detection are not included. *Chi-square test for categorical variables and Kruskal-Wallis test for continuous variables.

with asthma, being lower in severe asthma patients than in mild-to-moderate asthma patients. The low rates of self-reported smoking among asthma patients in the present study are similar to those found in the literature[9] and might be due to the fact that smoking has a negative impact on the clinical status and quality of life of asthma patients, who therefore avoid cigarettes. Because of their disease, patients with asthma are less likely to continue smoking. Another factor that can play an important role in reducing smoking among patients with asthma is being followed at health care clinics that provide education on the harmful effects of smoking. However, the possibility of patient nondisclosure of smoking status should be taken into account.[9,11]

The fact that the proportion of former smokers in the present study was highest among severe asthma patients suggests that smoking is a risk factor for the development of severe asthma in asthma patients who smoke despite feeling discomfort and despite warnings about the effects of smoking. In asthma patients with an increased smoking history, increased asthma severity might be due to asthma-COPD overlap syndrome.

Among smokers and former smokers in the present study, smoking initiation was found to have occurred during adolescence, a finding that is consistent with those of Malcon et al.[28] and Abreu et al.[29] In the present study, smoking initiation was found to have occurred earlier in the group of patients with severe asthma than in that of those with mild-to-moderate asthma (15.9 years vs. 18.8 years), a finding that is consistent with the possibility that exposure to smoking is a risk factor for the development of severe asthma.[30]

Among smokers and former smokers, the median duration of smoking was shorter in those with mild-to-moderate asthma than in those with severe asthma. This suggests that smoking is associated with asthma severity. In the present study, mild-to-moderate asthma patients smoked less than did severe asthma patients and individuals without asthma. It is possible that the discomfort associated with cigarette smoke inhalation

Table 3. Creatinine-corrected urinary cotinine (in µg/g) in the study participants (n = 1,341), by self-reported smoking status.[a]

Smoking status	Number of participants		Urinary cotinine, µg/g[b]	p*
	n/N	%		
Daily smoker				0.35
Severe asthma	2/498	0.4	930.4 (807.8-1,053.1)	
Mild-to-moderate asthma	7/417	1.7	140.4 (11.9-2,189.7)	
No asthma diagnosis	23/426	5.4	710.8 (499.1-2,357.7)	
TOTAL	32/1,341	2.4	758.2 (433.2-2,066.8)	
Occasional smoker				0.17
Severe asthma	3/498	0.6	2,761.3 (97.1-5,425.5)	
Mild-to-moderate asthma	10/417	2.4	41.1 (16.2-129.1)	
No asthma diagnosis	10/426	2.3	635.1 (32.3-3,945.0)	
TOTAL	23/1,341	1.7	97.1 (30.7-1,036.9)	
Former smoker				0.17
Severe asthma	133/498	26.7	62.5 (19.2-409.5)	
Mild-to-moderate asthma	56/417	13.4	30.3 (13.0-110.3)	
No asthma diagnosis	84/426	19.7	40.9 (9.9-129.0)	
TOTAL	273/1,341	20.4	44.9 (17.4-147.9)	
Nonsmoker				< 0.01
Severe asthma	360/498	72.3	27.7 (14.3-69.5)	
Mild-to-moderate asthma	344/417	82.5	14.3 (6.8-39.9)	
No asthma diagnosis	309/426	72.5	28.2 (11.4-67.3)	
TOTAL	1,013/1,341	75.5	24.2 (10.9-58.5)	

[a]Values expressed as median (interquartile range). [b]Individuals presenting with results below the limit of detection are not included. *Kruskal-Wallis test.

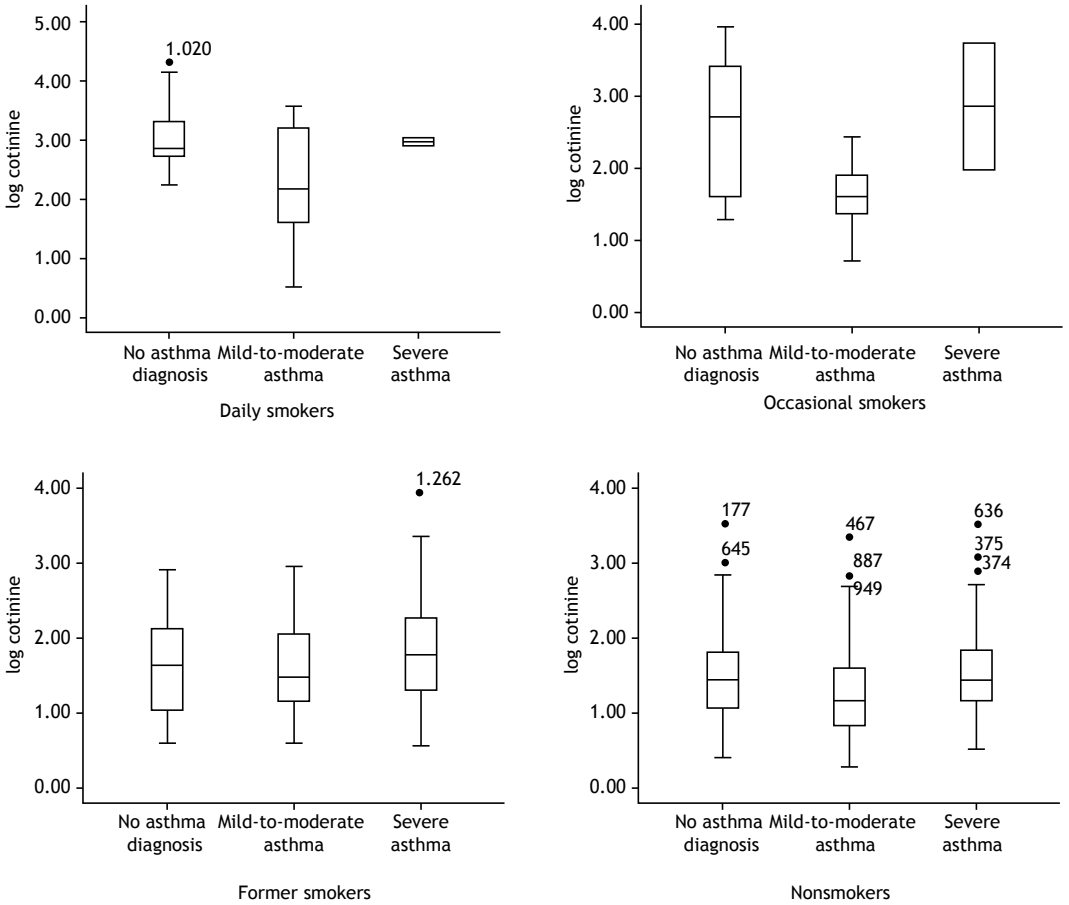

Figure 2. Creatinine-corrected urinary cotinine levels, by self-reported smoking status. Results expressed as (log) per µg/g of creatinine.

led mild-to-moderate asthma patients to quit smoking, whereas those who continued to smoke developed asthma that is more severe.

In the present study, patients with severe asthma were found to have a longer smoking history (in pack-years) than that of those with mild-to-moderate asthma, a finding that suggests an association between smoking and increased asthma severity.

In the present study, urinary cotinine levels varied among the groups, differences being found between urinary cotinine measurements and self-reported smoking status. Median urinary cotinine levels were found to be higher in self-reported daily smokers than in self-reported occasional smokers, except in the group of patients with severe asthma, a finding that suggests patient nondisclosure of smoking behavior. Cotinine levels are typically lower in individuals who do not smoke daily than in those who do, being high in those who smoke more cigarettes daily,[31] a single measurement of cotinine being sufficient to show that.[32]

Other studies have shown discrepancies between self-reported smoking status and cotinine measurements,[33,34] suggesting patient nondisclosure of smoking status. In a study conducted in the city of São Paulo, Brazil, urinary cotinine levels were found to be high in severe asthma patients who reported being former smokers, a finding that alerts us to the possibility of inaccurate self-reporting.[11]

Smoking is known to be associated with a poor asthma prognosis, reducing patient response to inhaled corticosteroids, increasing asthma symptoms, increasing the need for emergency room visits, increasing the need for hospitalization, and increasing treatment costs, as well as having a negative impact on quality of life. Cessation of smoking and smoke exposure can improve the clinical status of patients with asthma.[8,35]

Although our sample was large, the present study has limitations that should be taken into account. Urinary cotinine measurements might have been affected by passive exposure to tobacco smoke, ethnicity, and consumption of nicotine-containing foods, such as tomatoes, potatoes, and black tea.[36,37] However, there were no differences in cotinine levels among nonsmokers or self-reported ethnicities exposed to secondhand smoke (exposure being expressed as number of hours). The influence of dietary habits on urinary cotinine levels was not investigated in the present study. The low frequency of current smokers in our sample reduced the power of subgroup analyses. During patient recruitment, asthma patients who reported a smoking history ≥ 10 pack-years were excluded in order to avoid mistaking COPD for asthma and ensure that the inclusion criteria were similar for patients with severe asthma and those with mild-to-moderate asthma. This might have introduced a bias in the comparison with the individuals without asthma. However, the bias would have favored a shorter smoking history among asthma patients; the fact that this was not observed in the severe asthma group reinforces the internal validity of our study. The proportion of former smokers was considerably higher in the severe asthma group (i.e., 27%) than in the remaining groups.

In conclusion, the prevalence of self-reported smoking was low among patients with varying degrees of asthma severity, being particularly low among those with severe asthma. However, among patients with severe asthma, findings of an increased proportion of self-reported former smokers, an increased smoking history, and increased urinary cotinine levels suggest patient nondisclosure of smoking status and an association between exposure to active smoking and severe asthma. Patients with severe asthma should be thoroughly screened for smoking via interviews and objective assessment.

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Mitomycin C in the endoscopic treatment of tracheal stenosis: a prospective cohort study

Daniele Cristina Cataneo[1,a], Aglaia Moreira Garcia Ximenes[2,b], Antônio José Maria Cataneo[1,c]

1. Departamento de Cirurgia, Faculdade de Medicina de Botucatu, Universidade Estadual Paulista – UNESP – Botucatu (SP) Brasil.
2. Programa de Pós-Graduação em Medicina, Faculdade de Medicina de Botucatu, Universidade Estadual Paulista – UNESP – Botucatu (SP) Brasil.

a. http://orcid.org/0000-0002-3400-2309
b. http://orcid.org/0000-0001-7677-8124
c. http://orcid.org/0000-0003-2330-9337

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ABSTRACT

Objective: To evaluate the efficacy of mitomycin C (MMC) in the endoscopic treatment of tracheal stenosis. **Methods:** Patients with laryngotracheal, tracheal, or tracheobronchial stenosis were treated with dilation and topical MMC. The inclusion criteria were as follows: being ineligible for surgery (for medical reasons) at the time of evaluation; membranous stenosis responding well to dilation; and postoperative stenosis at the anastomosis site. Etiology of stenosis and indication for treatment with MMC, as well as site, length, and percentage of stenosis, together with presence of tracheostomy and duration of follow-up, were analyzed. The outcomes evaluated were symptom-free interval ≥ 12 months, number of dilations with topical application of MMC, and complications. **Results:** Twenty-two patients (15 men and 7 women) were treated between 2003 and 2010. Stenosis was due to endotracheal intubation in 15 patients and surgery in 8. Pure tracheal stenosis was encountered in 13 patients, subglottic stenosis was encountered in 4, tracheobronchial stenosis was encountered in 3, and complex stenosis was encountered in 2. The length of stenosis ranged from 0.5 cm to 2.5 cm, and the percentage of stenosis ranged from 40% to 100%. Nine patients had undergone tracheostomy and had a Montgomery T-tube in situ. Treatment was successful in 14 patients, who remained free of symptoms for at least 12 months. The number of topical applications of MMC ranged from 1 to 5, and complications included fungal infection, keloid scarring, granuloma, and mediastinal emphysema. **Conclusions:** MMC appears to be effective in the endoscopic treatment of tracheal stenosis.

Keywords: Tracheal stenosis; Mitomycin; Endoscopy.

INTRODUCTION

Tracheal stenosis was first described in 1880 by MacEwen in patients undergoing endotracheal intubation.[1] In 1886, Colles described it in patients with diphtheria treated with tracheostomy.[2] As a consequence of the introduction of advanced life support in the intensive care setting in the early 1950s, endotracheal intubation became more common, as did cases of tracheal injury secondary to trauma. In the mid-20th century, tracheal stenosis was treated with dilation, a form of treatment that allowed weaning from tracheal intubation in many cases. However, advances in surgical techniques made tracheal resection the treatment of choice for tracheal stenosis. Nevertheless, the treatment of inoperable tracheal stenosis remains a challenge; new endoscopic treatment techniques have been proposed, with good results.[3] Endoscopic procedures can therefore serve as a bridge to surgical treatment, but they can also be a definitive treatment for many patients, including those who are potential surgical candidates, with success rates ranging from 32% to 66%.[4]

Topical substances such as steroids, anticoagulants, and mitomycin C (MMC) have been used in order to optimize endoscopic treatment. Mitomycin is a natural antibiotic produced by *Streptomyces caespitosus*. In 1956, Hata et al. described mitomycin A and B.[5] In 1958, Wakaki et al. described MMC.[6] In addition to being an antibiotic, MMC acts as an antineoplastic or alkylating agent by inhibiting DNA synthesis. It was first used in 1963 by ophthalmologists for pterygium surgery, with excellent results,[7] and it is currently widely used as a topical agent to prevent scar formation following cataract surgery.

The potential effects of MMC on the airways were first studied in 1998 by Ingrams et al.[8] The authors investigated the effect of MMC on paranasal sinus mucosal healing in rabbits and found inhibition of fibroblasts when MMC was used at a concentration of 0.04 mg/mL.[8] Although animal and human studies have examined the use of MMC in the upper and lower airways, there is still uncertainty on this issue because of the heterogeneous nature of human studies and the scarcity of histological specimens in experimental studies. Nevertheless, on the basis of previous studies, MMC came to be used in the endoscopic treatment of lower airway stenosis at our institution in 2003. Therefore, the objective of the present study was to evaluate the efficacy of MMC in the endoscopic treatment of tracheal stenosis.

Correspondence to:
Daniele Cristina Cataneo. Departamento de Cirurgia, Faculdade de Medicina de Botucatu, Universidade Estadual Paulista, CEP 18618-687, Botucatu, SP, Brasil.
Tel.: 55 14 3880-1529. Fax: 55 14 3880-1669. E-mail: dcataneo@fmb.unesp.br
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METHODS

This was a prospective cohort study conducted between 2003 and 2010. The study was approved by the local research ethics committee and involved patients who had tracheal stenosis and in whom surgery was not indicated. MMC was handled in accordance with the Brazilian Department of Health Care guidelines.[9]

The inclusion criteria were as follows: being bedridden (having been discharged from the ICU but showing incomplete disease resolution); recent acute myocardial infarction; recent stroke (with neurological deficit or a high risk of reintubation); psychiatric disorder not controlled by medications; immature stenosis (with or without a tracheostomy performed within the first 3 months after injury); stenosis with acute inflammation; early or late postoperative restenosis responding well to dilation; membranous stenosis responding well to dilation; and complex stenosis (i.e., stenoses at more than one site or an old stenosis with a Montgomery T-tube in situ). The exclusion criteria were as follows: having indication for surgery at the time of initial evaluation; having a congenital disease or presenting with acute-phase infectious disease such as tuberculosis and blastomycosis; having extensive stenosis not amenable to dilation or without a fibrous ring (malacia); having undergone post-dilation; having no open wound; and presenting with tracheal or tracheobronchial infection.

In order to evaluate the efficacy of MMC, an initial evaluation was performed by rigid bronchoscopy. Subsequently, dilation of the stenotic area was performed and was followed by topical application of MMC at a concentration of 0.5 mg/mL for 2 min, MMC being reapplied for another 2 min immediately after dilation. Patients with a tracheostomy (a Montgomery T-tube in situ) were reevaluated after 1 month, whereas those without a tracheostomy were reevaluated after 2 weeks, MMC being applied again as described above if necessary. Treatment was discontinued in patients with drug-related complications such as tracheal infection and allergy, as well as in those with no response to the first application. In patients who had an incomplete response to MMC but were eligible for surgery, treatment was discontinued and surgery was indicated.

We analyzed the following variables: sex; etiology of stenosis; indication for treatment with MMC; site, length, and percentage of stenosis (as evaluated by bronchoscopy); presence of tracheostomy; and duration of follow-up. We evaluated the following outcomes: resolution (i.e., stenosis of less than 20% with no symptoms for at least 12 months); number of dilations with topical application of MMC; and complications. Descriptive statistics were calculated, including frequency, proportion, mean, and standard deviation.

RESULTS

A total of 22 patients met the inclusion criteria, being evaluated in the period between 2003 and 2010. Of those 22 patients, 15 were male and 7 were female. In addition, 15 received primary treatment with MMC. Stenosis was caused by endotracheal intubation in those patients, 9 of whom had been intubated because of trauma and 6 of whom had been intubated because of complications of acute or chronic disease (Table 1).

Of the 22 patients included in the study, 8 received secondary treatment for postoperative stenosis (restenosis at the anastomosis site). Of those 8 patients, 2 had undergone laryngotracheoplasty, 3 had undergone tracheoplasty, and 3 had undergone tracheobronchoplasty (Table 2). Of the 3 patients who had undergone tracheoplasty, 1 had received primary treatment with MMC.

There were two cases of stenosis at the tracheobronchial anastomosis site after right main bronchus resection: one was due to leiomyosarcoma, and the other was due to tuberculosis. In addition, there was one case of stenosis at the tracheobronchial anastomosis site after resection for complete occlusion of the left main bronchus, the cause of which was unknown.

Of the 22 patients included in the study, 13 had tracheal stenosis, 4 had subglottic stenosis, 3 had tracheobronchial stenosis, and 2 had complex stenosis. Of those 2 patients, 1 had laryngotracheal stenosis and 1 had stenosis of the larynx and left main bronchus. The length of stenosis ranged from 0.5 cm to 2.5 cm (mean, 1.25 cm), and the percentage of stenosis ranged from 40% to 100% (mean, 76%).

Of the sample as a whole, 9 had undergone a tracheostomy procedure and had a Montgomery T-tube in situ. Of those, 4 were in the group of patients with postoperative stenosis and 6 were in that of those with stenosis following endotracheal intubation (meaning that 1 of the 9 patients was in both groups).

Of the 8 patients with postoperative stenosis, 6 (75%) responded well to treatment and 2 did not. Of those, one had stenosis after left tracheobronchoplasty (a carinal prosthesis therefore being required), and the other had keloid scarring at the anastomosis site, tracheal lumen size having therefore decreased by 50%. Of the 15 patients with stenosis following endotracheal intubation, 8 (53%) responded well to treatment. The number of dilations per patient ranged from 1 to 5 (mean, 2.4).

Complications resulting from MMC use occurred in 1 patient, who had a tracheobronchial infection after the first application. Other complications resulted from dilation (mediastinal emphysema) or surgery (keloid scarring at the anastomosis site). The mean follow-up period was 30 months, ranging from 12 months to 72 months.

DISCUSSION

Surgical treatment of laryngotracheal stenosis by resection of the stenotic segment followed by end-to-end anastomosis has proven effective[10]; however, not all patients are amenable to it. It is therefore important to have an effective endoscopic treatment

Table 1. Patients with stenosis following endotracheal intubation.

Age, years/ gender	Indication for MMC use	Site of stenosis	Percentage/ length of stenosis[a]	Reason for intubation	T-tube in situ	Outcome		Complications	Final outcome/ follow-up period, months
						Free of symptoms for at least 12 months	Topical applications of MMC, n		
28/F	Waiting for surgery	Subglottis	100%/2.5 cm	Diabetic coma	No	No	2		Tracheoplasty/12
45/M	Waiting for surgery	Trachea	90%/2.5 cm	Acute abdomen	No	No	5		Tracheoplasty/12
38/F	Waiting for surgery	Trachea	80%/2.5 cm	Stroke	No	No	2		Tracheoplasty/12
60/M	Waiting for surgery	Trachea	90%/1.0 cm	AMI	No	Yes	2		Resolution/12
23/M	Tetraplegia	Trachea	70%/1.0 cm	Trauma	Yes	Yes	1		Resolution/12
25/F[b]	Membranous stenosis	Trachea	90%/1.0 cm	Trauma	Yes	No	1	Keloid scarring	Tracheoplasty/26
47/M	Neurological deficit	Trachea	40%/2.5 cm	Trauma	Yes	Yes	1	Fungal infection	Resolution/29
12/F	Membranous stenosis	Trachea	80%/0.5 cm	Trauma	No	Yes	5		Resolution/18
33/M	Neurological deficit	Trachea	90%/0.5 cm	Trauma	No	Yes	4		Resolution/14
48/M	Waiting for surgery	Trachea	80%/1.0 cm	AMI	No	No	4		Tracheoplasty/12
24/M	Complex stenosis	Larynx + trachea	40%/1.0 cm	Trauma	No	Yes	2		Resolution/24
19/F	Complex stenosis	Trachea + LMB	60%/2.5 cm	Trauma	Yes	Yes	4		Tracheal stenosis, resolution/ stenosis of the LMB, carinal prosthesis/24
19/M	Waiting for surgery	Subglottis	90%/2.0 cm	Trauma	No	No	2		Tracheoplasty/12
29/M	Old stenosis	Trachea	40%/2.5 cm	Trauma	Yes	No	3		T-tube placement/12
26/M	Psychiatric disorder	Subglottis	80%/2.0 cm	Suicide attempt	Yes	Yes	1		Resolution/24

MMC: mitomycin C; AMI: acute myocardial infarction; and LMB: left main bronchus. [a]As assessed by bronchoscopy. [b]Patient with stenosis following endotracheal intubation as well as postoperative stenosis.

Table 2. Patients with postoperative stenosis.

Age, years/ gender	Site of stenosis	Percentage/ length of stenosis[a]	Surgical treatment	Montgomery T-tube in situ before surgery	Outcome			Final outcome/follow-up period, months
					Free of symptoms for at least 12 months	Topical applications of MMC, n	Complications	
29/M	Subglottis	100%/0.5 cm	Laryngotracheoplasty	Yes	Yes	1	Restenosis	Resolution after MMC use/72
48/M	Trachea + bronchi	40%/1.5 cm	Tracheobronchoplasty	No	Yes	3		Resolution after MMC use/72
32/F	Trachea + bronchi	90%/0.5 cm	Tracheobronchoplasty	No	No	2	Mediastinal emphysema	Carinal prosthesis/12
50/F	Trachea	80%/1.0 cm	Tracheoplasty	No	Yes	3		Resolution after MMC use/72
22/M	Trachea + bronchi	80%/0.5 cm	Bronchial sleeve resection	No	Yes	4	Mediastinal emphysema	Resolution after MMC use/72
47/M	Trachea	90%/2.0 cm	Tracheoplasty	Yes	Yes	2		Resolution after MMC use/13
53/M	Trachea	50%/1.5 cm	Tracheoplasty	Yes	Yes	2		Resolution after MMC use/12
25/F[b]	Trachea	90%/1.0 cm	Tracheoplasty	Yes	No	1	Granuloma	Stenosis of 50%/72

MMC: mitomycin C. [a]As assessed by bronchoscopy. [b]Patient with stenosis following endotracheal intubation as well as postoperative stenosis.

for laryngotracheal stenosis. Endoscopic treatment is based on dilation of the stenotic area; however, wound healing can result in restenosis. Drugs that prevent fibroblast proliferation can slow down or even inhibit this process.

MMC was first used in the airways in the late 20th century, and, since then, few studies have demonstrated its efficacy,[11,12] whereas others have shown it to be ineffective.[13] Although there has been an increase in the number of cases of laryngotracheal stenosis—an increase that is probably due to the success of intensive care medicine—the prevalence of laryngotracheal stenosis is still low; however, there has been an increase in the number of cases of complex stenosis.[14] Our study demonstrates that dilation with topical application of MMC is effective in maintaining airway patency, the probability of resolution, characterized by a symptom-free interval ≥ 12 months, being approximately 60%. Although we did not compare dilation alone and dilation with topical application of MMC in the present study, retrospective studies have shown that the latter method yields better results.[15-17]

The present study shows that ICU patients can be safely discharged from the ICU and wait for surgery without a tracheostomy if the hospital has a respiratory endoscopy department where dilation and topical application of MMC can be performed. None of the 6 patients who were waiting for surgery required a tracheostomy, dilations and topical applications of MMC being sufficient to maintain airway patency. Another advantage is that dilation with topical application of MMC can result in resolution of tracheal stenosis without surgical intervention. Four of our patients with neurological or psychiatric disorders achieved complete resolution without a more invasive procedure, reintubation sometimes being required in such patients because of their underlying disease. Reduced hospital costs constitute yet another advantage of endoscopic treatment. One of our patients who were waiting for surgery achieved complete resolution of stenosis after endoscopic treatment. It has been reported that endoscopic treatment with topical application of MMC is cost-effective if 1 of 17 patients requires one less operation.[18] Endoscopic treatment with topical application of MMC costs US$ 455.00 per patient, whereas open surgery costs US$ 7,840.00, meaning that the latter is 17 times more expensive than the former. Although these data are not directly comparable between the two countries (i.e., the USA and Brazil), surgical treatment is much more costly than endoscopic treatment with MMC in Brazil as well.

Previous studies have shown that MMC appears to be effective in the treatment of postoperative stenosis.[19] Of the 8 patients with postoperative stenosis in the present study, only 2 had no resolution, the reasons being idiopathic bronchial stenosis (in 1) and keloid scarring (in 1).

Despite the advantages of using MMC in the endoscopic treatment of tracheal stenosis, several issues require further investigation. In our study, there were two

cases of complex stenosis (i.e., stenoses at more than one site), and only one responded to treatment. In addition, there were two cases of membranous stenosis. Although we expected that they would be easily resolved by endoscopic treatment with topical application of MMC, 1 patient did not respond to treatment, tracheoplasty therefore being required.

There is no consensus in the literature regarding the number of procedures required. In a randomized, prospective, double-blind, placebo-controlled clinical trial,[20] two applications of MMC were found to be more effective than only one in the endoscopic management of laryngotracheal stenosis.

Airway obstruction is the major complication caused by MMC and its local toxicity. Although there were no cases of airway obstruction in the present study, there was one case of rapid accumulation of fibrinous debris at the surgical site, resulting in partial airway obstruction, as described elsewhere.[21] The only MMC-related complication identified in the present study was fungal infection, emphysema and hypertrophic scarring being attributed to dilation and individual predisposition, respectively.

Although treatment with MMC led to stenosis resolution in little more than half of the cases in the present study, MMC was found to be effective when used in combination with tracheal dilation for the treatment of postoperative stenosis and stenosis following endotracheal intubation. In cases of stenosis following endotracheal intubation, MMC is effective in maintaining airway patency without the need for a prosthesis or a tracheostomy, leading to complete resolution of stenosis or maintaining lumen patency until patients can be operated on. Therefore, topical application of MMC is a treatment option for patients who cannot undergo surgery and those with post-surgical restenosis.

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ORIGINAL ARTICLE

Trend of self-reported asthma prevalence in Brazil from 2003 to 2013 in adults and factors associated with prevalence

Felipe Moraes dos Santos[1,a], Karynna Pimentel Viana[1,b], Luciana Tarbes Saturnino[1,c], Evelyn Lazaridis[1,d], Mariana Rodrigues Gazzotti[1,e], Rafael Stelmach[2,f], Claudia Soares[1,g]

1. GlaxoSmithKline, Rio de Janeiro (RJ) Brasil.
2. Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.

a. http://orcid.org/0000-0002-3512-4543
b. http://orcid.org/0000-0001-8288-1398
c. http://orcid.org/0000-0002-5415-1491
d. http://orcid.org/0000-0001-9984-3486
e. http://orcid.org/0000-0002-6061-785X
f. http://orcid.org/0000-0002-5132-1934
g. http://orcid.org/0000-0002-8425-2066

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Study carried out at GSK, Rio de Janeiro (RJ) Brasil.

ABSTRACT

Objectives: To determine the trend of self-reported asthma diagnosed prevalence and to describe the factors associated with asthma in Brazilian adults. **Method:** Epidemiological cross-sectional study based on databases analysis from three national household **surveys:** Pesquisa Nacional por Amostra de Domicílios (PNAD) 2003, PNAD 2008 and Pesquisa Nacional de Saúde (PNS) 2013. Participants between 18–45 years old were included. Trend analysis of asthma diagnosed prevalence was conducted using a logistic general linear model. A hierarchical logistic regression model was used to select factors significantly associated with asthma prevalence. **Results:** Asthma diagnosed prevalence was 3.6% (2003), 3.7% (2008) and 4.5% (2013), showing a statistically significant increased trend. Asthma diagnosed prevalence also increased when analysed by gender (annual change for men: 2.47%, $p < 0.003$; women: 2.16%, $p < 0.001$), urban area (annual change for urban: 2.15%, $p < 0.001$; rural: 2.69%, $p = 0.072$), healthcare insurance status (annual change without healthcare insurance: 2.18%, $p < 0.001$; with healthcare insurance: 1.84%, $p = 0.014$), and geographic regions (annual change North: 4.68%, $p < 0.001$; Northeast: 4.14%, $p < 0.001$; and Southeast: 1.84%, $p = 0.025$). Female gender, obesity, living in urban areas and depression were associated with asthma diagnosed prevalence. **Discussion:** PNAD and PNS surveys allow for a very large, representative community-based sample of the Brazilian adults to investigate the asthma prevalence. From 2003 to 2013, the prevalence of self-reported physician diagnosis of asthma increased, especially in the North and Northeast regions. Gender, region of residence, household location (urban/rural), obesity, and depression diagnosis seem to play significant roles in the epidemiology of asthma in Brazil.

Keywords: Adults; Asthma; Logistic models; Prevalence; Risk factors.

INTRODUCTION

Asthma is a chronic heterogeneous disease characterized by recurrent attacks of breathlessness and wheezing, which vary in severity and frequency from person to person.[1,2] Common risk factors for asthma include allergies, air pollution, obesity, respiratory viral infections, and occupational exposures.[3] Asthma is a serious global health problem, and it is estimated that 235 million people have asthma worldwide and over 80% of asthma deaths occur in low and lower-middle income countries. The prevalence of asthma varies according to geographic location, climate, lifestyle, and economic development of a specific region in the world.[1,2] In Brazil, it is estimated that five patients dies per day[4] due to asthma and the average of 100,000 hospitalizations per year occurs in the public healthcare system, highlighting the impact of this disease.[4]

Despite knowledge that asthma affects every age group,[2] the focus of local Brazilian research to date has primarily been on children and adolescent populations. For example, in Brazil, the Pesquisa Nacional de Saúde do Escolar (PeNSE) indicated high prevalence of asthma symptoms (23.2%) and previous medical diagnosis of asthma (12.4%) in children and adolescents.[5] Three of five state capitals from PeNSE survey presented increased asthma symptoms prevalence when compared with the International Study of Asthma and Allergies in Childhood (ISAAC).[5] There are just two publications providing prevalence data for adults, one conducted in 2002–2003 for 18 and 45 years old, and the other using the National Health Survey in 2013 for individuals aged 18 or older.[6,7] No studies to date have evaluated trends in asthma prevalence in the adult population.

Local studies, mainly derived from the ISAAC survey, reported that asthma prevalence in adolescents was associated with female gender, having pets, parents smoking behaviour, having rhinitis, and others factor.[8] However, studies describing asthma prevalence associated factors for adults are limited to two publications, restricted to the urban area of Pelotas city, South region of Brazil, conducted in 2000 and 2010.[7,9]

Correspondence to:
Felipe Moraes dos Santos. Estrada dos Bandeirantes, 8464, Jacarepaguá, CEP 22783-110, Rio de Janeiro, RJ, Brazil. Tel.: 55 21 2141-6411. E-mail: felipe.s.moraes@gsk.com
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In order to add to the understanding of the magnitude of asthma in Brazilian adults, and trends in asthma prevalence, this study aimed to:

- determine the trend of self-reported asthma diagnosed prevalence in Brazil from 2003 to 2013 in adults by gender, healthcare insurance, household location (urban and rural), and geographic region;
- describe the factors associated with prevalence of self-reported asthma diagnosed in Brazilian adults.

METHOD

This was an epidemiological cross-sectional study based on analysis of three different national household surveys: Pesquisa Nacional por Amostra de Domicílios (PNAD) 2003,[10] PNAD 2008[11] and Pesquisa Nacional de Saúde (PNS) 2013.[12] PNAD and PNS microdata are available in the public domain via Instituto Brasileiro de Geografia e Estatística (IBGE), at http://www.ibge.gov.br.

PNAD is a household survey conducted since 1967 in Brazil with annual application since 1971. Starting in 1998, it also included a health supplement collecting data of health characteristics of residents at five year intervals. The health supplement of PNAD became an independent survey in 2013, named as PNS. Both PNAD and PNS have a complex sample design. For PNAD, information about all residents in the sampled households was collected,[13] whereas for PNS only one resident aged 18 or older was selected by simple random sampling.[14] More information on the sampling methods for PNAD and PNS can be retrieved in the literature.[13,14]

In summary, PNAD 2003 and PNAD 2008 have a probabilistic sampling of households. In the first stage, the counties were selected; some were classified as autorepresentative, with 100% of selection probability, and the others as non-autorepresentative, with selection probability proportional to the resident population. In the second stage, the census tracts were selected with selection probability proportional to the number of existing households in the census tracts. In the third stage, the households were sampled with equal probability in each census tract. Information about all residents in the sampled households was collected.

The PNS 2013 sample, however, is a subsample of the integrated household surveys master sample from the IBGE. The primary sampling units (PSUs) were formed by area units which were selected to meet different surveys of the IBGE's integrated household surveys. The PSU was stratified using four different criteria:

- administrative: capital, rest of the metropolitan area or integrated economic development region, and rest of the federal unity;
- geographic: subdivision of capitals and other large counties in more strata;
- situation: urban or rural;
- statistic: homogeneous strata using information regarding total income of households and total permanent households, in order to improve the accuracy of estimates.

Finally, the PNS sample was then selected in three stages. The first stage of selection was a PSU subsample selection, with probability proportional to size (given by the number of permanent households in each unit using the 2010 demographic census as reference) in each stratum of the master sample. In the second stage, there was a selection of households by simple random sampling in each PSU selected in the first stage. At the last stage, one household adult (≥ 18-year-old) was selected by simple random sampling to answer the complete version of the interview. Basic information of all residents in the sampled households was also collected.

The individuals participating in the surveys answered questions through a face-to-face interview conducted by trained interviewers. For 2008 and 2013, the interviewers had a Personal Digital Assistance (PDA) to assist with the interview.

The three surveys are representative of the Brazilian population, its regions, federal unities, and for nine metropolitan regions, except PNAD 2003, whose samples did not include households located in the rural area of the North region, providing a unique data source to generate national and regional estimates of asthma prevalence.

In accordance to the study objectives, a trend analysis was conducted using the three aforementioned Brazilian cross-sectional surveys; factors associated with asthma diagnosed prevalence were investigated using the 2013 survey only. All participants aged between 18 and 45 years old that participated in these surveys were included in the study. We excluded from the analysis those aged > 45 years due to the increased prevalence of chronic obstructive pulmonary disease (COPD) in older adults and the misdiagnosis between asthma and COPD that could bias the asthma diagnosed prevalence results. The PNAD and PNS samples were composed as follow:

- 384,834 individuals from 133,255 households were surveyed in PNAD 2003;
- 391,868 individuals from 150,591 households were surveyed in PNAD 2008;
- 60,202 individuals from 64,348 households were surveyed in PNS 2013.

Asthma cases were identified using the following questions:

- "Has a physician or healthcare professional ever told you that you have bronchitis or asthma?" (PNAD 2003[10] and 2008);[11]
- "Has any physician ever given you asthma diagnosis (or asthmatic bronchitis)?" (PNS 2013).[12]

The question used in PNS 2013 was more specific to evaluate asthma diagnosed prevalence compared with the other two surveys, since it did not include bronchitis and the diagnosis was limited to diagnosis only made by a physician and not by any healthcare professional, as in 2003 and 2008.

The self-reported asthma diagnosed prevalence rates were calculated as the proportion of adults that reported "Yes" to either of these questions by the total of the adult population sample for each year (2003, 2008 and 2013). The mean annual change in prevalence rates was calculated as the geometric mean between 2003 and 2013 rates.

Initially, generalized estimating equations with an identity matrix were considered to analyse trends in asthma diagnosed prevalence. However, as very low correlations between time and all study variables ($\rho < 0.06$) were observed, a logistic general linear model was used. The trend analysis of asthma diagnosed prevalence was conducted overall and stratified by gender, insurance status, household location, and geographic regions. Wald tests (t) were applied to test the significance of observed trends in asthma prevalence.

Hierarchical logistic regression model was used to evaluate statistically significant factors associated with asthma diagnosed prevalence. The group of variables selected considered an adapted version of the conceptual model developed by Bernat et al.[15] for respiratory symptoms and the availability of variables in PNAD/PNS databases. Sex (male/female), age (18–25/26–35/36–45 years), race/ethnicity (white/black/other), household location (urban/rural) and region (North/Northeast/South/Southeast/MidWest) were selected as demographic variables (first block of variables). Education level (no instruction/primary level education or equivalent/high school degree or equivalent/college degree or equivalent) and healthcare insurance (yes/no) were selected as socio-economic factors (second block of variables). Behaviour aspects, health status, and household characteristics composed the third block of variables: house material (brickwork/others), type of stove fuel (cooking gas or piped gas or electricity/others), smoking status (current smoker/ex-smoker/never smoker), access to healthcare in the last two weeks (yes/no), body mass index (BMI) (underweight (< 18.5 kg/m^2), eutrophic (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), and obese (≥ 30 kg/m^2), depression (yes/no) and mental disease (yes/no).

A backward model selection method was executed, which included all variables in the first block, retaining all covariates with $p < 0.05$. Next, all variables in the second block were added and retained if $p < 0.05$; variables in the first block were not taken out from the model even if statistical significance were lost. This process was repeated for variables in the third block. *Odds ratio* (OR) with their respective 95% confidence interval (95%CI) were derived from the final adjusted regression model.

Data was analysed considering the sample weights and also the structural information of the PNAD/PNS sampling plan — that is, the sample weights were used to correct the variance measures according to the sample plan for each survey, which allows comparability between PNAD and PNS.

Statistical Package for the Social Sciences (SPSS) version 19 was used for the analysis.

This study presents analyses of databases of three national household surveys, whose data are not identified. In addition, no interaction with humans was done to collect additional data, using exclusively the data presented in the databases available by IBGE. Thus, it was not necessary to have approval of an ethics committee to conduct the research and elaboration of this manuscript.

RESULTS

The asthma diagnosed prevalence in Brazil was 3.6% in 2003, 3.7% in 2008, and 4.5% in 2013, representing a 2.3% average annual increase between 2003 and 2013 ($p < 0.001$). Higher asthma diagnosed prevalence was observed for women in all years than for men, although the annual change was higher in men (2.5%) compared to women (2.2%) (Figure 1).

Asthma diagnosed prevalence also increased in urban areas (2.2%) and in rural areas (2.7%), although the increase was not statistically significant for rural areas (Figure 2). Both those with (1.8%) and without (2.2%) healthcare insurance showed increase in the prevalence of asthma diagnosed (Figure 3).

Significant increases in asthma diagnosed prevalence were observed for the North, Northeast and Southeast geographic regions, but not for the South and Midwest (Figure 4).

In relation to factors associated with asthma diagnosed prevalence, depression was the most strongly associated factor (Table 1). Subsequently, living in urban areas, being from the South, Southeast, and North regions, female gender, and obesity were also associated with asthma diagnosed prevalence. Older age was inversely associated, though. Other variables including race/ethnicity, education level, type of fuel stove, house material, smoking status, and access to healthcare in the last two weeks were not included in the final model.

DISCUSSION

The results of our study showed increase of asthma diagnosed prevalence in Brazilian adults — overall and stratified by gender, healthcare insurance, household location (urban and rural), and geographic regions. The multivariable regression analysis showed positive association between asthma diagnosed prevalence and depression, living in urban areas, being from the Northeast, Southeast, and North regions, female gender and obesity.

A rising prevalence of asthma diagnosed had been described in adults from other countries.[16-19] However, in Brazil, before the present study, similar results were only described for children[20] and adolescents.[5]

A possible explanation for the increase in asthma diagnosed prevalence in Brazil is the general improvement in diagnosis in primary healthcare services

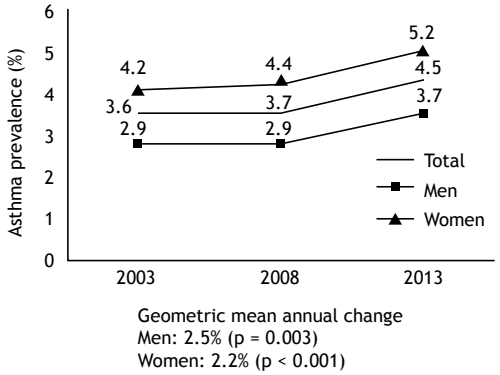

Figure 1. Trends in asthma prevalence according to gender in Brazilian adults, 2003–2013.

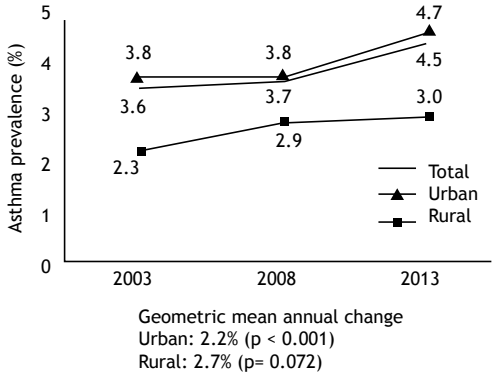

Figure 2. Trends in asthma prevalence according to household location in Brazilian adults, 2003–2013.

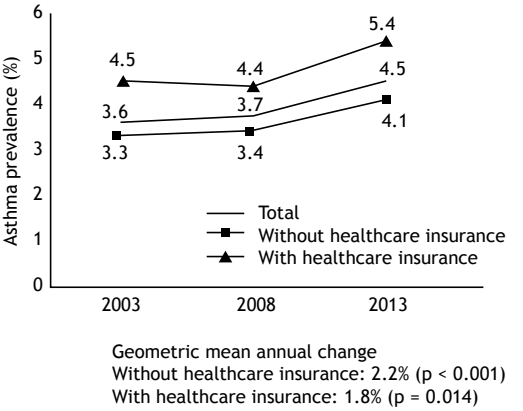

Figure 3. Trends in asthma prevalence according to healthcare insurance in Brazilian adults, 2003-2013.

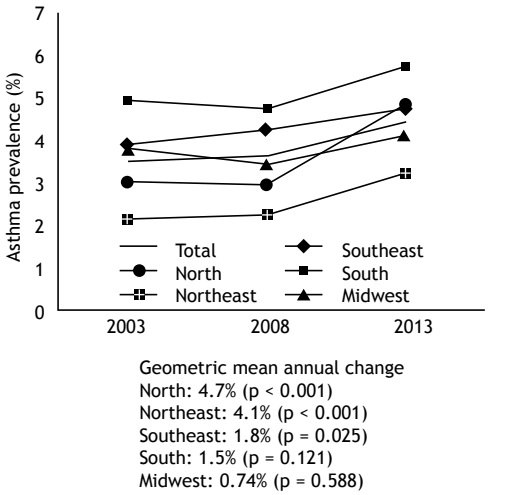

Figure 4. Asthma prevalence in adults by Brazilian regions, 2003–2013.

and family health teams over time.[21] The increase observed in access to health in recent years could explain the increase of asthma diagnosed prevalence, as more asthmatics would be receiving the disease diagnosis. Another hypothesis is the expansion in urbanization,[18,22] since evidence suggested that asthma and asthma-related symptoms occurred more frequently in urban than in rural areas. That association was also found in our study. Previous studies have suggested that this observation may be related to differences in environmental risk exposure, socioeconomic class, and healthcare access.[18]

Remarkably, the prevalence of asthma diagnosed in adults varied considerably between regions. Higher prevalence rates were observed in the South and Southeast regions, but the increase in prevalence was more marked in North and Northeast regions. However, there was no evidence that the improvement in healthcare access in North and Northeast was higher than in the other regions in recent years. In fact, Nunes et al.[23] evaluated the time trend on the demand and lack of access to public healthcare services in Brazil from 1998 to 2013, and the higher improvement on healthcare access was shown in Southeast and South regions. Additionally, the increase in urbanization rate from 2000 until 2010[24] in North, Northeast and South had been found similar according to national statistics reports, opposed to our study, in which the increase in asthma diagnosed prevalence was higher in North and Northeast region. Our findings reinforce the importance of other studies specifically investigating the geographic changes in asthma diagnosed prevalence in Brazil, preferably considering the disparities in each region. This is especially important, since the prevalence is influenced by mortality rates, which are different between the regions.[25]

The positive association between asthma among women was also described in other studies.[5,7,26] Possible explanation of this finding could be attributed to hormone, behavioral changes about the time of puberty and genetic polymorphisms, which evidence suggested to lead women to be more susceptible to asthma in adulthood.[5,26] However, as our study evaluated the diagnosed prevalence of asthma, the increased prevalence in women could be related to a higher use of healthcare system by women.[27]

Regarding the association between asthma and depression, we found an approximately 2.1 times higher chance of reporting to have asthma diagnosed

Table 1. Analysis of the factors associated with self-reported asthma in Brazilian adults aged 18–45 years old in Pesquisa Nacional de Saúde (PNS) 2013.

Characteristic	aOR	95%CI	
Gender			
Man	Ref.		
Woman	1.368	1.083	1.727
Age			
18-25y	Ref.		
26-35y	0.736	0.570	0.951
36-45y	0.678	0.517	0.889
Household location			
Urban	1.576	1.004	2.474
Rural	Ref.		
Region			
Northeast	Ref.		
Southeast	1.439	1.094	1.893
South	1.723	1.313	2.262
Midwest	1.093	0.832	1.436
North	1.596	1.235	2.062
Healthcare insurance			
No	Ref.		
Yes	1.231	0.979	1.547
BMI			
Underweight	1.547	0.711	3.367
Eutrophic	Ref.		
Overweight	1.294	1.000	1.675
Obese	1.493	1.137	1.959
Depression			
No	Ref.		
Yes	2.094	1.525	2.876

aOR: adjusted *odds ratio*; 95%CI: 95% confidence interval; Ref.: reference; BMI: body mass index.

in patients who have depression. However, it was not possible to evaluate the temporality between depression and asthma, which is an inherent limitation of the cross-sectional design. Nevertheless, a meta-analysis of prospective studies[28] pointed depression as a marker for incident adult-onset asthma. This finding highlights the importance of physician and healthcare providers to be aware of the potential for new onset asthma in their patients with depression.

Our results also found that obesity was associated with asthma. The relationship between obesity and asthma has been observed in other studies and is complex.[29-32] A recent cross-sectional study[33] showed that mean BMI was significantly increased in groups of asthmatic aged 18–60 years compared to a control group of healthy patients, and the result was statistically significant ($p < 0.001$). In some cases, asthma patients, due to their increasingly sedentary lifestyle and the use of corticosteroids, develop obesity later, causing disease worsening.[31,34] Other studies also found that obesity may affect asthma expression,[35] asthma exacerbations, decreasing asthma control, and steroid responsiveness. For example, a study conducted in Brazil in a moderate to severe asthma cohort of obese patients showed a gain in asthma control after dietary, pharmacologic and rehabilitation interventions.[36,37] In addition to that, studies suggested that programs to increase opportunities for physical activities and healthy food choice may decrease the prevalence of obesity and may directly affect the prevalence and severity of asthma.[34]

PNAD 2003, PNAD 2008, and PNS 2013 are nationally representative surveys designed to assess the health status of the Brazilian population, and their representativeness is a strength of our study. However, some limitations should be noted. The increase in asthma diagnosed prevalence observed in our study is probably underestimated due to two changes in the question adopted in PNS 2013 compared with the question in PNAD 2003 and PNAD 2008. The question used in PNS 2013 provided a more specific definition for asthma diagnosed prevalence assessment, since it did not include the term *bronchitis* and restricted to asthma physician diagnosis instead of including any healthcare professional as in the PNAD 2003 and 2008 surveys. Even with a more specific question in the last survey, we observed an increase in asthma prevalence throughout the years. Also, to mitigate the inclusion of other respiratory diseases, *e.g.*, COPD, we limited the analysis to patients aged 18–45 years since in this age group COPD prevalence is expected to be lower than in older patients.

Another limitation of our analysis was that the exclusion of the rural area in PNAD 2003 could overestimate the prevalence in North in 2003 since only urban areas were included. Despite this, the asthma prevalence observed in the North region for 2003 was lower than 2008 and 2013.

Potential reverse causality is another limitation of this study, since temporality could not be ascertained in cross-sectional designs. Changes in time to the exposures could also bias the associations observed. For example, individuals with asthma living in rural/urban areas or Brazilian regions could live in different areas in their childhood and only move out to another area in their adulthood. This is especially important because the majority (81.1%) of asthma patients identified in PNS 2013 were diagnosed in childhood (data not shown). In addition, it is important to reinforce that the increase in asthma diagnosed prevalence could not mean that more subjects have been affected by asthma, but could be a result of more individuals getting access to healthcare facilities and diagnosis. Other studies evaluating not only the self-reported diagnosis of asthma in adults are need to understand if the prevalence of self-reported asthma increase due to changes in access or other causes over the year.

Our study suggested that asthma diagnosed prevalence has been increasing in Brazil, which may result in a significant societal and healthcare burden due to asthma and its related complications. We also identified that trends in asthma diagnosed prevalence vary by geographic regions and were associated with factors including depression, obesity, female gender, and living in urban areas. These results may help to

gain insight into developing effective interventions for the early diagnosis of asthma and preventive strategies for the control of the disease in these groups. Due to the country size and differentiated geography, the creation of a disease management program, better healthcare professional capabilities in primary care, and an increase of asthma-awareness in society are possible initiatives.[25]

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ORIGINAL ARTICLE

Genetic and phenotypic traits of children and adolescents with cystic fibrosis in Southern Brazil

Katiana Murieli da Rosa[1,a], Eliandra da Silveira de Lima[2,b], Camila Correia Machado[3,c], Thaiane Rispoli[4,d], Victória d'Azevedo Silveira[3,e], Renata Ongaratto[2,f], Talitha Comaru[2,g], Leonardo Araújo Pinto[5,h]

1. Pediatric Residency Program, Pontifícia Universidade Católica do Rio Grande do Sul, Porto Alegre (RS) Brazil.
2. Post-Graduate Degree in Pediatrics and Children's Health, Pontifícia Universidade Católica do Rio Grande do Sul, Porto Alegre (RS) Brazil.
3. Medical School , Pontifícia Universidade Católica do Rio Grande do Sul, Porto Alegre (RS) Brazil.
4. Post-Graduate Degree in Cell and Molecular Biology, Universidade Federal do Rio Grande do Sul, Porto Alegre (RS) Brazil.
5. Centro Infantil, Instituto de Pesquisas Biomédicas, Pontifícia Universidade Católica do Rio Grande do Sul, Porto Alegre (RS) Brazil.

a. http://orcid.org/0000-0001-7120-3022
b. http://orcid.org/0000-0003-2350-9443
c. http://orcid.org/0000-0001-5138-3046
d. http://orcid.org/0000-0003-4421-8995
e. http://orcid.org/0000-0002-3264-0374
f. http://orcid.org/0000-0003-0217-3792
g. http://orcid.org/0000-0002-3574-6318
h. http://orcid.org/0000-0002-3906-5456

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ABSTRACT

Objectives: To characterize the main identified mutations on cystic fibrosis transmembrane conductance regulator (CFTR) in a group of children and adolescents at a cystic fibrosis center and its association with the clinical and laboratorial characteristics. **Method:** Descriptive cross-sectional study including patients with cystic fibrosis who had two alleles identified with CFTR mutation. Clinical, anthropometrical, laboratorial and pulmonary function (spirometry) data were collected from patients' records in charts and described with the results of the sample genotyping. **Results:** 42 patients with cystic fibrosis were included in the study. The most frequent mutation was F508del, covering 60 alleles (71.4%). The second most common mutation was G542X (six alleles, 7.1%), followed by N1303K and R1162X mutations (both with four alleles each). Three patients (7.14%) presented type III and IV mutations, and 22 patients (52.38%) presented homozygous mutation for F508del. Thirty three patients (78.6%) suffered of pancreatic insufficiency, 26.2% presented meconium ileus, and 16.7%, nutritional deficit. Of the patients in the study, 59.52% would be potential candidates for the use of CFTR-modulating drugs. **Conclusions:** The mutations of CFTR identified more frequently were F508del and G542X. These are type II and I mutations, respectively. Along with type III, they present a more severe cystic fibrosis phenotype. More than half of the sample (52.38%) presented homozygous mutation for F508del, that is, patients who could be treated with Lumacaftor/Ivacaftor. Approximately 7% of the patients (7.14%) presented type III and IV mutations, therefore becoming candidates for the treatment with Ivacaftor.

Keywords: Cystic fibrosis; Mutations; Genetics; Phenotype; Child.

INTRODUCTION

Cystic fibrosis (CF) is a genetic autosomal recessive disorder, more common in Euro-descendant populations, caused by variations in the gene sequence which codifies the cystic fibrosis transmembrane conductance regulator (CFTR) protein.[1] This gene is located in the long arm of chromosome 7 (*locus* 7q31), and is divided in 27 exons, generating a protein composed of 1,480 amino acids.

The estimated prevalence in several countries is of 1 for every 2,800-3,500 live births.[2] In Brazil, about 1 out of 10 thousand live births presents with the disorder.[3] Mutations in CFTR establish a multisystemic aspect for the disease, characterized by pulmonary, gastrointestinal and sweat gland disorders.[4]

Life expectancy in patients with CF has been improving, and, nowadays, more than half of them have reached adulthood.[2] Such an improvement, among other factors, is owed to the increment in innovative treatments and the advancement of interdisciplinary care addressed to the patient with CF.[5] Recently, specific therapies addressed to the CFTR channel, which are able to correct the basic flow, have been developed and approved for use in several countries. These targeted drugs aim at

Corresponding address:
Leonardo Araújo Pinto. Centro Infant, Instituto de Pesquisas Biomédicas, Pontifícia Universidade Católica do Rio Grande do Sul, Avenida Ipiranga, 6.690, 2º andar, Jardim Botânico, CEP 90610-000, Porto Alegre, RS, Brazil.
Tel.: 55 51 3320-3000. E-mail: leonardo.pinto@pucrs.br
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transforming CF therapy, making the prescription of drugs more accurate.[6]

Some protocols include genetic evaluation to complement neonatal screening and clinical diagnosis of CF, allowing the identification of patients who are eligible to mutation-specific therapies.[7] The variants identified in CFTR are divided in six classes of mutations, based on their functional effects.[1] The relationship between genotype and the clinical consequences of all variants, however, requires further understanding.

This study aimed at reporting the main CFTR mutations identified in a group of children and adolescents followed-up at a multidisciplinary center for CF treatment in the South of Brazil, and at associating such mutations to specific clinical and laboratory characteristics.

METHOD

This is a cross-sectional, descriptive study. Patients who were followed-up at a reference center in the South of Brazil were included. The subjects with suggestive clinical history who were included had their diagnosis confirmed by laboratory examinations (sweat electrolyte test), and had the identification of two mutations in the CFTR. Figure 1 presents the flow chart of the inclusion of individuals in the study.

The reference center has multidisciplinary staff composed of physicians, nutritionists, physical therapists and psychologists, who regularly follow-up more than 100 patients (children and adults). The patients are periodically followed-up with clinical examinations (assessment of nutritional status and body mass index – BMI), laboratory examinations (albumin, glucose, liver function and stool elastase, according to indication) and spirometry (forced expiratory volume in 1 second – FEV1). Besides, the analysis of sputum culture or oropharyngeal swab is routine, in order to identify the colonization by *Pseudomonas aeruginosa* (PA). The molecular analysis of CFTR is carried out for all patients with clinical diagnosis (based on the symptoms and chloride in the sweat > 60), but without a definitive genetic diagnosis, in the following order: F508del genotype, kits for the study of mutations and sequencing; the investigation is interrupted when two alleles are identified.

The genotyping of the F508del mutation is the most frequent one in the population with CF, so it was presented in patients with clinical diagnosis. Heterozygotic individuals, or the ones who did not present with this mutation, carried out a panel of mutations with commercial kits of 32 to 97 mutations. In cases in which the genetic change had not been identified in both alleles, the complete sequencing of

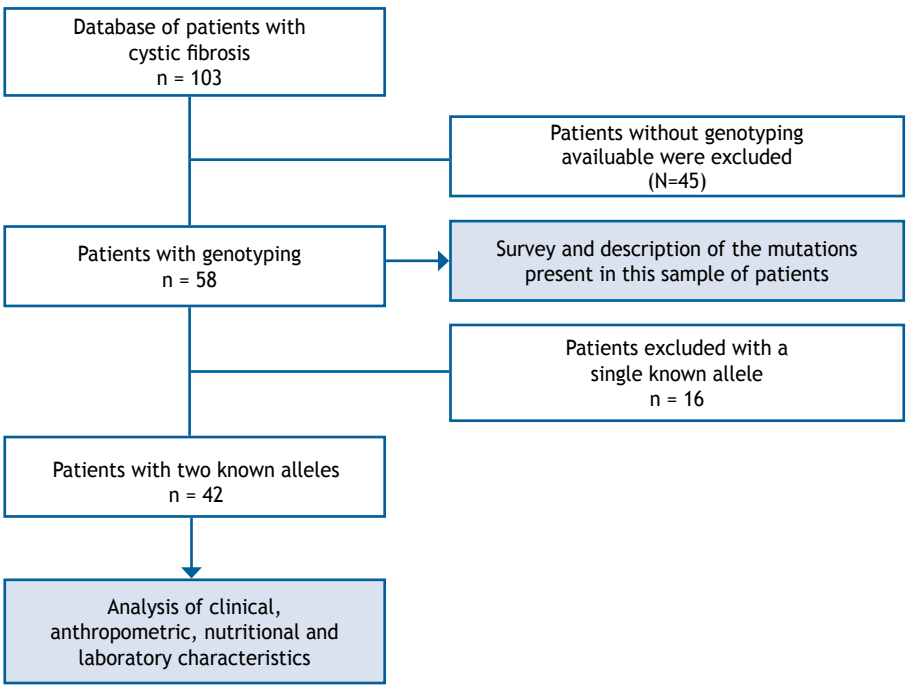

Figure 1. Flowchart of the inclusion of patients in the study.

the CFTR was performed. The analyses were conducted by different laboratories, according to the availability of the health system or private health insurance plan.

All of the collected data (age, immunoreactive trypsin dosage – IRT, chloride in the sweat, genotype, colonization, spirometry and clinical aspects) were obtained based on the information from the patients' charts. Simultaneously, a literature review was carried out regarding the phenotype described for the most frequent mutations found in our sample.

This study was approved by the Research Ethics Committee of Pontifícia Universidade Católica do Rio Grande do Sul (PUC-RS) and is registered by n. 49692115.7.0000.5336.

RESULTS

Of the 103 patients with CF followed-up at the multidisciplinary center, 58 (56.3%) have been genotyped. Of these, 42 (72.4%) were included in the study for presenting both known alleles of CFTR. Table 1 contains data referring to the sweat test and age of the patients, and Table 2 shows the clinical, nutritional, and pulmonary function characteristics according to the identification of the mutations in each one of the alleles. The most frequent mutation was class II, represented by F508del (p.Phe508del), present in 38 patients (90.48%), and comprehending 71.43% (60 alleles) of the total identified alleles. Among the patients who presented with alterations for p.Phe.508del, 57.89% were homozygous for the mutation. The second most common mutation was class I, with mutation G542X (p.Gly542X), present in six alleles (7.14%), followed by the mutations N1303K (p.Asn1303Lys) and R1162X (p.Arg1162X), also class I, in four alleles (4.76%) each.

Of the 42 patients analyzed, 11 (26.2%) had meconium ileus, in which the following mutations were identified: F508del, G542X and R1162X. All of these represented mutation F508del, and seven patients (63.6%) were homozygous for this mutation. Three patients (27.3%) pointed mutation G542X as the second allele, and one patient showed mutation R1162X.

Regarding nutritional status, seven patients (16.7%) had deficit, characterized by BMI being below the lower limit of normal before or after the condition was diagnosed, and in these cases the following mutations were identified: F508del, R1162X e R347X; all of them contained mutation F508del. Of these, four were homozygous for F508del, two presented R1162X, and one, mutation R347X.

The patients were colonized by different types of bacteria: *Staphylococcus aureus* (SA), *Pseudomonas aeruginosa* (PA), *Burkholderia cepacia* (BC), *Haemophilus influenzae* and *Methicillin-resistant Staphylococcus aureus* (MRSA). The most common bacteria was SA, present in 28 of the 42 analyzed patients. PA was observed in 14 patients, all of whom presented the allele F508del; nine (64.3%) were homozygous for this mutation. BC was present in four patients, who had mutations F508del (3/8 alleles), R1162X (2/8 alleles) and N1303K, 711+5G>A, 1078delT.

Table 1. Mutations of the *cystic fibrosis transmembrane conductance regulator* (CFTR), values of chloride in the sweat test (sweat Cl) and current age of patients with cystic fibrosis (CF).

Patients (n)	Allele 1	Mutation Class allele 1	Allele 2	Mutation Class allele 2	Sweat Cl (mEq/L)	Current Age (years)
22	F508del	II	F508del	II	86.51 ± 26.54	9.01 ± 7.20
5	F508del	II	G542X	I	84.66 ± 16.50	11.262 ± 7.3
3	F508del	II	N1303K	II	67.9 ± 0.00*	13.56 ± 3.66
3	F508del	II	R1162X	I	102 ± 19.09	6.66 ± 2.57
1	F508del	II	D1152H	IV	28	3.4
1	F508del	II	3272-26A>G	V	89	11.8
1	F508del	II	R347H	IV	88	2.11
1	F508del	II	G85E	II	76	9.7
1	F508del	II	R1066C	II	-	20
1	G542X	I	G551D	III	-	20.5
1	P205S	IV	3132delTG	I	92	13.1
1	N1303K	II	1078delT	I	79	7.6
1	711+5G>A	I	R1162X	I	-	17.1

Data presented in mean and standard deviation; *only 1/3 of the patients had these data collected.

Regarding pulmonary function, of the 22 patients who were homozygous for the change in class II p.Phe508del, 12 underwent spirometry, with FEV1 values ranging from 24 to 100% of the predicted value. The lowest values were observed in patients aged more than 18 years, showing reduction in pulmonary function with age. Of the three heterozygous patients for both mutations F508del/N1303K, one of them underwent spirometry with FEV1 value being 77%, and this patient was also colonized by SA. Of the five patients who were heterozygous for both mutations, three presented FEV1 ranging from 72 and 100%; they were all aged more than 15 years, one colonized by PA, and the other two, by SA. Of the two patients who were heterozygous for both mutations F508del/R1162X, FEV1 corresponded to 46 to 54%, in percentile, and these patients were aged between 5 and 10 years. In cases in which mutations only appeared once (F508del/3272-26A>G, F508del/G85E, F508del/R1066C, F508del/G551D, P2055/3132delTG, N1303K/1078delT, 711+5G>A/R1162X), FEV1 ranged from 43 to 104% of the predicted value.

DISCUSSION

Genotype-phenotype associations in CF, modifier genes, epigenetic factors, and environmental influence help to understand the broad spectrum of disease manifestations, which can range between single to multisystemic involvement, and between mild to severe disease.[8]

In this sample of patients with CF, F508deI was the most common mutation, affecting more than 50% of the homozygous individuals. This class II mutation, responsible for the incorrect processing of the CFTR protein, present in approximately 70% of the Caucasian population with CF[9], is considered as a severe mutation, showing the classic phenotype of the disease. Individuals who are homozygous for this mutation usually present with high sweat chloride test results (mean of 98 mEq/L), early signs of respiratory symptoms, reduced pulmonary function, pancreatic insufficiency and delayed growth[10]. It is the most known and studied mutation that causes CF.

Three other mutations were observed often in our sample: G542X, R1162X and N1303K. Mutation G542X (class I), characterized by a change that results in the absence of the CFTR protein, was the second most prevalent in this sample of patients (six alleles, 7.14%), and its frequency is estimated between 2.7 and 8.5% in Brazil.[11,12] This mutation is responsible for the high incidence of meconium ileus.[13] In our sample, most patients who presented with one allele of the mutation G542X also had pancreatic insufficiency (66.7%). A study that assessed clinical variables in 148 patients with this mutation verified that all of them had pancreatic insufficiency, which shows its severity.[14] Patients with mutation R1162X (class I) presented high sweat chloride test results (mean of 103 mEq/L), mild to moderate pulmonary disease and pancreatic insufficiency. Class II mutation N1303K is

Table 2. Genotyping and clinical characteristics of the patients with cystic fibrosis.

n	Allele 1	Allele 2	MI	PI	BMI (percentile)	PA	FEV1 (% of the prediction)
22	F508del	F508del	31.82% (7)	77.3% (17)	47.27 ± 33.29	40.9% (9)	71.91 ± 25.48
5	F508del	G542X	60% (3)	60% (3)	58.2 ± 27.14	20% (1)	89 ± 19.31
3	F508del	N1303K	0	100% (3)	53 ± 39.23	33.33% (1)	77 ± 0.00*
3	F508del	R1162X	33.33% (1)	66.66% (2)	70.66 ± 28.99	33.33% (1)	50 ± 5.65
1	F508del	D1152H	no	no	26	no	-
1	F508del	3272-26A>G	no	yes	75	yes	73
1	F508del	R347H	no	yes	91	no	-
1	F508del	G85E	no	yes	99	no	104
1	F508del	R1066C	no	yes	92	yes	78
1	G542X	G551D	no	yes	40	no	82
1	P205S	3132delTG	no	yes	21	no	43
1	N1303K	1078delT	no	yes	51	no	29
1	711+5G>A	R1162X	no	yes	79	no	103

MI: meconium ileus; PI: pancreatic insufficiency with laboratory confirmation; BMI: body mass index; PA: colonization by *Pseudomonas aeruginosa*; FEV1: Forced expiratory volume in 1 second; *only 1/3 of the patients had this data collected 1/3.
Data presented in mean and standard deviation or percentage and absolute number.

among the most common ones[10] for patients with CF, whose frequency is higher than 1%, and shows great variation between countries and ethnicities.[15-17] Considered as a severe mutation, its phenotype is related to severe pancreatic consequences, and may lead to pancreatic insufficiency and diabetes mellitus.[15,16,18] Regarding pulmonary phenotype, the severity of the disease indicates great variability between the different mutations.[15,18] In this sample, patients identified with mutation N1303K in one of the alleles had pancreatic insufficiency.

The other mutations that were found, being each of them presented in one patient, were revised next. Mutation 3132del TG (class I) is rare, and ongoing population studies[10] will help to determine its disease phenotype. Mutation 711+5G>A (class I) is more common among Hispanic Americans and in Northeast Italy. A study that included two patients with this mutation associated with F508del showed that these patients had chronic colonization by PA and SA, liver disease and pancreatitis more often.[19]

The class III G551D mutation, which is related to the obstruction of the chloride passage through the CFTR protein channel, is associated with pulmonary disease, pancreatic insufficiency, infection by PA and sweat test with increased values. Of the 2,915 patients analyzed, with mean age of 20 years, with this mutation and another mutation for CF, pulmonary function, expressed by spirometry predicted values (FEV1%), in children aged less than 10 years, ranged from 73 to 128%, and between 10 and 20 years of age, from 49 to 121%. Ninety percent (n = 2,480) of the patients presented with pancreatic insufficiency, and 59%, with colonization by PA.[10]

Of the patients with CF, 0.7% have at least one copy of the G85E mutation (class II).[20,21] Patients with genotype G85E/F508del are similar to the ones homozygous for F508del, when it comes to mean age of diagnosis, mean values of chloride in the sweat, weight/height ratio, spirometry (FEV1), and colonization by PA.[22]

Mutation P205S (class IV, characterized by changes in the conduction of chloride through the CFTR protein channel) is associated with a mild phenotype of the disease, being characterized by pancreatic sufficiency[10,23] and lack of gastrointestinal symptoms in most patients.[23] These present sweat chloride test with mean of 84 mEq/L. About 50% of the patients present colonization by PA or other pathogens,[10] but, in general, demonstrate good evolution.

Mutation 3272-26A>G (class V, result of the insufficient amount of the normal CFTR protein present in the cellular surface) is associated with the mild phenotype of the disease. Patients with one 3272-26A>G allele and another one in class I-III have less severe clinical manifestations (late diagnosis, better pulmonary function and lower incidence of PA) when compared to patients with two mutations of class I-III.[24,25]

Mutation R347H (class IV) is related with pancreatic insufficiency and infection by PA. Of the 161 patients analyzed, with mean age of 23 years who have this mutation and another one for CF, pulmonary function, expressed by the spirometry predictive value (FEV1%), in children aged less than 10 years ranged from 95 to 139%; among individuals aged from 10 to 20 years, from 78 to 131%, and for those aged more than 20 years, from 34 to 107%.[10]

Mutation R1066C (class II) represents 5% of mutations for CF in Portugal, and 1% in Spain, places where a study assessed 28 patients with this mutation. It is a severe mutation, similar to that observed in patients homozygous for F508del.[26]

The presence of mutation D1152H (class IV), combined with another mutation that causes CF, does not manifest the disease in all patients. Individuals who have this mutation associated with another one, which is known to cause CF, must undergo frequent check-up sessions, even if asymptomatic.[10] Most chloride values in the sweat test is 45 mEq/L, and most patients have sufficient pancreas. Mean age at the time of diagnosis is 33 years. According to clinical studies, when it is concomitant to other mutations, D1152H usually causes pulmonary symptoms; however, these are not severe and associated with prolonged survival rates.[27] Mutation 1078delT (class I) can be phenotypically manifested by pancreatic insufficiency,[10] and individuals who have it may present with cirrhosis and mild pulmonary disease.[10,28,29]

Currently, the development of drugs which improve CFTR function have shown promising results in the course of the disease, and may be able to contribute with the increasing life expectancy in patients with CF. Two systemic modulators of CFTR were assessed in clinical trials involving patients with CF, and approved by the American agency Food and Drug Administration (FDA).

Ivacaftor (VX-770) is a drug that potentializes the CFTR regulator, increasing the ionic function in the cellular surface, improving the obstruction of airways due to the retention of water and increasing mucus purification. This drug can be used for patients who have one of the 33 mutations of classes III and IV — among them, mutations G551D, R347H and 1152H, present in three patients (7.14%) of this study.[30-33]

Lumacaftor (VX-809) is a CFTR corrector, which increases the amount of protein located in the surface of the cell; its effect is added to Ivacaftor, whose effect potentializes the chloride channels.[33] A study published in 2014, which included patients of 24 centers of cystic fibrosis in Australia, Belgium, Germany, New Zealand and the United States, showed that the association of Ivacaftor/Lumacaftor does not have significant effects for patients heterozygous for the class II mutation (p.Phe508del); however, patients who are homozygous for the mutation presented a reduction in the frequency of exacerbations and improvement of FEV1.[34]

Recently, the FDA has approved the drug that combines Tezacaftor (VX-661) and Ivacaftor as therapy for patients with CF aged 12 years or more, who carry two copies of the F508del mutation, or for patients who are heterozygous for this mutation associated with a second mutation, which results in the residual function of CFTR. Tezacaftor helps the CFTR protein to dislocate to the cellular surface, and then Ivacaftor helps the ionic CFTR channel to stay open for longer periods of time. Results of two phase 3 studies showed that the treatment with this medication has significantly improved pulmonary function and other health measures in comparison to placebo, showing a favorable safety profile. In our sample of patients, 27 (64.2%) of them would potentially benefit from this drug.

In conclusion, the mutations more often identified were F508del and G542X, which have higher severity profiles. In our sample, 22 patients (52.38%) would be potential candidates for the use of the compound Lumacaftor-Ivacaftor, which has proven to be effective in subjects aged more than 6 years homozygous for the F508del mutation. Besides, three patients (7.14%) would be candidates for the use of Ivacaftor, drug that can be used in individuals who present with 33 class III or IV mutations, such as G551D, R347H and 1152H, which were present in these patients.

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ORIGINAL ARTICLE

Proportional weight loss in six months as a risk factor for mortality in stage IV non-small cell lung cancer

Guilherme Watte[1,2,5,a], Claudia Helena de Abreu Nunes[1,b], Luzielio Alves Sidney-Filho[3,c], Matheus Zanon[2,4,d], Stephan Philip Leonhardt Altmayer[4,5,e], Gabriel Sartori Pacini[4,f], Marcelo Barros[5,g], Ana Luiza Schneider Moreira[4,h], Rafael José Vargas Alves[1,i], Alice de Medeiros Zelmanowicz[4,j], Bashir Mnene Matata[2,k], Jose da Silva Moreira[1,l]

1. Programa de Pós-Graduação em Ciências Pneumológicas, Faculdade de Medicina, Universidade Federal do Rio Grande do Sul – UFRGS – Porto Alegre (RS) Brasil.
2. Department of Clinical Research and Radiology, Liverpool Heart and Chest Hospital NHS Foundation Trust, Liverpool, United Kingdom.
3. Faculdade de Medicina, Universidade Federal do Espírito Santo, Vitória (ES) Brasil.
4. Departamento de Medicina Clínica e Saúde Pública, Universidade Federal de Ciências da Saúde de Porto Alegre, Porto Alegre (RS) Brasil.
5. Programa de Pós-Graduação em Medicina e Ciências da Saúde, Faculdade de Medicina, Pontifícia Universidade Católica do Rio Grande do Sul, Porto Alegre (RS) Brasil.

a. http://orcid.org/0000-0002-6948-3982
b. http://orcid.org/0000-0002-1737-7440
c. http://orcid.org/0000-0001-9284-884X
d. http://orcid.org/0000-0001-7851-5125
e. http://orcid.org/0000-0001-9214-1916
f. http://orcid.org/0000-0002-4822-7082
g. http://orcid.org/0000-0002-4985-6374
h. http://orcid.org/0000-0001-6428-6421
i. http://orcid.org/0000-0002-6294-917X
j. http://orcid.org/0000-0001-9121-6365
k. http://orcid.org/0000-0003-2896-8059
l. http://orcid.org/0000-0003-1345-0476

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Study carried out at Hospital Santa Rita, Complexo Hospitalar Santa Casa de Porto Alegre, Porto Alegre (RS) Brasil.

ABSTRACT

Objective: To evaluate different weight loss (WL) cut-off points as prognostic markers of 3-month survival after diagnosis of stage IV non-small cell lung cancer (NSCLC). **Methods:** This was a prospective study involving 104 patients with metastatic (stage IV) NSCLC who were admitted to a cancer treatment center in southern Brazil between January of 2014 and November of 2016. We evaluated total WL and WL per month, as well as WL and WL per month in the 6 months preceding the diagnosis. The patients were followed for 3 months after diagnosis. A Cox proportional hazards regression model and Kaplan-Meier curves were used in order to evaluate 3-month survival. **Results:** The median WL in the 6 months preceding the diagnosis was 6% (interquartile range, 0.0-12.9%). Patients with WL ≥ 5% had a median survival of 78 days, compared with 85 days for those with WL < 5% ($p = 0.047$). Survival at 3 months was 72% for the patients with WL ≥ 5% ($p = 0.047$), 61% for those with WL ≥ 10% ($p < 0.001$), and 45% for those with WL ≥ 15% ($p < 0.001$). In the multivariate analysis, the hazard ratio for risk of death was 4.51 (95% CI: 1.32-15.39) for the patients with WL ≥ 5%, 6.34 (95% CI: 2.31-17.40) for those with WL ≥ 10%, and 14.17 (95% CI: 5.06-39.65) for those with WL ≥ 15%. **Conclusions:** WL in the 6 months preceding the diagnosis of NSCLC is a relevant prognostic factor and appears to be directly proportional to the rate of survival at 3 months.

Keywords: Weight loss; Carcinoma, non-small-cell lung; Prognosis.

INTRODUCTION

Weight loss (WL) is a common complaint of patients with lung cancer and a common reason for patient referral to a specialist.[1-3] Cancer cachexia, resulting from an imbalance between energy intake and consumption, is associated with a combination of poor caloric intake and increased resting energy expenditure, probably due to a cytokine-induced systemic inflammatory response.[4-7] Some studies have demonstrated that this increase in resting energy expenditure can also vary depending on the type of tumor.[8,9] Other factors that contribute to cancer cachexia include nausea, vomiting, constipation, diarrhea, pain, altered taste perception, and depression.[1]

Despite its potential benefit for the clinical evaluation of patients with non-small cell lung cancer (NSCLC), the definition of cachexia varies significantly across studies and many WL cut-off points have been proposed in the attempt to classify the syndrome in an objective manner.[10-14] A recent consensus suggested that WL be defined as any decrease greater than 5% in relation to the usual weight or greater than 2% in individuals with a body mass index < 20 kg/m^2.[13] However, setting up a single cut-off point to classify cachexia can underestimate its real prognostic value. Different levels of cachexia severity can have various effects on the prognosis of cancer and could serve as a valuable clinical indicator.

The objective of this study was to evaluate 3-month survival in a population of patients with stage IV NSCLC. We also tested the prognostic value of different WL cut-off points.

Correspondence to:
Gabriel Sartori Pacini. Rua Sarmento Leite, 245, CEP 90050-170, Porto Alegre, RS, Brasil.
Tel.: 55 51 99995-2543. Fax: 55 51 3214-8080. E-mail: gabrielsartorip@gmail.com
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METHODS

Study population

This prospective cohort study was conducted at Santa Rita Hospital, an oncology referral center and part of the Santa Casa de Misericórdia de Porto Alegre Hospital Complex, in the city of Porto Alegre, located in southern Brazil. We included consecutive patients newly diagnosed with metastatic (stage IV) NSCLC and admitted to Santa Rita Hospital between January of 2014 and November of 2016. Patients were treated at the discretion of the attending physician. All patients received a nutritional consultation at admission, regularly received high-calorie meals, and were instructed to rest before meals. However, they did not receive any type of nutritional supplementation as part of the palliative care or during chemotherapy. The follow-up period was ≤ 3 months after the diagnosis of cancer, as confirmed by reviews of medical records, hospital records, and phone calls. All diagnoses required clinical, radiological, and histological confirmation. Patients who had previously undergone antineoplastic treatment were excluded, as were those who were under 18 years of age. Survival and mortality rates were calculated from the time of the histological diagnosis until death or until the end of the third month of follow-up. Patient charts were reviewed, and tumor-node-metastasis variables were upgraded in accordance with the revised stage groupings established by the International Association for the Study of Lung Cancer.[15] Performance status was assessed with the Eastern Cooperative Oncology Group scale.[16] The study was approved by the local institutional review board. All participating patients gave written informed consent.

WL classification

Each patient was prospectively evaluated following the standards established in previous reports.[17] Definitions of WL-related variables were also based on those established in other studies[10]: total WL—the difference between weight at the time of diagnosis and usual weight; WL per month—total WL divided by the number of months of WL; and WL per month in 6 months—total difference between weight at the time of diagnosis and weight in the preceding 6 months. Patients were also subjectively evaluated in terms of their self-awareness of WL at the time of NSCLC diagnosis in relation to their usual weight. Different WL cut-off points (5%, 10%, and 15%) were tested in order to classify cachexia and to correlate the different degrees of cachexia with the survival rates.

Statistical analysis

Continuous variables are expressed as medians and interquartile range (IQR). Univariate analyses of survival were based on the Kaplan-Meier method.[18] Survival was calculated by Cox proportional hazards regression model in a multivariate analysis.[19] The Wald test was used in order to calculate significance for each factor. All parameters associated with mortality ($p < 0.1$) in the univariate analysis were included in a multivariate model, in which values of $p < 0.05$ were considered statistically significant. All tests were two-tailed, with the level of significance set at 0.05. All results were analyzed with the SPSS Statistics software package, version 20.0 (IBM Corporation, Armonk, NY, USA).

RESULTS

Patient characteristics are summarized in Table 1. The median age was 63 years (IQR, 52.5-69.0 years). Of a total of 104 patients evaluated, 63 (60.6%) were male. The most prevalent histological type of NSCLC was adenocarcinoma, which was seen in 57 (54.7%) of the patients, followed by squamous cell carcinoma, seen in 36 (34.6%), and mixed/undefined, seen in 11 (10.6%). The median Eastern Cooperative Oncology Group performance status was 2 (IQR, 1-3). Most (60.6%) of the patients underwent chemotherapy after diagnosis. Of the 104 patients, 44 (42.3%) underwent radiation therapy and 10 (9.6%) received supportive care exclusively. The 3-month mortality rate was 20.1% (95% CI: 12.9-29.1), 21 patients dying within the first 3 months after being diagnosed with cancer. The median WL in 6 months was 6% (IQR, 0.0-12.9%).

Patient outcomes, stratified by WL cut-off points, are summarized in Table 2. All cut-off points for WL in 6 months were statistically associated with a poorer prognosis as assessed by mean days of survival in 3 months. Patients with WL ≥ 5% had a mean survival of 78 days, compared with 85 days for those with WL < 5% ($p = 0.047$). When the WL cut-off points of ≥ 10% and ≥ 15% were applied, the mean survival decreased to 73 days and 66 days, respectively ($p < 0.001$ for both). However, there was no statistically significant difference between the patients who were aware of their WL and those who were not in terms of the 3-month survival rate ($p = 0.081$).

Kaplan-Meier survival curves for the first 3 months after diagnosis are shown in Figure 1. We observed a direct linear trend between the proportional WL and mortality. Event-free survival at 3 months was 88% for the patients with WL < 5%, compared with 72% for those with WL ≥ 5% ($p = 0.047$), 61% for those with WL ≥ 10% ($p < 0.001$), and 45% for those with WL ≥ 15% ($p < 0.001$).

The outcomes of the Cox proportional hazards regression model are summarized in Table 3. The univariate and multivariate (adjusted) analyses both demonstrated that the risk of death during the 3-month follow-up period was higher when the higher WL cut-off points were applied. The adjusted multivariate analysis showed that the risk of death increases exponentially as the cut-off points of WL increase, the hazard ratios for the 5%, 10%, and 15% cut-off points being 4.51 (95% CI: 1.32-15.39), 6.34 (95% CI: 2.31-17.40), and 14.17 (95% CI: 5.06-39.65), respectively.

DISCUSSION

In the present study, our aim was to determine the value of WL as a prognostic factor in patients with

Table 1. Baseline anthropometric and clinical characteristics of the study sample.

Characteristic	N = 104
Male gender, n (%)	63 (60.6)
Age (years), median (IQR)	63 (52.5 to 69.0)
Body weight at diagnosis (kg), median (IQR)	63 (53.0 to 70.7)
Patient awareness of WL, n (%)	67 (64.4)
Smoking status, n (%)	
Non-smoker	18 (17.3)
Former smoker	51 (49.0)
Current smoker	35 (33.7)
Total WL, median (IQR)	−6.0% (−12.9% to 0%)
WL per month, median (IQR)	−1.0% (−2.1% to 0%)
WL in 6 months, median (IQR)	−6.0% (−12.4% to 0%)
WL in 6 months ≥ 5%, n (%)	59 (56.7)
WL in 6 months ≥ 10%, n (%)	36 (34.6)
WL in 6 months ≥ 15%, n (%)	22 (21.2)
ECOG PS, median (IQR)	2 (1 to 3)
Tumor cell type, n (%)	
Adenocarcinoma	57 (54.8)
Squamous cell carcinoma	36 (34.6)
Mixed or undefined histology	11 (10.6)
Main treatment, n (%)	
Chemotherapy	63 (60.6)
Supportive care only	10 (9.6)
Radiation therapy	44 (42.3)

IQR: interquartile range; WL: weight loss; and ECOG-PS: Eastern Cooperative Oncology Group performance status.

Table 2. Kaplan-Meier survival analysis, by weight loss-related variable.

Variable	Mean survival Days (95% CI)	χ^2	p*
WL, self-awareness			
Yes	85 (80-89)	3.05	0.080
No	78 (73-84)		
Proportional WL in 6 months			
< 5%	85 (80-89)	3.94	0.047
≥ 5%	78 (72-84)		
< 10%	85 (81-89)	11.58	< 0.001
≥ 10%	73 (64-82)		
< 15%	85 (81-88)	23.78	< 0.001
≥ 15%	66 (53-78)		

WL: weight loss. *Log-rank test.

NSCLC, as well as whether that association differs among four WL cut-off points. We have shown that greater WL translates to shorter overall survival for patients with NSCLC. We found that, among patients with advanced NSCLC, the 3-month mortality rate was almost two times higher for those with WL ≥ 15% than for those with WL < 5%. Our results suggest that pre-treatment WL is an important clinical parameter with relevant prognostic value in patients with advanced NSCLC.

Our findings are consistent with those of previous studies that evaluated survival and WL in populations of lung cancer patients that were more heterogeneous, including patients in different stages of the disease.[1-3,10-12,20-22] The prognostic significance of WL in stage IV NSCLC could be attributed to the potential link to cachexia. Defined as a multifactorial syndrome of progressive loss of skeletal muscle mass that cannot be completely reversed, cachexia has a heterogeneous clinical presentation that varies according to tumor type, site, and stage.[13,21] Lung cancer is often accompanied by malnutrition, sarcopenia, and cachexia. Following the cancer-specific cachexia classifications, van der Meij et al.[23] demonstrated that, at the time of diagnosis, approximately 18% and 23% of stage III NSCLC patients had cachexia or were in a state of pre-cachexia, respectively. However, the exact basis of these prognostic differences remains unknown.

Several hypotheses have been proposed to explain the association between cachexia and poorer prognosis. Some authors have suggested that the survival advantage associated with obesity is due to the relatively large energy stores.[21-23] Conversely,

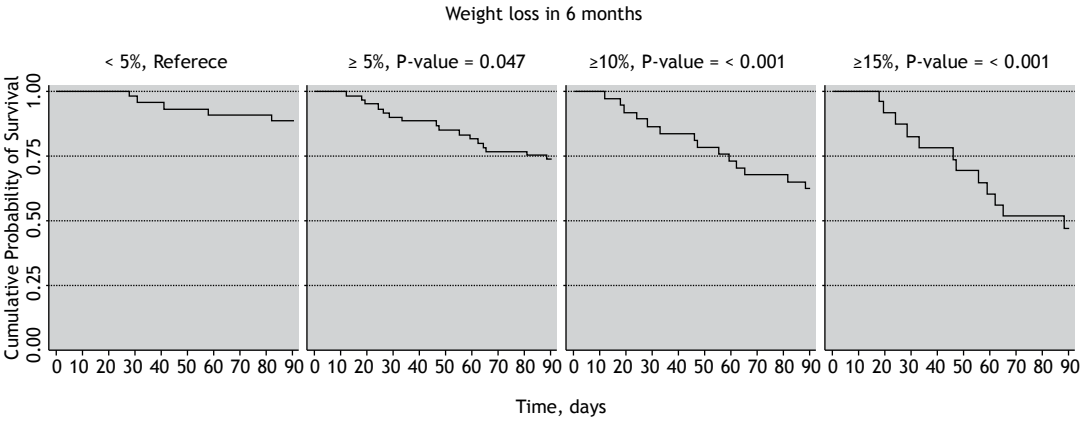

Figure 1. Kaplan-Meier curves of cumulative survival probability, by weight loss cut-off point.

Table 3. Crude and adjusted hazard ratios for weight-loss related prognostic factors.

Variable	Crude HR (95% CI)	p	Adjusted HR* (95% CI)	p
WL, self-awareness	2.54 (0.86-7.49)	0.089	3.59 (1.03-12.48)	0.044
WL in 6 months ≥ 5%	2.65 (0.97-7.21)	0.055	4.51 (1.32-15.39)	0.016
WL in 6 months ≥ 10%	4.45 (1.80-10.99)	0.001	6.34 (2.31-17.40)	< 0.001
WL in 6 months ≥ 15%	6.53 (2.76-15.44)	< 0.001	14.17 (5.06-39.65)	< 0.001

HR: hazard ratio; and WL: weight loss. *Cox proportional hazards regression model analysis, adjusted for gender, age, Eastern Cooperative Oncology Group performance status, and tumor cell type.

when the stores are depleted, the energy balance is negative.[21-23] Cachexia and a loss of skeletal muscle mass are associated with poor prognosis in patients with advanced NSCLC who are receiving chemotherapy.[10,24] Another hypothesis is that individuals with sarcopenia are susceptible to infections during hospitalization and residence in nursing homes, where such infections and premature termination of treatment are both possible contributors to shortened survival.[25] Accordingly, the well-recognized poor prognosis in advanced lung cancer masks some heterogeneity that could be partially explained by WL stratification and other, as yet unconfirmed, biological factors.

Cachexia is a multifactorial syndrome with a complex pathogenesis. Therefore, multimodal interventions should be used in order to prevent WL among patients with cachexia.[26] Frequent high-calorie meals and rest before meals are recommended. Currently, there is little evidence that nutritional supplementation is efficacious.[27] Physical activity has an anti-inflammatory effect and is effective in reducing muscle catabolism, increasing protein synthesis, and reversing protein degradation.[28] Pharmacological treatment can also be used to prevent cachexia. Corticosteroids and progesterone analogs have been shown to increase appetite, thus resulting in modest weight gain. However, such drugs do not improve survival or quality of life.[29]

Our study has some limitations, not the least of which is the small sample size. In addition, there are many confounding variables that could influence the analysis of 3-month survival of patients with advanced NSCLC. One such variable is the main treatment adopted, which, in our sample. was quite heterogeneous, therefore potentially affecting the prognosis. However, we believe that using a Cox proportional hazards regression model was an effective strategy to reduce the influence of those confounders, and the associations detected retained their significance even after the multivariate analyses. Studies including larger patient samples are needed in order to corroborate our findings. Further studies should also include biomarkers linked to aggressive behavior of lung cancer, such as circulating tumor cells and circulating cell-free nucleic acids, which could also affect survival rates, and patients who have such biomarkers might show different rates of WL.[30]

Although increased efforts have been directed toward the identification of biological markers as prognostic indicators of lung cancer, there are some important clinical indices that should be also considered more thoroughly. In conclusion, our results indicate that proportional WL is an important prognostic factor for 3-month survival after diagnosis in patients with stage IV NSCLC.

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REVIEW ARTICLE

Obesity hypoventilation syndrome: a current review

Rodolfo Augusto Bacelar de Athayde[1,2,a], José Ricardo Bandeira de Oliveira Filho[1,b], Geraldo Lorenzi Filho[2,c], Pedro Rodrigues Genta[2,d]

1. Serviço de Pneumologia, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.
2. Laboratório do Sono, Disciplina de Pneumologia, Instituto do Coração, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.

a. http://orcid.org/0000-0003-2482-3127
b. http://orcid.org/0000-0001-7976-2988
c. http://orcid.org/0000-0002-7011-7373
d. http://orcid.org/0000-0002-6764-165X

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ABSTRACT

Obesity hypoventilation syndrome (OHS) is defined as the presence of obesity (body mass index ≥ 30 kg/m²) and daytime arterial hypercapnia ($PaCO_2$ ≥ 45 mmHg) in the absence of other causes of hypoventilation. OHS is often overlooked and confused with other conditions associated with hypoventilation, particularly COPD. The recognition of OHS is important because of its high prevalence and the fact that, if left untreated, it is associated with high morbidity and mortality. In the present review, we address recent advances in the pathophysiology and management of OHS, the usefulness of determination of venous bicarbonate in screening for OHS, and diagnostic criteria for OHS that eliminate the need for polysomnography. In addition, we review advances in the treatment of OHS, including behavioral measures, and recent studies comparing the efficacy of continuous positive airway pressure with that of noninvasive ventilation.

Keywords: Obesity; Obesity hypoventilation syndrome; Noninvasive ventilation.

INTRODUCTION

Obesity hypoventilation syndrome (OHS) is defined as the presence of obesity and daytime hypoventilation ($PaCO_2$ ≥ 45 mmHg) in patients without central, pulmonary, neuromuscular, metabolic, or chest wall disease that explains the hypercapnia.[1] Therefore, OHS is a diagnosis of exclusion, and other causes of hypercapnia should be investigated. Obesity is the hallmark of the disease, there being a correlation between body mass index (BMI) and disease prevalence.[1-5] The identification of OHS is important because of the possibility of clinical exacerbation leading to respiratory failure and the high mortality rate in untreated patients. OHS is accompanied by obstructive sleep apnea (OSA) in more than 90% of cases, and both share the same major risk factor, that is, obesity; however, the presence of OSA is not necessary for the diagnosis of OHS. This explains why polysomnography is not necessary for this diagnosis. Signs of right heart failure can be present in OHS and are secondary to chronic hypoxemia and pulmonary hypertension, both of which can accompany the clinical picture. In addition, arterial hypertension and insulin resistance are more prevalent in patients with OHS than in obese individuals without OHS.[1-3]

Since OHS is associated with high morbidity and mortality,[5-7] the objective of the present study was to conduct a current review of the epidemiology, pathophysiology, and treatment of OHS.

HISTORY

Obesity-related sleepiness was described in 1889, even prior to the recognition of OSA.[8] Bickelmann et al. published a case report in 1956[3] and popularized the term "Pickwickian syndrome" (an eponym that has fallen into disuse) in a reference to the character Fat Boy Joe from Charles Dickens's "The Posthumous Papers of the Pickwick Club," who was always sleepy and hungry and would often fall asleep on the job any time during the day.[9] The patient reported by Bickelmann et al.[3] had daytime hypoventilation, chronic hypoxemia, polycythemia, and pulmonary hypertension, with evidence of *cor pulmonale*. Several studies have since characterized the epidemiology, clinical picture, and pathophysiology of OHS.[1,2,4,7] Since 1999, the American Academy of Sleep Medicine has defined the diagnostic criteria for OHS.[10,11]

EPIDEMIOLOGY

The prevalence of OHS is unknown because of the lack of population-based studies. The prevalence of OHS is estimated to be 10-20% in patients with OSA[7,12-16] and is estimated to be even higher in extremely obese patients.[7,14] Mokhlesi et al.[7] evaluated a population in the USA referred to a sleep medicine center for suspicion of OSA—180 patients were retrospectively selected, and 410 patients were prospectively selected. Of the patients diagnosed with OSA in the retrospective and prospective samples, 30% and 20%, respectively, met

Correspondence to:
Rodolfo Augusto Bacelar de Athayde. Avenida Dr. Enéas de Carvalho Aguiar, 44, 8° andar, Pinheiros, CEP 05403-000, São Paulo, SP, Brasil.
Tel.: 55 11 2661-5000. E-mail: rodolfobacelar1@hotmail.com
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the criteria for OHS, and those percentages increased with increasing BMI. Laaban et al.[14] retrospectively evaluated patients receiving home treatment for OSA in France. The sample included 1,114 adults, of whom approximately 10% met the diagnostic criteria for OHS, and a positive association was also found with increasing BMI.[14] Akashiba et al.[12] evaluated 611 patients in Japan referred to sleep medicine centers for OSA and diagnosed OHS in 9% of the patients. The patients with OHS were younger, were more obese, and had more severe OSA when compared with those without OHS. In a different approach, Kessler et al.[17] evaluated patients with OHS and detected OSA in most of the patients (90%); in addition, OHS patients with OSA were found to have poorer gas exchange and poorer pulmonary hemodynamics than did those without OSA.

Seeking to determine the prevalence and, consequently, the degree of underdiagnosis of OHS, Nowbar et al.[5] conducted a study involving obese patients admitted to internal medicine services for any cause. Of 29 obese inpatients with a BMI > 50 kg/m^2, 14 (48%) were diagnosed with OHS. In the same study, 31% of 150 obese inpatients did not have a previous diagnosis of OHS, although they met the criteria for this diagnosis.[5]

Because of the lack of studies on the prevalence of OHS in the general population, an exercise on epidemiological correlations has been repeatedly cited. Mokhlesi[18] infers that if approximately 3% of the general population in the USA are severely obese (BMI > 40 kg/m^2), half of those individuals would have OSA. Considering, therefore, the estimate that 10-20% of severely obese patients with OSA would have OHS, a conservative estimate indicates a prevalence of OHS of 0.15-0.30% in the general population in the USA (ranging approximately from 1:300 to 1:600 adults).[18]

MORBIDITY AND MORTALITY

Patients with OHS use more health care resources in the period prior to the diagnosis than do obese individuals without OHS or the general population.[19] Obesity *per se* leads to a greater likelihood of diseases such as systemic arterial hypertension, diabetes, dyslipidemia, and hypothyroidism. Comorbidities such as heart failure, coronary artery disease, and *cor pulmonale* are more common in patients with OHS, and the likelihood that such patients will require invasive mechanical ventilation or ICU admission is also increased.[5,20] In addition, pulmonary hypertension is more common (50% vs. 15%) and more severe in patients with OHS than in patients with OSA.[16,21,22]

Berg et al.[19] conducted a study involving 20 patients with OHS, who were matched to control subjects by age, gender, and zip code (to try to equate socioeconomic factors). A comparison with controls revealed that the most common morbidities in patients with OHS were cardiovascular diseases: congestive heart failure (OR = 9.0; 95% CI: 2.3-35.0); angina pectoris (OR = 9.0; 95% CI: 1.4-57.1); and *cor pulmonale* (OR = 9.0; 95% CI: 1.4-57.1). In a retrospective study conducted by Basoglu & Tasbakan, having a BMI > 40 kg/m^2 and obesity-related complications showed a strong association with an increased risk of premature death in hospitalized patients.[2] Nowbar et al.[5] reported that, at 18 months following hospital discharge, mortality was 23% in patients with obesity-related hypoventilation, which was almost twice as high as that among obese patients without hypoventilation.

CLINICAL PRESENTATION AND DIAGNOSIS

OHS occurs within a triad: obesity; daytime gas exchange abnormalities (hypercapnia); and the absence of other causes for the findings (Chart 1).[23] The American Academy of Sleep Medicine defines OHS as follows: the presence of awake daytime alveolar hypoventilation ($PaCO_2$ > 45 mmHg as measured at sea level) in patients with a BMI ≥ 30 kg/m^2 in the absence of other causes of hypoventilation.[11]

The vast majority of patients with OHS have symptoms of OSA, including snoring, nighttime choking, witnessed apneas, nonrestorative sleep, excessive daytime sleepiness, and fatigue. In contrast to patients with OSA alone, patients with OHS complain of dyspnea, are often hypoxemic, and can have signs of *cor*

Chart 1. Diagnosis of obesity hypoventilation syndrome.

Diagnostic criteria
• Presence of awake daytime alveolar hypoventilation ($PaCO_2$ > 45 mmHg as measured at sea level)
• BMI ≥ 30 kg/m^2
• Absence of other causes of hypoventilation
Diagnoses of exclusion
• COPD or other severe obstructive lung diseases
• Severe interstitial lung disease
• Mechanical respiratory limitation such as in severe chest wall disorders (such as kyphoscoliosis)
• Neuropathic and myopathic conditions (such as amyotrophic lateral sclerosis, Duchenne muscular dystrophy, myasthenia gravis, myositis, and diaphragmatic paralysis)
• Electrolyte disturbances (such as hypophosphatemia, hypomagnesemia, hypermagnesemia, hypokalemia, and hypocalcemia)
• Central causes (such as cerebrovascular disease and untreated hypothyroidism)
• Congenital alveolar hypoventilation syndrome (Ondine's syndrome)
• Use of sedatives, hypnotics, opiates, or alcohol

pulmonale. Plethoric obese patients with hypoxemia, an increased neck circumference, a decreased airway area, a prominent P2 (a loud second heart sound) on cardiac auscultation, and leg edema, as determined by physical examination, are at risk of having OHS.[1]

OHS is a diagnosis of exclusion. Other causes of hypoventilation, such as COPD; severe interstitial lung disease; mechanical respiratory limitation (for example, chest wall disorders such as kyphoscoliosis); myopathies (such as myasthenia gravis); neurological diseases; central causes (such as cerebrovascular disease and untreated hypothyroidism); and congenital causes (such as Ondine's syndrome; Chart 1), should be ruled out.

Patients suspected of having OHS can initially be screened by pulse oximetry and by determination of serum levels of venous bicarbonate. Borderline oximetry values are common findings. Patients with OHS undergoing arterial blood gas analysis rarely have PaO_2 values > 70 mmHg. Consequently, SpO_2 values < 93% on pulse oximetry would be suggestive of hypoventilation. However, higher values are not exclusionary, which explains why this is not a necessary criterion to establish the diagnosis, although it helps in screening. Nocturnal oximetry showing sustained hypoxemia and no associated apneas strengthens the suspicion for hypoventilation. A serum bicarbonate level ≥ 27 mEq/L had a sensitivity of 92% and a specificity of 50%, justifying its use in screening.[7,24,25] After such screening, arterial blood gas analysis is mandatory. For excluding other causes of hypoventilation (Chart 1), pulmonary function testing and assessment of respiratory muscle strength (MIP and MEP), chest X-ray, electrocardiography, and thyroid function testing should be performed. In addition, the use of drugs and medications, such as sedatives, hypnotics, opiates, and alcohol (alcohol abuse), should be investigated. Polysomnography is not necessary for the diagnosis of OHS.[11] However, since it has been observed that individuals with OHS have obstructive events, as well as lower saturation in REM sleep (Figure 1), polysomnography is requested with a view to treating comorbid sleep apnea and to justifying possible treatments.[6]

Unfortunately, despite being simple in concept, the diagnosis of OHS is delayed in most cases, occurring during acute events of respiratory failure or cardiac decompensation.[5,26]

PATHOPHYSIOLOGY

Several mechanisms are related to the pathogenesis of OHS (Figure 2), including an abnormal organic response of the respiratory system in certain obese individuals, as well as an inappropriate central response to hypercapnia and hypoxemia, in addition to neurohumoral changes. In comparison with other obese individuals, patients with OHS have decreased lung compliance, important reductions in functional residual capacity and chest wall compliance, and increased pulmonary resistance.[23,27]

Changes in pulmonary function

Obesity and the resulting greater chest wall thickness cause an excessive increase in the work of breathing. Breathing smaller volumes affects respiratory mechanics, reducing respiratory system compliance and increasing its resistance (which, in

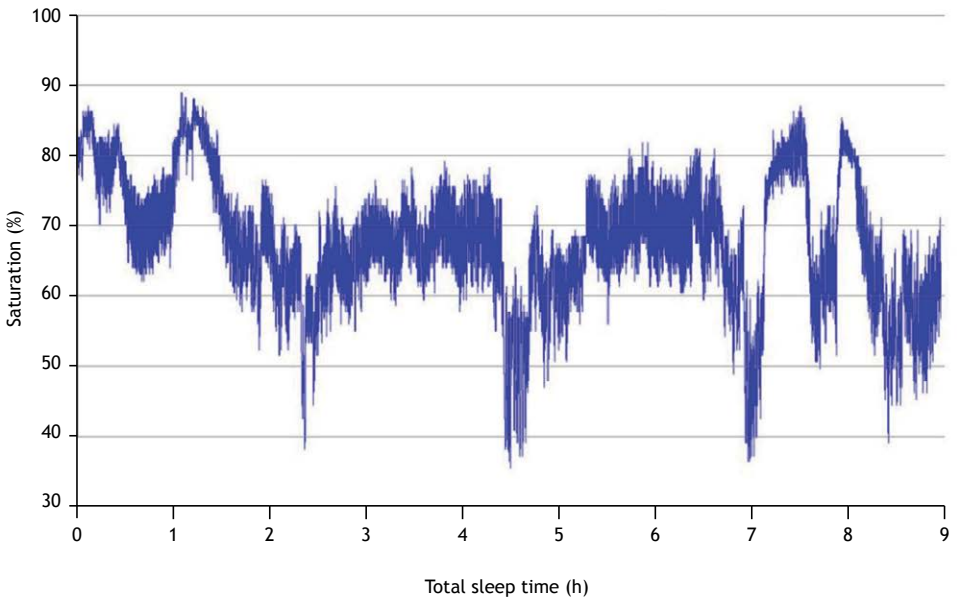

Figure 1. Female patient with a body mass index of 45 kg/m², $PaCO_2$ = 55.6 mmHg, obstructive sleep apnea, and obesity hypoventilation syndrome presenting with persistent hypoxemia and frequent desaturations, which were more pronounced at three time points (at between 2 and 3 h of sleep, at between 4 and 5 h of sleep, and at 7 h of sleep), suggestive of occurring during REM sleep.

individuals with OHS, is approximately 20% higher than in other obese individuals and 60% higher than in normal-weight individuals).[23,27] Gas exchange is also affected, worsening the ventilation/perfusion ratio. Individuals with OHS tend to have lower tidal volume and higher RR, which increases the dead space effect. Consequently, hypoxemia is a common finding, which leads to an equally common outcome of pulmonary hypertension secondary to hypoxia.[16,17] In addition, abdominal fat deposition compromises the diaphragm's influence on ventilation, compromising muscle function. Furthermore, there is thinning of the diaphragm and increased oxidative stress.[28]

Ventilatory control

Patients with OHS have arterial CO_2 retention. A reduction in CO_2 chemosensitivity was initially believed to be the possible cause of this finding, which was proven untrue.[29-31] Unlike what occurs in chronic hypoxia, low daytime and nighttime saturation can be the cause of decreased ventilatory response.[32] Chemosensitivity is progressively impaired by increased CO2 levels. Chronic hypercapnia is also believed to result from the inability to eliminate CO_2, which accumulates at night during apnea and hypopnea episodes, during the day (Figure 3).[30] A secondary mechanism that also impairs chemosensitivity is elevated serum and cerebrospinal fluid levels of bicarbonate.

Role of leptin

Leptin is a cytokine produced by adipocytes and may explain a causal relationship among obesity, ventilatory control, and chronic hypercapnia. Most data come from studies of mice. When obese, these animals, like humans, develop daytime hypercapnia and reduced ventilatory response to CO_2. In mice, there is deficiency of leptin. Leptin replacement reverses hypoventilation in mice with leptin deficiency.[33]

Unlike in the animal model, there is no deficiency but rather an increase in leptin levels in obese humans. Leptin is believed to initially have a protective effect, stimulating the ventilatory response. The persistence

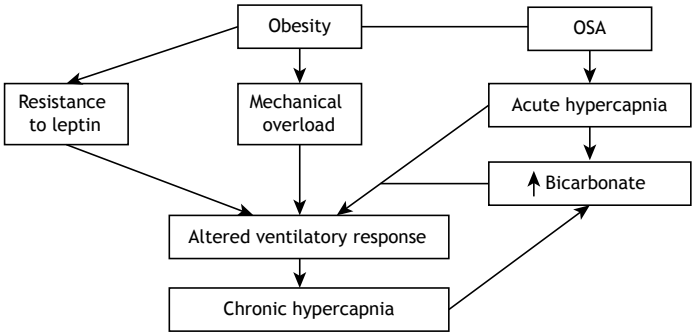

Figure 2. Pathophysiology of obesity hypoventilation syndrome. OSA: obstructive sleep apnea. Adapted from Mokhlesi.[18]

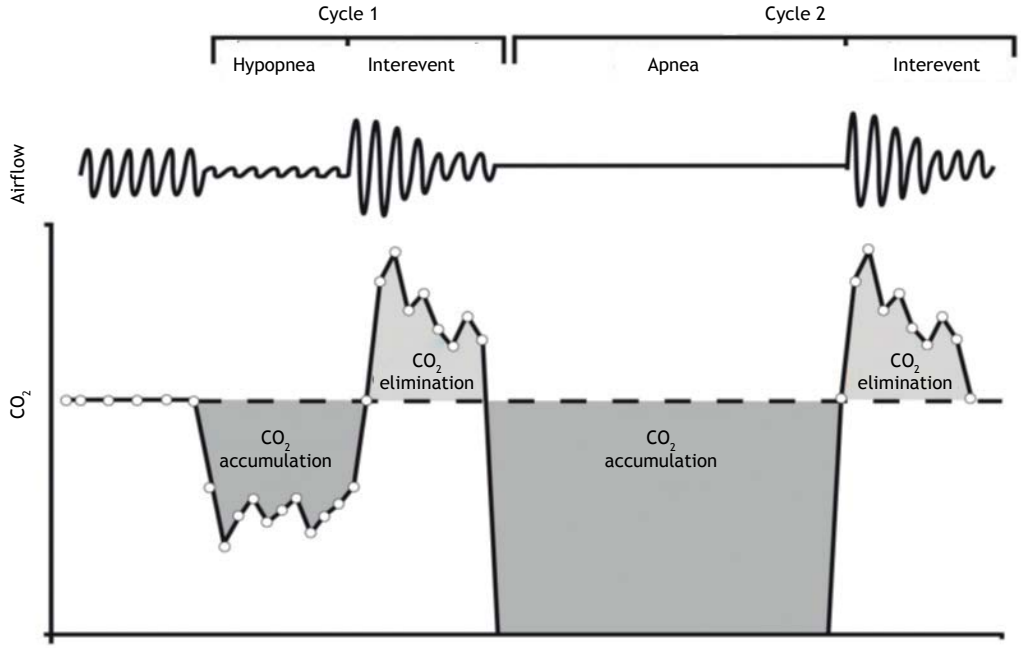

Figure 3. Influence of obstructive sleep events on hypercapnia. Adapted from Berger et al.[31]

of obesity would lead to leptin resistance (which is conceptually similar to insulin resistance), and thus, a consequent decrease in the ventilatory response to CO_2.[25,32,34]

GENERAL TREATMENT MEASURES

Weight loss

Significant weight loss promotes improvement in ventilatory parameters.[3,32] Bariatric surgery is the intervention resulting in the best outcome.[35] However, low-calorie diets may have satisfactory results. Bariatric surgery is the treatment of choice in the management of morbidly obese patients, but not every patient is a candidate for the procedure, given that the number of comorbidities that increase surgical risk is high. In fact, in some cases, the procedure will be contraindicated because of such comorbidities.

Although treatment improves ventilatory variables, it does not always resolve the problem. In a study conducted by Dixon et al.[36] involving 60 obese patients with a diagnosis of OSA who were divided into two groups—those undergoing calorie restriction and those undergoing bariatric surgery—weight loss was greater in the bariatric surgery group, but there was no statistically significant difference regarding the apnea-hypopnea index. Greenburg et al.[37] published a meta-analysis that included 12 studies involving 342 patients who underwent polysomnography before bariatric surgery and after maximal weight loss. There was a 71% reduction in the apnea-hypopnea index, from 55 events/h (95% IC: 49-60 events/h) to 16 events/h (95% CI: 13-19 events/h). It is known that 7% to 20% of such patients are unable to maintain a BMI loss of at least 20% after 5-10 years,[38,39] which requires continued surveillance even after the procedure. Only one study evaluated the impact of bariatric surgery in patients with OHS. Sugerman et al.[40] evaluated 61 patients with OHS undergoing bariatric surgery. In 31 patients, there was improvement in PaO_2 (from 53 mmHg to 73 mmHg) and in $PaCO_2$ (from 53 mmHg to 44 mmHg) at 1 year. At 5 years, only 12 patients underwent arterial blood gas analysis, which revealed marked worsening (mean PaO_2 = 68 mmHg and mean $PaCO_2$ = 47 mmHg); in addition, the mean BMI was found to have increased (from 38 kg/m^2 to 40 kg/m^2), having been high since the first postoperative year.

Oxygen therapy alone

Oxygen therapy alone is not appropriate, even in acute events, because it increases nocturnal CO_2 retention (Haldane effect or "dead space" ventilation effect), which worsens sleep quality, and is considered a common error in the management of patients with OHS (this subject will be discussed below).[41]

Phlebotomy

There are no studies that examine the indications for phlebotomy in patients with OHS. Our group uses the indications for phlebotomy for heart disease patients and lung disease patients (hematocrit > 56% or symptoms of hyperviscosity).[42]

Tracheostomy

Tracheostomy was the first treatment instituted for OHS; however, today, tracheostomy is reserved only for patients who are refractory to noninvasive ventilation (NIV), because of risk and complications inherent in the procedure and in obese patients.[34]

Pharmacotherapy

Several medications (such as medroxyprogesterone and acetazolamide) have been tried to increase ventilatory response, without success, and are not recommended for the treatment of OHS.[25,32,34,43]

Positive pressure

Continuous positive airway pressure (CPAP) is the treatment of choice for stable OHS. CPAP improves alveolar ventilation by decreasing upper airway resistance, relieving the respiratory muscle load, and/or increasing central respiratory activity.[6,19,24,41,44-52] Patients with OHS should be initially treated with CPAP if they are clinically stable and if $PaCO_2$ is not severely altered (< 55 mmHg). If either of these conditions is not met, NIV should be used. In OHS patients without OSA, NIV should also be used. CPAP therapy is typically administered via a nasal mask. Some studies have shown that oronasal masks are less efficient and are associated with poorer adherence and greater side effects than are nasal masks in patients with OSA.[53] Therefore, for long-term use, nasal masks are recommended. In critically ill patients with respiratory failure, oronasal masks are preferred.

In a randomized multicenter study involving 221 patients conducted in Spain, NIV, CPAP, and lifestyle change were compared. NIV and CPAP were more effective than lifestyle change in improving clinical symptoms and polysomnographic parameters. However, there were no significant differences between NIV and CPAP, although NIV resulted in slightly improved pulmonary function values.[54] Howard et al.[55] conducted a double-blind, randomized trial of CPAP versus NIV in 57 patients with OHS admitted to either the emergency room or an outpatient clinic. There were no differences in treatment failure between CPAP and NIV, and there were similarities in ventilatory parameters, quality of life, and cardiovascular risk markers at 3 months, regardless of OHS severity. Although there was a trend toward early improvement in the group treated with NIV, use of CPAP was safe even in patients who were more severely ill, provided that it occurred in the emergency room after stabilization with NIV and that patients were monitored for treatment failure ($PaCO_2$ > 60 mmHg at 3 months of treatment or a 10-mmHg increase in $PaCO_2$ at any given time point).[55] However, further long-term comparative studies are needed to compare NIV versus CPAP in terms of variables such as length of hospital stay, cardiovascular events, and

mortality. In patients with refractory hypoventilation ($PaCO_2$ > 45 mmHg despite proven adherence to treatment and use of PAP determined by titration and despite the elimination of obstructive events) or with persistent desaturation (SpO_2 < 90% despite proven adherence to treatment and use of PAP determined by titration and despite the elimination of obstructive events), NIV should be used.[43,46,47,49,52,56,57]

Treatment objectives

The objective of therapy in OHS is to reverse the major abnormalities that give rise to the disease, that is, to normalize ventilation during sleep and to reduce body weight. The therapeutic goals for patients with OHS include normalization of $PaCO_2$ during wakefulness and sleep; prevention of desaturations during sleep and wakefulness; control of erythrocytosis, pulmonary hypertension, and *cor pulmonale*; and relief of hypersomnia. Poor adherence to PAP is associated with incomplete clinical improvement. Adherence can be assessed by reviewing the memory card of NIV and CPAP devices.

Management in the emergency room: common errors in caring for patients with OHS

Overuse of supplemental oxygen

Hypercapnia can be aggravated by hyperoxia via several mechanisms: an increase in FiO_2 can result in a decrease in minute volume and, consequently, a decrease in tidal volume due to the activity of peripheral chemoreceptors; oxygenation of hypoxic areas causes vasodilation that changes blood flow to previously poorly ventilated areas, causing an increase in dead space; and the Haldane effect causes a reduction in hemoglobin affinity for CO_2 and decreases correction of hypoxia, causing increased release of CO_2 in plasma, which increases hypercapnia.[29,41,58] Therefore, oxygen therapy alone is best indicated in hemodynamically stable patients with no excessive work of breathing (RR ≤ 30 breaths/min without use of accessory muscles or with other signs of risk of ventilatory failure), under clinical surveillance, with an SpO_2 target of 89-92%.[41]

Overuse of loop diuretics

Patients with OHS are commonly affected by conditions that cause edema due to *cor pulmonale*. Since decompensation of *cor pulmonale* can be the cause for seeking medical care, a loop diuretic (furosemide) usually is used for the initial treatment of these patients in order to achieve a euvolemic state. However, overuse of diuretics can lead to acute prerenal renal failure. Contraction alkalosis secondary to the use of diuretics can worsen CO_2 retention. In addition, overuse of furosemide can cause hypokalemia. Cautious use of diuretics is indicated in OHS, at the lowest dose possible to achieve a favorable clinical response and minimize the electrolytic and acid-metabolic impact.[41] The use of spironolactone for the prevention of hypokalemia is plausible.

Overuse of psychotropic drugs

The use of sedative/hypnotic drugs not only increases airway collapsibility but also decreases ventilatory response, which is harmful to patients with OHS.

Diagnostic confusion with COPD

Patients with chronic CO_2 retention, such as patients with OHS, are commonly diagnosed with COPD, despite the absence of documented obstructive ventilatory disorders. A retrospective study by Marik & Desai[59] showed that, of the morbidly obese patients admitted to the ICU for respiratory failure secondary to OHS, 75% had been erroneously treated for COPD and 86% had been treated for congestive heart failure (Chart 2).

PERIOPERATIVE PERIOD IN PATIENTS WITH OHS

Patients with OHS commonly have a consultation with a pulmonologist in the preoperative period. In addition to comorbidity care and the required cardiovascular evaluation in obese patients or in those who are known to have or are highly suspected of having OSA, specific perioperative care is required for these patients whatever the procedure. In addition to the already suggested screening with pulse oximetry and determination of serum bicarbonate, other measures are required. If screening is positive and OHS is confirmed by arterial blood gas analysis, treatment should be started immediately, even a few days or weeks after the procedure; there is significant evidence of improved gas exchange and improved ventilatory control, either with one-level positive pressure or with two-level positive pressure.[60]

Obesity is a risk factor for difficult mask ventilation.[61] A retrospective study by Rose & Cohen, involving 18,500 patients, showed that obesity is also an independent risk factor for difficult intubation.[62] ≥Kheterpal et al.[63] evaluated 22,660 procedures and identified five risk factors (limited mandibular protrusion, increased neck circumference, OSA, snoring alone, and BMI ≥ 30 kg/m^2) as independent predictors of difficult mask ventilation and difficult intubation during anesthesia induction. This suggests that patients with OHS are among those at highest risk for airway complications.[64] During anesthesia induction, patients with OHS should be placed in the ramp position with elevation of the torso and head (preferably at a 25° tilt). This has been shown to improve ventilation and the glottic view,[65] as well as oxygenation.[66]

Patients with OHS are more sensitive to the respiratory depressant effects of anesthetic agents and opioids because they are prone to airway collapse and

Chart 2. Common errors in the emergency care of patients with obesity hypoventilation syndrome.

- Overuse of supplemental oxygen
- Overuse of loop diuretics
- Overuse of psychotropic drugs
- Diagnostic confusion with COPD

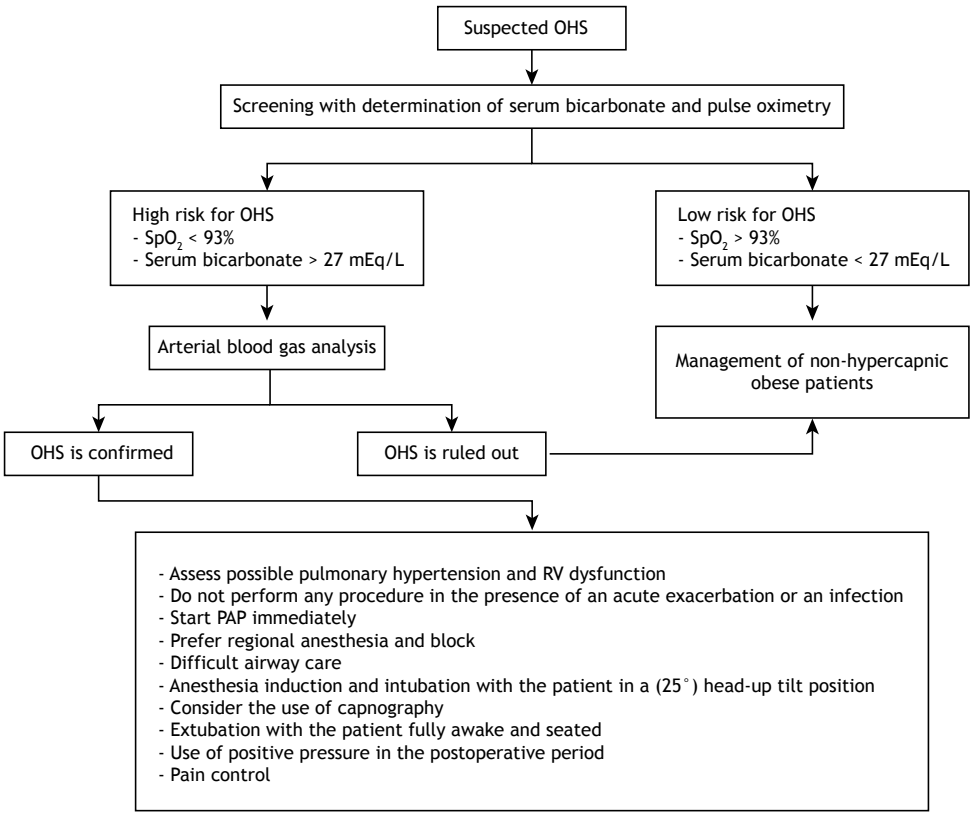

Figure 4. Suggested algorithm for the screening and perioperative management of patients with suspected or confirmed obesity hypoventilation syndrome (OHS). PAP: positive airway pressure; and RV: right ventricle. Adapted from Chau et al.[64]

inappropriate physiological response to hypercapnia and hypoxemia. Regional block should be chosen, when possible. In addition, during the procedure if possible, patients with OHS should be monitored with a capnograph. At the end of the procedure, it is recommended that patients be placed in the ramp position or in the lateral decubitus position for improved oxygenation and maintenance of the airways, and tracheal extubation should be performed only after the patient is fully conscious.[64]

With regard to postoperative care, the use of CPAP for 24-48 h after extubation can reduce the risk of postoperative complications and extubation failure in severely obese patients admitted to the ICU (an absolute risk reduction of 16%), with a reduction in mortality in patients with hypercapnia.[67,68] In addition, pain control has an impact on ventilatory status. Therefore, optimal analgesia is also required.

Figure 4 outlines a suggested algorithm for the screening and perioperative management of patients with suspected or confirmed OHS.

FINAL CONSIDERATIONS

OHS is still a poorly recognized entity in Brazil. Delayed diagnosis of OHS is associated with an increase in morbidity, mortality, and costs of care of patients who are more severely ill. However, breaking free from myths and paradigms regarding diagnosis, such as that related to polysomnography, which is unnecessary, the possibility of screening for OHS with determination of venous bicarbonate, and the possibility of treatment with CPAP enable the diagnosis and treatment of OHS in a larger number of patients.

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Pulmonary involvement in Crohn's disease

Rodolfo Augusto Bacelar de Athayde[1,a], Felipe Marques da Costa[1,b], Ellen Caroline Toledo do Nascimento[2,c], Roberta Karla Barbosa de Sales[1,d], Andre Nathan Costa[1,e]

TO THE EDITOR:

A 34-year-old White nonsmoking male was admitted to hospital with a history of cough and sputum production. The patient had severe intestinal Crohn's disease (CD), which had been diagnosed by colonic biopsy. He presented with gastrointestinal symptoms such as diarrhea, blood in stool, and abdominal pain refractory to 5-aminosalicylic acid therapy, and had been under treatment with infliximab since 2015. His respiratory symptoms (i.e., cough and sputum production) began 2 years later and were treated with amoxicillin/clavulanate for 10 days, without improvement. Two weeks later, the patient developed chest pain, fever, and dyspnea, with no gastrointestinal evidence of a flare-up of CD. At that time, his heart rate was 120 bpm, his SpO_2 was 96%, and his C-reactive protein levels were elevated (190 mg/dL). In addition, he had crackles in the left hemithorax. Blood, sputum, and urine cultures were negative. A CT scan of the chest showed consolidation with air bronchogram and perilesional ground-glass opacities in the left lower lobe (Figure 1A), and a CT scan of the abdomen was suggestive of splenic abscess. Fine-needle aspiration of the spleen was performed, and abscess fluid culture was positive for *Proteus mirabilis*, the patient being started on treatment with ceftriaxone and metronidazole. Bronchoscopy with BAL was performed, and polymerase chain reaction for tuberculosis, direct examination of BAL fluid, and BAL fluid culture were all negative. Given that the splenic fluid collection persisted, drainage was performed, and oral corticosteroid therapy (prednisone at 1 mg/kg per day) was prescribed.Twenty-one days later, the patient had made a full recovery and was therefore discharged to outpatient follow-up. A follow-up CT scan of the chest performed 1 month later showed resolution of the left lower lobe consolidation. The symptoms recurred 3 months later, during corticosteroid reduction. A CT scan of the chest showed splenic abscess and left lower lobe consolidation (Figure 1A). An open lung biopsy revealed fibroblastic plugs within bronchioles, alveolar ducts, and adjacent alveolar spaces. The alveolar septa were thickened by a prominent chronic inflammatory infiltrate associated with type II pneumocyte hyperplasia. In addition to the aforementioned histological changes, there were non-necrotizing granulomas (although not in a lymphatic distribution), consisting of aggregates of epithelioid histiocytes (Figures 1C and 1D). Special stains for microorganisms were all negative. The final diagnosis was aseptic non-necrotizing chronic granulomatous inflammation associated with organizing pneumonia. The reintroduction of corticosteroid therapy and immunomodulation with azathioprine and infliximab resulted in clinical and radiological resolution of the lung disease (Figure 1B). The splenic fluid collection resolved after 16 weeks of treatment with ciprofloxacin.

Inflammatory bowel disease (IBD) is associated with a variety of extraintestinal manifestations.[1-3] Since the original report by Kraft et al.[4] published in 1976 and describing six patients with IBD and unexplained chronic purulent sputum, pulmonary involvement in IBD, although rare, has increasingly been reported. Pulmonary complications include airway disease, interstitial lung diseases—particularly bronchiolitis obliterans organizing pneumonia, nonspecific interstitial pneumonia, and sarcoidosis—pulmonary vasculitis, necrotic pulmonary nodules, and serositis.[1,3,5-10] Other pulmonary manifestations include toxicity induced by azathioprine, sulfasalazine, mesalazine, and anti-TNF agents, as well as infections (including bacterial, mycobacterial, and fungal infections).[3] With regard to noninfectious pulmonary manifestations of IBD, organizing pneumonia is the most common and is usually associated with aseptic non-necrotizing chronic granulomatous inflammation.[1-3,5,8-10] In contrast, tuberculosis and nontuberculous mycobacterial infection have been associated with granulomatous bronchiolitis.[5]

In the case reported here, the final diagnosis was organizing pneumonia with granulomatous inflammation.[11-14] Organizing pneumonia is a histological pattern characterized by granulation tissue within alveolar ducts and alveoli, together with chronic inflammation of the adjacent lung parenchyma. Similar lesions are observed in the respiratory bronchioles. The distinction between cryptogenic and secondary organizing pneumonia is important because the treatment of the latter includes the treatment of organizing pneumonia itself and the treatment of the underlying disease or causative agent of organizing pneumonia. Common causes of secondary organizing pneumonia include inhalation injury, infections, drug hypersensitivity, and autoimmune diseases.[11-14] In the case reported here, organizing pneumonia was found in association with a granuloma. An epithelioid granuloma, detected on microscopic examination of a biopsy specimen, has been reported to be a reliable marker of CD.[14] Necrotizing (or caseating) and non-necrotizing (or noncaseating) lung granulomas are common and can occur either alone or in combination. The terms

1. Divisão de Pneumologia, Instituto do Coração – InCor – Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.
2. Divisão de Patologia, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.
a. http://orcid.org/0000-0003-2482-3127; b. http://orcid.org/0000-0001-5118-2033; c. http://orcid.org/0000-0002-2981-1419;
d. http://orcid.org/0000-0003-3074-445X; e. http://orcid.org/0000-0002-8025-6940

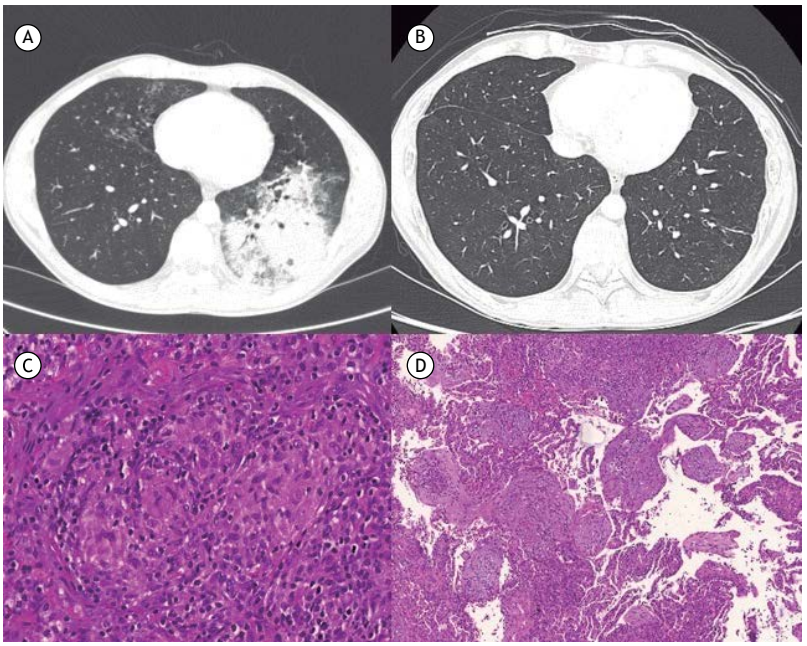

Figure 1. In A, CT scan of the chest showing left lower lobe consolidation with air bronchogram and perilesional ground-glass opacities. Note tree-in-bud opacities in the middle lobe. In B, CT scan of the chest showing resolution of the left lower lobe consolidation after treatment. In C, non-necrotizing granuloma, together with a chronic inflammatory infiltrate (H&E staining; magnification, ×40). In D, organizing pneumonia (H&E staining; magnification, ×8).

necrotizing and caseating are sometimes considered to be different from each other. The former is used in order to describe microscopic changes, whereas the latter refers to a gross, cheesy appearance. Infections usually cause necrotizing granulomas or a combination of necrotizing and non-necrotizing granulomas, although some organisms, such as *Cryptococcus* spp. and *Mycobacterium avium* complex, can induce predominantly non-necrotizing granulomas. Conversely, a purely non-necrotizing granulomatous process is more likely to be noninfectious (e.g., sarcoidosis, berylliosis, talc granulomatosis, granulomatosis with polyangiitis, Churg-Strauss syndrome, necrotizing sarcoid granulomatosis, bronchocentric granulomatosis, aspiration pneumonia, and rheumatoid nodules). Given that granulomas in CD are sarcoid-like granulomas, the differential diagnosis between sarcoidosis and CD is particularly important. In the case reported here, mycobacterial infection was excluded because of the absence of caseous necrosis and because no mycobacteria were detected by microbiological testing, molecular analysis, BAL fluid culture, or lung biopsy. A diagnosis of sarcoidosis was considered but ruled out because the patient presented with a solitary pulmonary lesion, without lymphadenopathy, lymphocytosis, increased CD4/CD8 ratio in BAL fluid, or systemic hyperkalemia.[5]

In conclusion, lung disease is a rare complication of IBD, particularly CD. The prognosis of lung disease in patients with CD is generally favorable, with a high response rate to therapy. Corticosteroids are the most common treatment, leading to rapid symptom improvement in up to 90% of patients. However, relapse occurs in 12-30% of patients after corticosteroid tapering or withdrawal, dose increase or drug readministration being required.[3] In the case reported here, a patient with CD was found to have organizing pneumonia with granulomatous inflammation, which was successfully controlled with corticosteroid therapy and immunomodulation with azathioprine and infliximab.

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Eosinophilic pneumonia: remember topical drugs as a potential etiology

Olívia Meira Dias[1,a], Ellen Caroline Toledo do Nascimento[2,b], Rodrigo Caruso Chate[3,c], Ronaldo Adib Kairalla[1,d], Bruno Guedes Baldi[1,e]

TO THE EDITOR:

A 32-year-old female patient was admitted to the emergency room with a 20-day history of asthenia, myalgia, fever, and dry cough. She reported no dyspnea or wheezing. There was no relevant exposure history except for the use of minocycline for 1 month as a topical treatment for facial acne. In addition, the patient reported no history of medication use, allergies, smoking, or illicit drug use.

Her physical examination upon admission was unremarkable, the patient being afebrile. There was no skin rash. Lung auscultation was normal. Her heart rate was 87 bpm, her respiratory rate was 18 breaths/min, and her SpO_2 was 98% on room air.

Laboratory tests showed leukocytosis (13 × 10^9 cells/L), with an eosinophil count of 1,300 cells/μL. Her C-reactive protein levels were elevated (206 mg/dL; reference value, < 10 mg/dL). Her platelet count, electrolyte levels, renal function, and liver function were all normal. Point-of-care tests for influenza and dengue were negative, as were urinalysis results. Rheumatoid factor, antinuclear factor, and antineutrophil cytoplasmic antibody test results were all negative. IgE levels were elevated (374 kU/L; reference value, < 100 kU/L). Examination of the stool for ova and parasites was negative.

An HRCT scan of the chest showed bilateral consolidations with ill-defined margins, predominantly at the lung apices and periphery (Figures 1A, B, and C). The patient underwent bronchoscopy with BAL and transbronchial biopsy. BAL fluid cytology revealed a predominance of eosinophils (35%), being negative for malignant cells. In addition, microbiological analysis of the BAL fluid was negative. The transbronchial biopsy revealed alveolar/interstitial inflammatory cell infiltrate (with a predominance of eosinophils and lymphocytes), as well as foci of non-necrotizing granulomatous inflammation in the arteriole walls (Figures 1D and E). A diagnosis of minocycline-induced chronic eosinophilic pneumonia (EP) was made after exclusion of other causes of peripheral and pulmonary eosinophilia, being based on HRCT findings consistent with the disease. Peripheral eosinophilia, dyspnea, and CT changes resolved after discontinuation of minocycline and initiation of prednisone at 30 mg/day.

EP comprises a heterogeneous group of diseases that share pulmonary eosinophilia as a common feature. A diagnosis of EP can be made on the basis of at least one of the following criteria: peripheral eosinophilia associated with pulmonary opacities on imaging; surgical or transbronchial biopsy findings of eosinophilia; and an increase in the proportion of eosinophils in BAL fluid.[1]

Although EP can present as acute respiratory failure (especially in patients with acute EP), the prognosis is generally good. Clinical history taking, investigation of extrapulmonary involvement, and evaluation of patient exposure are essential in making a diagnosis of EP. Because of the presence of nonspecific symptoms, diagnosis is often delayed.[1]

Although EP can be idiopathic, epidemiological factors should be considered when investigating pulmonary eosinophilia, including exposure to parasites (including *Ascaris* spp., *Ancylostoma* spp., *Necator* spp., and *Strongyloides* spp.), exposure to inhalation agents, first-time smoking, changes in smoking habits, toxic inhalation, medication use, and illicit drug use, as well as a history of asthma and atopy.[1-4] Drugs have been increasingly associated with EP; a complete and up-to-date list can be found at www.pneumotox.com.[5]

Although there have been reports of peripheral eosinophilia in patients with EP, it is not always observed in such patients, especially those with acute EP.[6] In such patients, BAL or biopsy can provide insight as to the likelihood of peripheral eosinophilia (eosinophil levels above 25% in differential cell counts in BAL fluid).

In the case reported here, the final diagnosis was chronic EP, an insidious disease with symptoms that range from 2 weeks to 4 weeks in duration. In patients with secondary EP, symptoms commonly appear after radiation therapy for breast cancer and exposure to drugs or parasites, and might be associated with collagen diseases, such as rheumatoid arthritis. Female patients in the 30- to 40-year age bracket are most commonly affected. Major symptoms include dry cough, dyspnea, fever, asthenia, and weight loss. Unlike patients with acute EP, those with chronic EP rarely develop acute respiratory failure.[3]

EP secondary to minocycline is rare, being underreported because minocycline is used as a topical agent in the treatment of acne vulgaris and is therefore not considered to be a drug or medication. The prognosis of minocycline-induced EP is often good.[7]

Drug-induced EP can mimic idiopathic acute EP or chronic EP on imaging. In patients with idiopathic acute EP, characteristic CT findings include diffuse interstitial infiltrates, patchy alveolar infiltrates, and diffuse

1. Divisão de Pneumologia, Instituto do Coração – InCor – Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.
2. Departamento de Patologia, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.
3. Divisão de Radiologia, Instituto do Coração – InCor – Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.
a. http://orcid.org/0000-0002-5926-2975; b. http://orcid.org/0000-0002-2981-1419; c. http://orcid.org/000-0002-4193-7647;
d. http://orcid.org/0000-0001-7194-0479; e. http://orcid.org/0000-0002-9609-5117

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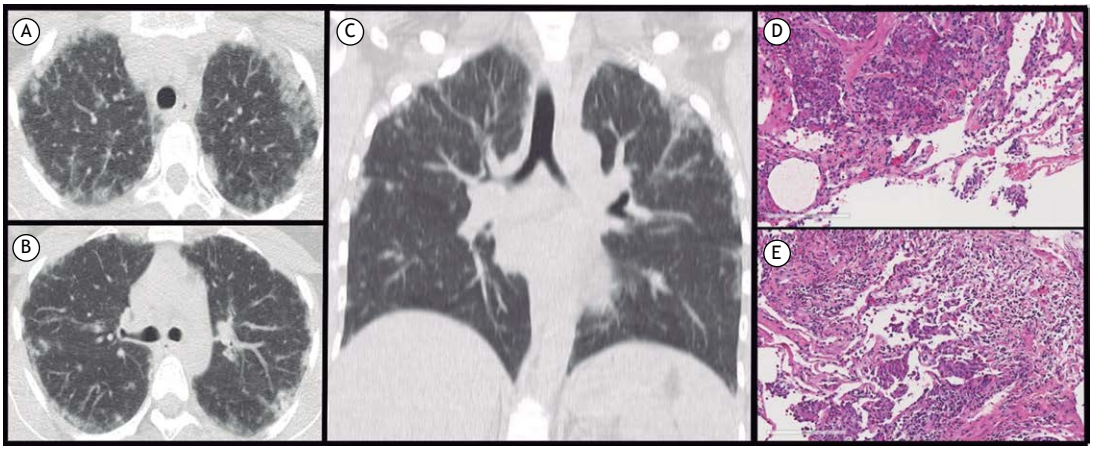

Figure 1. In A and B, axial HRCT scans of the chest. In C, coronal HRCT scan of the chest. Note bilateral consolidations with ill-defined margins, predominantly at the lung apices and periphery. Note also the presence of reticulation. In D, transbronchial biopsy specimen showing alveolar/interstitial inflammatory cell infiltrate, with a predominance of eosinophils and lymphocytes (H&E staining; magnification, ×100). In E, expansion of the pulmonary interstitium by an inflammatory cell infiltrate composed of lymphocytes, plasma cells, and eosinophils. In the upper left corner, note the non-necrotizing granulomatous inflammation in the arteriole walls (H&E staining; magnification, ×100).

ground-glass infiltrates. A crazy-paving pattern and bilateral pleural effusions can also be seen.[8]

In the case reported here, pulmonary consolidations had a patchy, peripheral distribution. In addition, subpleural confluent consolidations were found at the lung apices, resembling a photographic negative of cardiogenic pulmonary edema, classically described in idiopathic chronic EP.[9,10] Other common CT findings include the reversed halo sign, small nodules, septal thickening, and reticulation.[8] The most common radiological differential diagnosis is cryptogenic organizing pneumonia, in which pulmonary consolidations and migratory alveolar infiltrates can also occur.[11]

Histopathologically, EP is characterized by prominent eosinophilic infiltration of the alveolar spaces and associated interstitium, accompanied by a fibrinous exudate. The lung architecture is typically preserved. Eosinophilic microabscesses, non-necrotizing nongranulomatous vasculitis, and occasional multinucleated giant cells can also be found. The vessel infiltration observed in patients with EP should not be mistaken for that observed in patients with Churg-Strauss syndrome. In the latter, vasculitis is characterized by intimal and medial infiltration by chronic inflammatory cells, including numerous eosinophils; it can show granulomatous features or contain numerous giant cells reminiscent of giant cell arteritis, and fibrinoid necrosis is sometimes present.[12] In addition, necrotizing granulomas are typically found in the adjacent parenchyma, being composed of large foci of necrosis surrounded by a rim of epithelioid histiocytes (i.e., "palisaded granulomas").[12]

The differential diagnosis of EP includes the following: cryptogenic organizing pneumonia, particularly in the clinical context of collagen vascular diseases such as myositis, mixed connective tissue disease, and systemic lupus erythematosus; idiopathic hypereosinophilic syndrome; and Churg-Strauss syndrome. The last two are generally associated with a more pronounced extrathoracic involvement and longer symptom duration.

The prognosis of EP is usually excellent, which is due to its responsiveness to corticosteroids. In general, prednisone is used at 0.5 mg • kg^{-1} • day^{-1} for two weeks to six months with progressive tapering, depending on disease severity. In some cases, withdrawal from exposure is sufficient for clinical improvement. Re-exposure has been reported to result in recurrence.[4]

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Near-fatal pulmonary embolism: capnographic perspective

Marcos Mello Moreira[1,2,a], Luiz Claudio Martins[3,b], Konradin Metze[4,c], Marcus Vinicius Pereira[2,d], Ilma Aparecida Paschoal[1,e]

DEAR EDITOR,

Massive pulmonary embolism (MPE) is a condition that causes sudden changes to the cardiopulmonary system[1-5] and is associated with high morbidity and mortality. Methods that detect those changes in real time, especially noninvasive ones, can be very useful. They can also indicate whether the MPE is likely to improve or not.

To address the clinical scenario of MPE, one may make use of noninvasive devices with software that monitors respiratory mechanics and volumetric capnography (VCap) data, online and offline, providing information that may indicate ventilation-perfusion mismatch, in MPE or in other diseases.

The respiratory profile monitor (CO_2SMO PLUS DX-8100; Respironics, Murrysville, PA, USA) provides and records variables such as end-tidal partial pressure of CO_2 ($PetCO_2$), CO_2 output (VCO_2), the phase II slope of the capnogram (SII), the phase III slope of the capnogram (SIII)—also known as the alveolar plateau, respiratory rate (RR), inspiratory tidal volume (V_{Ti}), expiratory tidal volume (V_{Te}), inspiratory time, expiratory time, alveolar minute volume (MValv), peak inspiratory flow, and peak expiratory flow.

This was an observational study of pigs induced to MPE through the injection of autologous clots, during spontaneous ventilation (FiO_2 = 0.21). Our aim was to record, observe, and analyze the behavior of respiratory mechanics parameters, especially VCap data.

We evaluated numerical variables (Table 1) and curves (Figures 1A, 1B, and 1C).

This study was conducted in conjunction with the work published by Pereira et al.,[3] which has been approved by the Ethics Committee on the Use of Animals of the State University at Campinas Institute of Biology (Reference no. 2298-1).

At baseline (T_0, before the clots were injected), all of the variables were measured. The clots were injected in increments of 5 mL until a borderline (i.e., "near-fatal") mean pulmonary artery pressure (the primary endpoint) was reached. The mean quantity of clots injected was 24.7 ± 4.3 mL, and the mean clot injection time was 45 min. As can be seen in Table 1, gas exchange ($PaCO_2$) and hemodynamic changes (cardiac output) were evaluated at three different time points: T_1 (the endpoint), T_2 (30 min after T_1), and T_3 (1 h after T_1).

For the comparison between hemodynamic, gas exchange, and respiratory variables at T_0, T_1, T_2, and T_3, we used repeated-measures ANOVA (Winstat, version 3.1). Values of $p < 0.05$ were considered statistically significant.

$PetCO_2$, MValv, and the alveolar dead space volume presented significant differences among the various time points evaluated, whereas RR did not. It is well known that MPE leads to an increase in RR and in lung volumes. The increase in RR and in lung volumes can be evidenced by a significant increase in MValv, which, in turn, leads to alveolar washout and, as a consequence, to a significant decrease in $PetCO_2$. Another factor that contributed to the reduction in $PetCO_2$ was a significant decrease in pulmonary perfusion (resulting from a decrease in cardiac output). There was a significant increase in the volume of the alveolar dead space, which does not take part in gas exchange. Following the rationale of this variable behavior, the volumes of VCap phases I and II were obtained in mL and per respiratory cycle. Those volumes increased significantly over the study period.

Other variables were provided by VCap or associated with other variables: VCO_2; SII; SIII; VCO_2/V_{Te}; alveolar VCO_2/V_T; SII/exhaled CO_2 partial pressure (SII/P_ECO_2); $SIII/P_ECO_2$; $SIII/PetCO_2$; and $SIII/V_{Te}$. The expected decrease in VCO_2 at T_1 ($p < 0.001$ vs. T_0) can be attributed to the increase in MValv, as well as to a significant reduction in pulmonary blood flow (resulting from a decrease in cardiac output). There were also significant reductions in other metabolic variables, such as VCO_2/V_{Te}, and alveolar VCO_2/V_T.

With similar pathophysiologies, SII and SIII variables also presented significant variations ($p < 0.0001$). The SII represents removal of CO_2 from the alveoli, which are the most distal elements of the small airways. The SIII represents the elimination of CO_2 from most alveoli and, in normal organisms, its shape is similar to a plateau, with a slight upward slope. Higher $SIII/V_{Te}$ and $SIII/PetCO_2$ values suggest structural damage in the peripheral and distal part of the lungs, which promotes this heterogeneous distribution of ventilation.[5,6] The same principle applies to the significant drop in the normalization of SII/P_ECO_2, $SIII/P_ECO_2$, $SIII/PetCO_2$, and $SIII/V_{Te}$ ($p < 0.0001$ for all). Negative SIII values seem to be associated with vascular damage,[2,5] whereas an excessive increase in these values may be associated with airway damage

1. Disciplina de Pneumologia, Departamento de Clínica Médica, Faculdade de Ciências Médicas, Universidade Estadual de Campinas – Unicamp – Campinas (SP) Brasil.
2. Programa de Pós-Graduação em Ciências da Cirurgia, Faculdade de Ciências Médicas, Universidade Estadual de Campinas – Unicamp – Campinas (SP) Brasil.
3. Disciplina de Medicina Interna e Semiologia, Departamento de Clínica Médica, Faculdade de Ciências Médicas, Universidade Estadual de Campinas – Unicamp – Campinas (SP) Brasil.
4. Departamento de Patologia Clínica, Faculdade de Ciências Médicas, Universidade Estadual de Campinas – Unicamp – Campinas (SP) Brasil.
a. http://orcid.org/0000-0002-2148-5479; b. http://orcid.org/00000-0002-2920-2162; c. http://orcid.org/0000-0003-0742-8846;
d. http://orcid.org/0000-0002-7195-0404; e. http://orcid.org/0000-0002-0539-4243

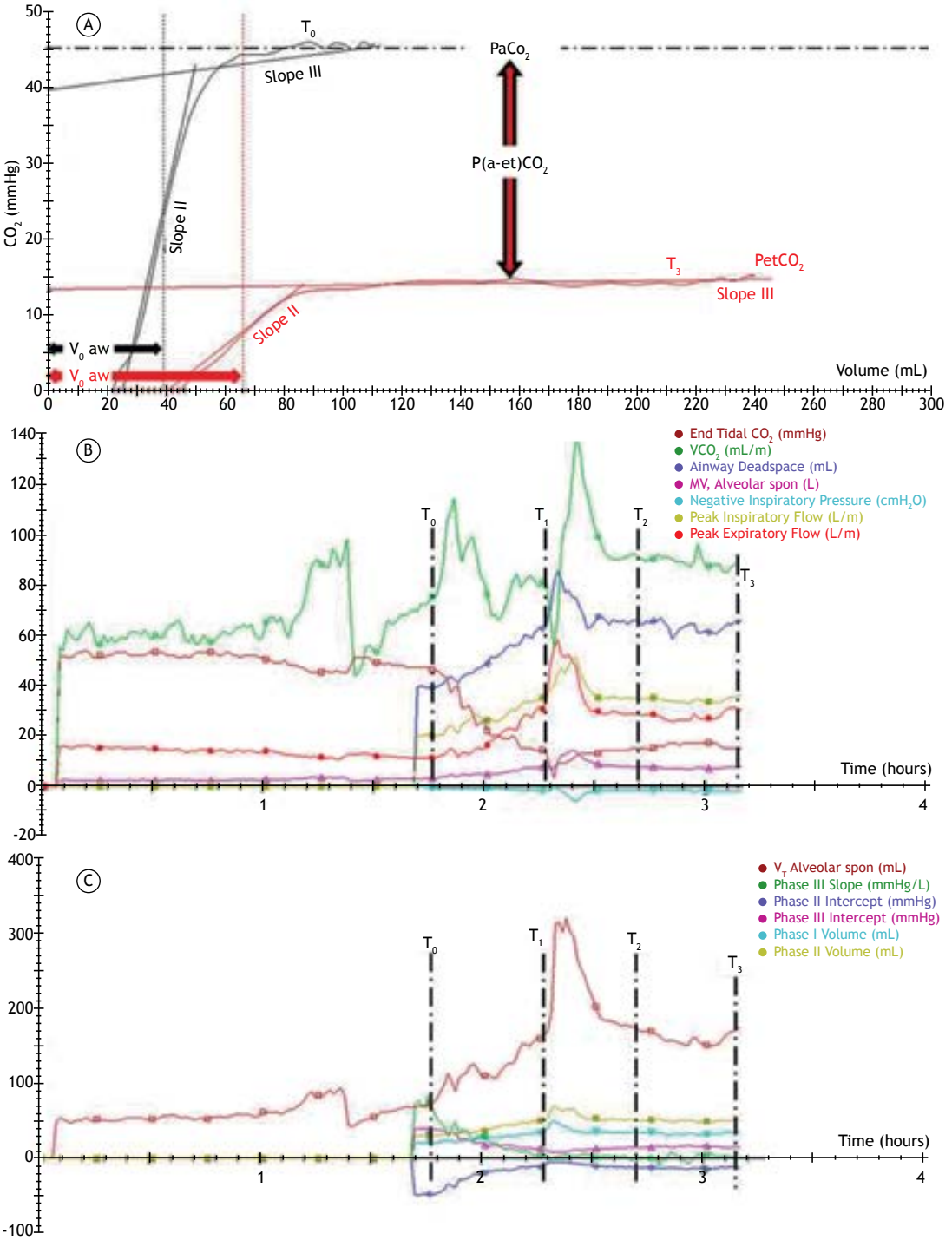

Figure 1. A: representative curves of the volumetric capnography (volume × CO_2) at baseline (T_0, black) and at 1 h after the endpoint (T_3, red). B and C: representative curves of trends seen throughout the experiment. Figures obtained and adapted from the Analysis Plus software (Novametrix, Wallingford, CT, USA). T_0: baseline; T_1: endpoint; T_2: 30 min after T_1; T_3: 1 h after T_1; V_0 aw: anatomical dead space volume; End-Tidal CO_2: end-tidal expiratory pressure of CO_2; VCO_2: CO_2 production (mL/m); Airway dead space: anatomical dead space volume; MV, Alveolar spon: spontaneous alveolar minute volume; V_T, Alveolar spon: spontaneous alveolar tidal volume; Phase III Slope: phase III slope of the capnogram; Phase II Intercept: intercept of the phase II slope of the capnogram; Phase III Intercept: intercept of the phase III slope of the capnogram; Phase I Volume: volume of the phase I slope of the capnogram; and Phase II Volume: volume of the phase II slope of the capnogram.

(such as that occurring in bronchiectasis, cystic fibrosis, and COPD).[7,8]

It was necessary to normalize VCO_2/V_{Te}, SII/P_ECO_2, $SIII/P_ECO_2$, $SIII/PetCO_2$, and $SIII/V_{Te}$, in order to allow

Table 1. Respiratory mechanics, gas exchange, and hemodynamic variables.

Variable	Time point				
	T_0	T_1	T_2	T_3	p
RR (breaths/min)	47 ± 9	48 ± 8	53 ± 11	54 ± 12	0.061
MValv (L)	4.0 ± 0.9	10.6 ± 2.9	9.9 ± 3.8	7.8 ± 1.6	< 0.0001
VDalv (L)	2.4 ± 0.6	4.0 ± 0.8	4.1 ± 1.4	3.8 ± 1.1	< 0.0001
$PetCO_2$ (mmHg)	40.1 ± 2.0	11.0 ± 2.7	16.9 ± 5.5	19.7 ± 4.6	< 0.0001
VCO_2 (mL/min)	95 ± 23	83 ± 20	126 ± 25	114 ± 27	0.001
VCO_2/V_{Te} (mL/L/min)	0.69 ± 0.10	0.28 ± 0.08	0.49 ± 0.10	0.53 ± 0.10	< 0.0001
VCO_2/V_Talv (mL/L/min)	1.09 ± 0.16	0.40 ± 0.13	0.70 ± 0.16	0.79 ± 0.15	< 0.0001
SII (mmHg/L)	1414.3 ± 232.5	185.1 ± 66.8	330.7 ± 128.4	441.1 ± 125.0	< 0.0001
SIII (mmHg/L)	56.73 ± 11.86	−1.10 ± 1.16	7.93 ± 10.06	13.02 ± 10.22	< 0.0001
SII/P_ECO_2	107.61 ± 33.42	31.15 ± 8.06	38.86 ± 12.09	51.35 ± 12.92	< 0.0001
$SIII/P_ECO_2$	4.247 ± 1.188	−0.185 ± 0.210	0.788 ± 0.898	1.366 ± 0.758	< 0.0001
$SIII/PetCO_2$	1.409 ± 0.247	−0.095 ± 0.108	0.378 ± 0.472	0.603 ± 0.362	< 0.0001
$SIII/V_{Te}$	0.427 ± 0.137	−0.004 ± 0.004	0.031 ± 0.037	0.060 ± 0.043	< 0.0001
Intercept Y2 (mmHg)	−48.7 ± 3.7	−9.5 ± 2.1	−15.0 ± 5.8	−19.2 ± 4.8	< 0.0001
Intercept Y3 (mmHg)	35.8 ± 1.7	11.8 ± 2.1	15.7 ± 4.1	18.2 ± 3.0	< 0.0001
P1V (mL)	28.0 ± 5.1	43.5 ± 5.9	41.5 ± 7.4	38.0 ± 6.0	< 0.0001
P2V (mL)	36.0 ± 5.0	63.0 ± 9.3	59.3 ± 11.4	52.7 ± 8.7	< 0.0001
PFI (L/min)	25.5 ± 3.6	38.7 ± 4.9	38.6 ± 7.7	34.6 ± 3.1	< 0.0001
PFE (L/min)	16.3 ± 3.4	49.2 ± 9.8	39.4 ± 16.2	31.8 ± 9.4	< 0.0001
T_i (s)	0.49 ± 0.06	0.65 ± 0.11	0.57 ± 0.09	0.53 ± 0.12	< 0.0001
T_e (s)	0.85 ± 0.20	0.74 ± 0.26	0.66 ± 0.21	0.65 ± 0.20	0.0348
$PaCO_2$ (mmHg)	44.92 ± 4.44	48.22 ± 5.97	45.37 ± 5.82	43.52 ± 6.21	0.158
$P(a\text{-}et)CO_2$ (mmHg)	4.8 ± 2.8	37.2 ± 5.8	28.5 ± 4.5	23.8 ± 3.5	< 0.0001
DC (L/min)	4.9 ± 1.0	2.7 ± 1.0	3.6 ± 1.1	3.9 ± 1.3	< 0.003

T_0: baseline; T_1: endpoint; T_2: 30 min after T_1; T_3: 1 h after T_1; RR: respiratory rate; MValv: alveolar minute volume; VDalv: alveolar dead space volume; $PetCO_2$: end-tidal CO_2 partial pressure; VCO_2: CO_2 production; V_{Te}: expiratory tidal volume; $V_T$alv: alveolar tidal volume; SII: phase II slope of the capnogram; SIII: phase III slope of the capnogram; P_ECO_2: partial pressure of CO_2 in exhaled air; Intercept Y2: intersection between SII and the y axis; Intercept Y3; intersection between SIII and the y axis; P1V: volumetric capnography phase 1 volume; P2V: volumetric capnography phase 2 volume; PIF: peak inspiratory flow; PEF: peak expiratory flow; T_i: inspiratory time; T_e: expiratory time; $P(a\text{-}et)CO_2$: arterial to end-tidal CO_2 gradient; and CO: cardiac output.

them to be compared to the equivalent CO_2 excretion rates (P_ECO_2, $PetCO_2$, and V_{Te}, respectively).[9]

Other variables that are not usually described in the literature are intercept Y2 and intercept Y3 (both in mmHg), which indicate an increase or a decrease in the caliber of the conducting airways. These variables refer to the intersection of SII and SIII with the y axis of the VCap curve and represent a mathematical increase of the inclination of the slopes. Scheffzek et al.[10] were able to verify that. In the present study, there was a significant variation in those two variables ($p < 0.0001$ for both).

In conclusion, recording, observing, and analyzing the behavior of the parameters of respiratory mechanics, especially VCap, made it possible to identify MPE. When carefully applied and analyzed, our results can make a major contribution to decreasing morbidity and mortality in patients presenting with a clinical profile suggestive of MPE.

Further studies of MPE, either experimental or clinical, are still needed. Such studies could broaden our knowledge of the disease and of its implications for the cardiopulmonary system.

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Empyema caused by infection with *Clostridium septicum* in a patient with lung cancer

Gabriel Afonso Dutra Kreling[1,a], Marilia Ambiel Dagostin[1,b], Marcelo Park[2,c]

TO THE EDITOR:

A 58-year-old man presented to our outpatient clinic with a 5-month history of weight loss (total weight lost, 18 kg). In the last two months, he also had a progressive cough and dyspnea, accompanied by right-sided chest pain on taking a breath. Computed tomography (CT) of the chest, performed for diagnostic investigation, showed a mass at the right lung base. The patient underwent CT-guided biopsy to obtain a tissue sample from the mass. On the day of the procedure, the patient was experiencing worsening symptoms of chest pain, cough, and dyspnea, which was associated with the onset of fever 2 days later.

The CT scan (Figure 1) showed right hydropneumothorax. The patient underwent diagnostic thoracentesis to obtain pleural fluid for analysis (Table 1), after which he underwent chest drainage.

The patient was hospitalized, receiving ceftriaxone and clarithromycin. On the second day of hospitalization, there was clinical worsening, with tachycardia and a decreased level of consciousness. Accordingly, the antibiotic treatment was changed to piperacillin-tazobactam. The patient then developed multiple organ dysfunction syndrome and was transferred to the ICU. At admission to the ICU, the Sequential Organ Failure Assessment score was 6 (indicative of pulmonary, renal, and hepatic dysfunction), and the Simplified Acute Physiology Score III score was 83. Considering the advanced stage of the disease and the clinical worsening of the patient, palliative care was preferred. The patient died comfortably on the sixth day of hospitalization. The examination of the lung mass biopsy confirmed the diagnosis of non-small cell lung cancer with a low degree of differentiation and extensive areas of necrosis. Culture of the pleural fluid showed growth of *Clostridium septicum.*

Clostridium septicum is a gram-positive anaerobic microorganism that is highly pathogenic because of the action of alpha-toxin and other enzymes such as hyaluronidase, fibrinolysin, deoxyribonuclease, and hemolysins.[1,2] Reports indicate that this microorganism can cause tissue necrosis, hemolysis, intravascular thrombosis, and disseminated intravascular coagulation.[3] *Clostridium septicum* is believed to be present in the normal intestinal flora,[4] although it has not been identified in studies of human fecal cultures.[5]

Clostridium septicum infection is known to be associated with gastrointestinal, laryngeal, breast, and prostate cancer, as well as with hematological malignancies. To our knowledge, this is the first description of a case of empyema caused by *C. septicum* in a patient with non-small cell lung cancer.

Clostridium septicum displays tropism for necrotic tissues, perhaps because anaerobic glycolysis may produce an acidic environment favoring germination of *Clostridium* spores. This acidic environment is found in malignant tumors and is probably the gateway to *C. septicum* infection,[1,4] which is known to be associated with neoplasms, as well as with some forms of immunosuppression.[2] Two reviews of the literature on *C. septicum* infection showed that cancer is found in 80%[1] and 85%[4] of cases, respectively, the main neoplasms being colorectal cancer and hematological malignancies. Other previously reported, although less common, neoplasms were cancer of the larynx, breast, and prostate.[4,6] There have been no reports of lung cancer associated with *C. septicum* infection.

Colorectal neoplasms usually have a necrotic aspect, and leukemia appears to predispose an individual to pseudomembranous colitis, agranulocytic lesions (ulcers or abscesses), and ischemic colitis, which can result in areas of the intestine becoming necrotic or inflamed,[7] providing gateways for *C. septicum* infection.

Among patients with *C. septicum* infection, the mortality rate for those who do not receive antibiotic therapy is virtually 100%, whereas the reported overall mortality rate ranges from 48% to 65%.[1,4] *Clostridium septicum* has the capacity to aggressively invade tissues, even in the absence of trauma.[8] *Clostridium septicum* has been found to cause metastatic infections in regions such as the meninges, thyroid, bone, joints, spleen, and anterior chamber of the eye.[1] The main forms of presentation of *C. septicum* infections are bacteremia; acute abdomen, caused by sepsis; and myonecrosis in the extremities and in the trunk.[1] The only reported case of empyema caused by *C. septicum* was in an immunocompetent woman with acute abdomen and an internal hernia, together with an incarcerated ileum and ischemia, which created the portal of entry for the microorganism.[9]

Nontraumatic cases of pleuropulmonary infection by anaerobic microorganisms alone are uncommon and are usually associated with some chronic disease or immune system impairment.[10] The main isolated species of *Clostridium* that are associated with pleuropulmonary infection are *C. perfringens* (the most common species), *C. sordellii*, *C. sporogenes*, *C. paraputrificum*, *and C. bifermentans*.[10] Most primary clostridial pleuropulmonary infections occur as a result of iatrogenic contamination of the pleural space. In a case report and review of the

1. Programa de Residência em Clínica Médica, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.
2. Unidade de Terapia Intensiva, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.
a. http://orcid.org/0000-0003-1212-3166; b. http://orcid.org/0000-0002-3203-768X; c. http://orcid.org/0000-0002-4201-2718

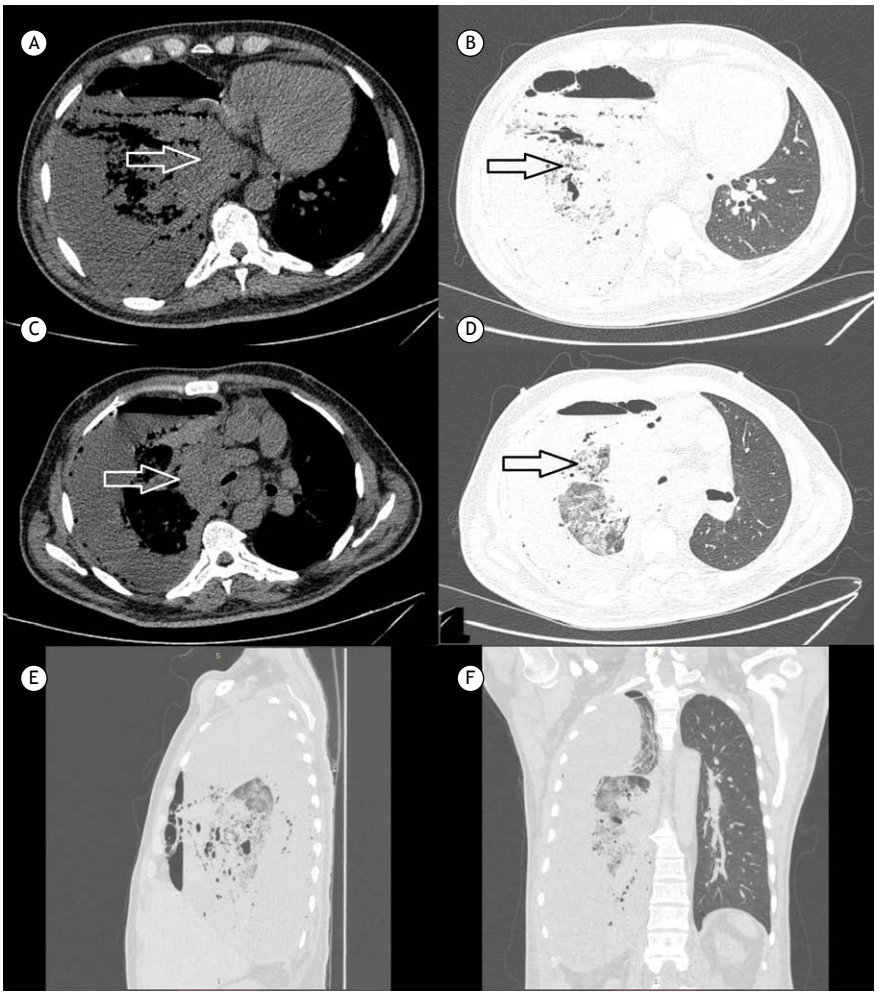

Figure 1. CT scans of the chest, showing massive hydropneumothorax in the right lung, with almost total restrictive atelectasis (A through F). Note the perihilar mass affecting the middle and lower lobes of the right lung (white arrow in A and C). In the remaining parenchyma of the right lung, there are consolidations with air bronchograms and bronchiectasis, accompanied by ground-glass opacities, suggestive of an inflammatory/infectious process (black arrow in B and D).

Table 1. Characteristics of the pleural fluid.

Aspect	Hemorrhagic
pH	6.2
LDH	> 10,000 U/L
Cytology	44,800 cells/mm^3
Glucose	132 mg/dL

LDH: lactate dehydrogenase.

literature, 17 cases of pleuropulmonary infection due to *Clostridium* spp. in the absence of a history of trauma were evaluated, and 30% of those cases were found to have occurred after thoracentesis or biopsy, both performed with sterile techniques.[10] In the case reported here, that was the likely port of entry of *C. septicum* infection. The mortality rate of pleuropulmonary infection due to *Clostridium* spp. is approximately 30%, and the prognosis improves after appropriate antibiotic therapy and adequate drainage of the infected pleural fluid.[10]

One limitation of our report is that, because of the performance status of the patient, we did not attempt to identify concomitant neoplasms in other organs or tissues. Nevertheless, given the strong association between *C. septicum* infection and cancer, patients infected with *C. septicum* should be screened for neoplasia (if there is no other diagnosis), mainly colorectal cancer and hematological malignancies, although other types of cancer should not be overlooked.

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On page 411, where is written:

"A recent study demonstrated that, if **procalcitonin** levels do not decrease by 50% within 3 days of treatment and remains above 75 mg/L, the risk of 30-day mortality is increased.[54] A study of 191 patients with CAP admitted to the ICU showed that mortality was 4.8% among those in whom **procalcitonin** levels decreased rapidly (n = 66), 17.3% among those in whom **procalcitonin** levels decreased slowly (n = 81), and 36.4% among those in whom **procalcitonin** levels did not decrease (n = 44).[55]"

It should be read:

"A recent study demonstrated that, if **C-reactive protein** levels do not decrease by 50% within 3 days of treatment and remains above 75 mg/L, the risk of 30-day mortality is increased.[54] A study of 191 patients with CAP admitted to the ICU showed that mortality was 4.8% among those in whom **C-reactive protein** levels decreased rapidly (n = 66), 17.3% among those in whom **C-reactive protein** levels decreased slowly (n = 81), and 36.4% among those in whom **C-reactive protein** levels did not decrease (n = 44).[55]"

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1. Neder JA, Nery LE, Castelo A, Andreoni S, Lerario MC, Sachs AC et al. Prediction of metabolic and cardiopulmonary responses to maximum cycle ergometry: a randomized study. Eur Respir J. 1999;14(6):1204-13.

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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All correspondence to the Jornal Brasileiro de Pneumologia should be addressed to:

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Jornal Brasileiro de Pneumologia e-mail address:

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E-mail: pneumoba@gmail.com; spba@outlook.com.br; montal59@hotmail.com

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Endereço: Galeria Pátio 22 - Rua 22 n. 69,
Sala 17 – Setor Oeste
CEP: 74.120-130 - Goiânia – GO
Telefone: (62)3251-1202 / (62) 3214-1010
E-mail: sgpt2007@gmail.com
karlacurado1@hotmail.com

SOCIEDADE MINEIRA DE PNEUMOLOGIA E CIRURGIA TORÁCICA
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Secretário: Leonardo Brant Rodrigues
Endereço: Av. João Pinheiro, 161 - sala 203 - Centro
CEP: 30.130-180 - Belo Horizonte – MG
Tel/fax: (31) 3213-3197 -
E-mail: smpct@smpct.org.br
Site: www.smpct.org.br

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Secretária: Gerlânia Simplício Sousa
Endereço: Rua José Florentino Jr. 333– Tambauzinho
CEP: 58042-040 – João Pessoa – PB
Telefone: (83)991219129
E-mail: rangelr@uol.com.br

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Secretária Geral: Áquila Andrade Carneiro
Endereço: Av. Sete de Setembro, 5402 - Conj. 105, 10ª andar Batel
CEP: 80240-000 - Curitiba – PR
Tel/fax: (41) 3342-8889
E-mail: contato@pneumopr.org.br
Site: www.pneumopr.org.br

SOCIEDADE PAULISTA DE PNEUMOLOGIA E TISIOLOGIA
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Secretária: William Salibe Filho
Endereço: Rua Machado Bittencourt, 205,
8° andar, conj. 83 - Vila Clementino
CEP: 04.044-000 São Paulo – SP
Telefone: 0800 17 1618
E-mail: sppt@sppt.org.br
Site: www.sppt.org.br

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Presidente: Adriana Velozo Gonçalves
Secretária: Danielle Cristina Silva Clímaco
Endereço: Rua João Eugênio de Lima , 235, Boa Viagem
CEP: 51030-360 - Recife – PE
Tel/fax: (81)988817435
E-mail: pneumopernambuco@gmail.com
adrianavelozo@hotmail.com

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Secretário: Ostílio Fonseca do Vale
Endereço: Av. Gonçalo Prado Rollemberg, 211,
Sala 11 Bairro São José
CEP: 49050-370- Aracaju - SE
Telefone: (79) 21071412 - (79)999780042
E-mail: anaelze.tojal@gmail.com

NACIONAIS

XIII Curso Nacional de Doenças Intersticiais (DIP)
Data: 29 e 30 de março de 2019
Local: Centro de Convenções Rebouças, São Paulo/SP
Informações: 0800616218
eventos@sbpt.org.br

XX Curso Nacional de Atualização em Pneumologia
Data: 25 a 27 de abril de 2019
Local: Othon Palace Copacabana Rio de Janeiro/RJ
Informações: 0800616218 ou
eventos@sbpt.org.br

TÓRAX 2019
XXI Congresso da Sociedade
Brasileira de Cirurgia Torácica
Data: 16 a 18 de maio de 2019
Local: Ouro Minas Palace Hotel – MG
Informações: (11)32530202
secretaria@sbct.org.br | www.sbct.org.br

IX Congresso Gaúcho de Pneumologia
III Congresso Gaúcho de Pneumologia Pediátrica
Data: 13 a 15 de junho de 2019
Local: Centro de Convenções
Barra Shopping Sul - Porto Alegre/RS
Informações: (51) 33842889 | www.sptrs.org.br

X Congresso Mineiro de Pneumologia e Cirurgia de Torácica
V Congresso Mineiro de Pneumologia Pediátrica
Data: 27, 28 e 29 de junho de 2019
Local: Associação Médica de Minas Gerais - Belo Horizonte – MG
Informações: (31)3213-3197
smpct@smpct.org.br | www.smpct.org.br

XII Congresso Brasileiro de Asma
VIII Congressos Brasileiros de DPOC e Tabagismo
Congresso Norte e Nordeste
Data: 14 a 16 de agosto de 2019
Local: Centro de Convenções de João Pessoa, João Pessoa/PB
Informações: 0800616218
eventos@sbpt.org.br

XVII Congresso de Pneumologia e Tisiologia do Estado do Rio de Janeiro
Data:12 a 14 de setembro de 2019
Local: Centro de Convenções SulAmérica
Rio de Janeiro/RJ
Informações: 21 2548-5141
pneumo2019@metodorio.com.br

10º Congresso do Centro-Oeste de Pneumologia e Tisiologia
Data: 25 a 27 de outubro 2019
Local: Associação Médica do Mato Grosso do Sul (AMMS)
Av. Des. Leão Neto do Carmo, 155 - Jardim Veraneio, Campo Grande - MS
Informações: (67) 3327-4110 (Luciane)
especialidades@amms.com.br
(67)98162-8382 (Henrique Brito)
hfbrito@icloud.com

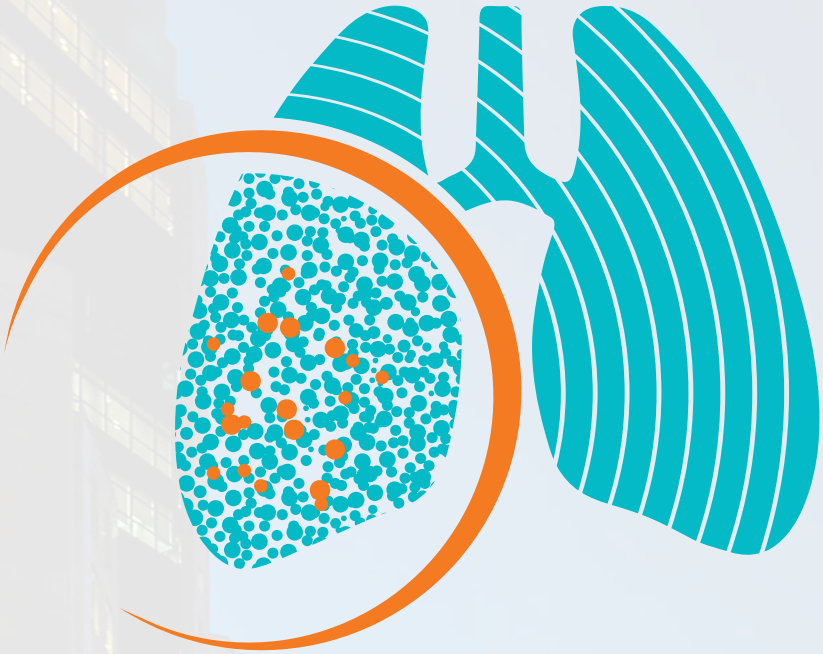
18º Congresso Paulista de Pneumologia e Tisiologia
Data: 20 e 23 de novembro de 2019
Local: Centro de Convenções Rebouças
Informações: 0800161718
www.sppt.org.br

INTERNACIONAIS

ATS 2019
Data: 17 a 22 de maio de 2019
Local: Dallas, Texas/USA
Informações: www.thoracic.org

ERS 2019
Data: 29 de setembro a 02 de outubro de 2019
Local: Madrid/Espanha
Informações: www.ersnet.org

CHEST 2019
Data: 19 a 23 de outubro 2019
Local: New Orleans/EUA
Informações: www.chestnet.org



XIII CURSO DE DOENÇAS INTERSTICIAIS

22 E 23/março 2019

GRANDE AUDITÓRIO DO CENTRO DE CONVENÇÕES REBOUÇAS, SÃO PAULO/SP

As inscrições para o DIP 2019 já estão abertas!

Acesse o site e garanta sua vaga: https://sbpt.org.br/dip2019/

XII CONGRESSO BRASILEIRO DE ASMA

VIII CONGRESSO BRASILEIRO DE DPOC E TABAGISMO

XVIII CONGRESSO NORTE E NORDESTE DE PNEUMOLOGIA E TISIOLOGIA

14 A 16 DE AGOSTO DE 2019

CENTRO DE CONVENÇÕES DE JOÃO PESSOA/PB