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HIGHLIGHT

Use of nintedanib in patients with idiopathic pulmonary fibrosis in Brazil

Case series of familial pulmonary fibrosis in Brazil

Hookah use among medical students

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Waterpipe smoking, a form of tobacco consumption that is on the rise

Stella Regina Martins[1,a], Ubiratan de Paula Santos[1,b]

The waterpipe apparatus (also known as shisha, hookah, or narghile), used mainly in North African and Asian countries, probably originated in India in the 16th century.[1] Tobacco smoking using a waterpipe has been increasing worldwide and, especially among young people, has become epidemic.[2]

A study involving more than 11,000 US Air Force military recruits revealed that 28% had used a waterpipe in their lifetime and 10% had used it in the past month. Waterpipe use was higher among cigarette smokers, younger individuals, and single individuals.[3]

In the current issue of the JBP, Araújo et al.[4] report on a survey of third- and sixth-year students at a medical school in the state of Goiás, Brazil, which, although involving a small number of students, revealed a worrying situation. The prevalence of waterpipe experimentation was found to be about 60%, with one third of students reporting having used a waterpipe in the past six months and 28% reporting having used it in the past 30 days. The prevalence was higher among smokers (80%) and among those who consumed alcohol (72%). Most students were aware that waterpipe smoking is harmful; this proportion was higher among sixth-year students. However, despite their greater knowledge of the attendant risks, there were no differences in the prevalence of use. These data reveal a higher prevalence than that reported in the aforementioned study of recruits[3] and that reported in a survey of medical students at a Brazilian university.[5]

In Brazil, there have been few population-based studies of the prevalence of waterpipe use. In the period between May and December of 2015, a study of 16,273 individuals aged 12 to 65 years was conducted, through face-to-face interviews, in 26 state capitals and the Federal District of Brasília.[6] The results showed that the overall proportion of waterpipe use in the past 12 months was 1.65%, which corresponds to approximately 2.5 million individuals. Among younger people (12- to 24-year-olds) who reported being smokers, 18.96% had smoked a waterpipe in the past 12 months, whereas among nonsmokers, that proportion was 2.71%. That same study revealed that the prevalence of waterpipe use, as compared with that of cigarette use, is highest among young people of high socioeconomic status and in the non-heterosexual population.[6]

For many centuries, waterpipe smoking was seen as a safer form of tobacco smoking and as being less harmful to health. However, the currently available scientific evidence no longer supports this hypothesis.[7] An important factor in the increasing use of waterpipes is the misperception of safety, supported, on the one hand, by the belief that the toxic substances would be filtered by the water in the waterpipe and, on the other hand, by the fact that waterpipes are smoked less frequently than cigarettes, given that their use is impractical during usual activities. Increasingly extensive and intensive advertising, easy access, inclusion of additives with numerous attractive flavors and aromas in the tobacco, and peer group smoking behavior are other major determinants.[8]

We know that, during waterpipe use, there occurs not only the burning of coal but also the incomplete combustion of tobacco, given that waterpipe combustion occurs at a temperature close to 500°C, which is lower than the combustion temperature of conventional cigarettes. At that temperature, high concentrations of toxicants are released into the air and are inhaled by waterpipe users and by those who are in the same environment not only at the time of use, because deposited carcinogenic particulate matter remains in the venue for days.[9]

About 300 chemicals have been identified in waterpipe smoke.[10] Among those chemicals, there are 82 toxic substances, 23 of which are carcinogenic, including polycyclic aromatic hydrocarbons, heterocyclic compounds, primary aromatic amines, N-heterocyclic amines, tobacco-specific nitrosamines, and metals, responsible for cardiopulmonary diseases and cancer, as well as nicotine, which causes dependence.[8]

On the market, there are numerous tobacco and non-tobacco products available for use in waterpipes. The products that are labeled as not containing tobacco, also known as herbal products, are nicotine free. On the labels of herbal products, which are marketed as being "a healthier alternative to waterpipe tobacco", we find the descriptors "tobacco free", "0% nicotine", and "0% tar," which makes them more attractive to young people.[9] However, research has shown that herbal products are sweetened with sugarcane, which forms molasses. Upon heating, high levels of carcinogenic volatile aldehydes are generated in the smoke.[11] The only difference found in mainstream waterpipe smoke between tobacco and non-tobacco products was the absence of nicotine in the latter. All other toxic and carcinogenic substances, such as tar, carbon monoxide, nitric oxide, fluoranthene, pyrene, formaldehyde, acetaldehyde, and acetone, were present at equal or higher concentrations in herbal products compared with tobacco products.[8]

Findings from countless research studies and data from studies conducted in Brazil,[5,6] as well as those published in the current issue of the JBP,[4] underscore the need for further measures, based on the articles of the World Health Organization Framework Convention

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on Tobacco Control, which was ratified by Brazil in 2005,[12] to protect current and future generations from the harms of waterpipe smoking. Among the recommended measures are a ban on symbols, images, and words that lead to the erroneous conclusion that waterpipes and waterpipe products and accessories are less harmful to health; a ban on attractive additives; a ban on waterpipe venues and the sale of waterpipes and waterpipe products near schools; and the addition of warning labels about the harms of waterpipe use to the waterpipe itself and to waterpipe accessories. It is also essential to raise awareness of and educate health care professionals, educators, and the general public about the health hazards caused not only by waterpipe smoking (of tobacco or non-tobacco products) but also by new classes of tobacco products, such as electronic cigarettes and heated tobacco products, with which the tobacco industry is attempting to reverse the global decline in the prevalence of smoking.[7,13-15]

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How and why to review articles for the *Jornal Brasileiro de Pneumologia*

Bruno Guedes Baldi[1,2,a], Pedro Rodrigues Genta[1,3,b]

In 1731, the Royal Society of Edinburgh adopted a system of review of scientific articles by its members. That system is now recognized as the precursor of the peer review process. The peer-review system continues to be used by the entire scientific community, a major change, which was the invitation of peer reviewers from outside the scientific societies, being implemented in the second half of the twentieth century.[1] The peer review process is the driving force on which scientific publications depend.

The reviewer has the responsibility to improve the quality of the article and the clarity of the message conveyed by minimizing errors in various aspects, such as methodology, writing, and quality of language use, as well as the presentation and interpretation of results, thereby providing impressions that assist the editor in decision making.[2,3] Ideally, an article becomes polished through the review process, which encourages the authors to incorporate improvements in the format of the article and improve the scientific accuracy of the study.

This editorial aims to underscore the reasons for members of the scientific community to participate in the review of articles submitted to the *Jornal Brasileiro de Pneumologia* (JBP) and to summarize suggestions on how to evaluate a scientific paper.

WHY REVIEW A SCIENTIFIC ARTICLE?

- To assist the scientific community: If you are a renowned author, you will be giving back to the community for the reviews you have received on your work and will be able to provide considerable support to a young scientist by offering guidance. If you are a young scientist, you will surely benefit by gaining experience. Regardless of your level of experience, you should recognize that reviewing articles is a fundamental activity for scientific publications worldwide, including the JBP. The availability of reviewers attuned to the purpose of the JBP will enable the journal to improve progressively by reducing the time an article awaits review, as well as by constantly improving the quality of the evaluations. The result will be the submission of progressively higher quality articles that reflect the maturing of our scientific community, which contributes to the evolution of science in the field of respiratory medicine and in similar fields.
- To stay up to date in your area of study: By reviewing articles, you will have the opportunity to review relevant literature and be exposed to current scientific production. In addition, you will be able to learn new methods and different approaches to common problems.
- To improve your reviewing and critical analysis skills: Reviewing articles not only enhances your ability to evaluate and review scientific texts but also improves your article writing skills.
- To become co-responsible for the article: The reviewer becomes co-responsible for the article, and that in itself is a huge compensation.
- To gain prestige on the subject among your peers: Being listed as a reviewer for a given journal indicates that you are a trusted authority in the respective field.

HOW TO REVIEW A SCIENTIFIC ARTICLE?

Recommendations for the review of a scientific paper are presented in Chart 1. Before agreeing to review an article, reviewers should check three fundamental points[2-4]: 1) if the article in question is in their area of expertise; 2) if they have any conflict of interest regarding the article; and 3) whether they will be able to meet the deadlines established.

In the review process, it is important to read the instructions to reviewers and to be aware of the scope of the journal. The reviewer must demonstrate care, transparency, ethics, and professionalism. Make constructive comments and provide explanations, bearing in mind that the main objective is to improve the quality of the article.[2-4] Be patient with less experienced authors, especially when you see potential in the research presented. Be respectful in your comments, because a discourteous review may be enough to cause a young researcher to lose sleep and become discouraged. Be clear and concise in your requests for changes and do not request significant modifications of the manuscript. A paper with too many deficiencies should be rejected in the first review.[3,5] Rejecting such a paper after an extensive review is very disappointing to the author.

Carry out an initial reading to familiarize yourself with the article and get a general impression of it. Next, proceed to a section-by-section evaluation, making comments as you go. In preparing the review, we recommend the writing of an opening paragraph that summarizes the main results. We suggest then dividing your evaluation, in a didactic way, into major and minor concerns, numbering each comment. It is essential to contextualize the results found in relation to existing knowledge and to observe the relevance and originality of the topic.

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Chart 1. Recommendations for the review of a scientific article.

General comments
• Check if the topic is included in your area of study, if you have is a conflict of interest, and if you will be able to meet the deadlines. • Be clear, concise, respectful, and ethical. • Avoid offensive comments. • Evaluate the methodological aspects, writing, quality of language use, and presentation/interpretation of the results. • Determine the relevance and originality of the work. • Carry out an initial reading to get a general impression of the article. • When writing the review, begin with an opening paragraph that summarizes the key findings, then dividing your evaluation into major and minor concerns, numbering each comment.
Section by section
• Title Should be objective and clear Should be consistent with the text • Abstract Should reflect the key points of the article • Introduction Should be brief (2-3 paragraphs) Should describe the scope of the problem and gaps in the literature Must be rational and should include the study hypotheses in the final paragraph • Methods Should be sufficiently detailed to enable replication Should present the study characteristics, including type, design, population, inclusion and exclusion criteria, outcomes, and sample size Should describe techniques appropriate to the topic Must describe the statistical analysis used, local ethics committee approval, and informed consent (if relevant). • Results Should clearly reflect what was presented in the methodology Should not include interpretations or speculations Should include illustrations (tables or figures) with appropriate presentation and quality Should not, in general, repeat information contained in the tables and figures • Discussion In the first paragraph, should summarize the results obtained Should contextualize the results in relation to findings in the literature Should included a paragraph on the limitations of the study • Conclusions Should be consistent with the results and the hypothesis put forth May address future directions • References Must be current and relevant Must conform to the standards of the journal

Title

The title should be objective, clear, and consistent with the content presented in the text.[2,5]

Abstract

Begin by reading the abstract and determining the scope of the article. Check whether the abstract actually reflects what the article presents and provides sufficient details of the key points.[2] Make sure that it concerns a subject that you understand. Read it in full for an overview of the general quality of the writing, the relevance of the study, and the quality of the research.[2,6]

Introduction

As a general rule, the introduction should contain two to three paragraphs that describe the scope of the problem and the gaps in the literature, as well as the rationale of the study.[5] The reader should be convinced that the work is original and relevant. A hypothesis that summarizes the objectives of the study is desirable.

Methods

The methods should be described in sufficient detail to enable another researcher to reproduce the study. The type/design of the study, the population evaluated, and

the inclusion/exclusion criteria, as well as the primary and secondary outcomes, should be presented.[5] The techniques used should be appropriate for the purpose of the study and capable of producing precise, reliable results. The technique employed in calculating the appropriate sample size should be described in sufficient detail for the reader to reproduce it. It is recommended to describe in detail the statistical analysis and how the hypothesis was tested. When the reviewer deems it appropriate, further analyses may be suggested. Information regarding local research ethics committee approval and informed consent (if required) should be provided in this section.

Results

The results section should reflect what was presented in the methodology, and the findings should be summarized in a clear, appropriate manner. Interpretations and speculations should be presented in the discussion rather than in the results section. The tables should be well organized, facilitating understanding of the results and analyses. In general, tables and figures should not repeat the results presented in the text.

The figures accurately reflect the quality of the article, whether it be the originality of the data presented or the manner, painstaking or otherwise, by which the figures were constructed. Make sure that you can clearly understand the data displayed in the figures.

Discussion

In the first paragraph of the discussion, the authors are expected to summarize the main results of their study. Subsequently, they should make a critical analysis of the main results of their study, comparing them with those of previously published studies. In the penultimate paragraph, the authors should outline the limitations of the study.

Conclusions

Conclusions finalize the discussion section. The reviewer should verify that the results support the conclusions and are related to the hypothesis put forth. Future directions in relation to the topic may be included.

References

Determine whether the references cited are current and relevant. Make sure that the authors have cited original articles, rather than review articles. Verify that the references conform to the standards of the journal.

Our journal depends on a strong, active editorial board and a sufficient influx of submissions, as well as on the availability and responsiveness of reviewers. We thank all of the reviewers who have participated in the review of the manuscripts submitted. We hope that new colleagues will be able to review articles for the JBP with care and excellence, an effective peer review process being fundamental for the improvement and international recognition of our journal. If you are interested in participating as a reviewer, please contact us, making sure to mention your area of expertise. The future of the JBP is in our hands.

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Familial pulmonary fibrosis: a world without frontiers

Raphael Borie[1,a], Bruno Crestani[1,b]

There has been an incredible progress in our understanding of fibrotic lung disorders in the past 20 years. That has led to the development of well-accepted diagnostic criteria for idiopathic pulmonary fibrosis (IPF),[1,2] as well as to the development of two drugs, pirfenidone and nintedanib,[3,4] which are able to slow the progression of the disease and may improve survival. This has been shown in different clinical registries from Australia,[5] Europe,[6,7] and the United States,[8] with an acceptable tolerance profile. In the same period, rare gene mutations associated with familial pulmonary fibrosis (FPF), involving surfactant-related genes (*SFTPA1, SFTPA2, SFTPC, ABCA3*, etc.) and telomere-related genes (TRGs), such as *TERT, TERC, RTEL1, PARN, NAF1, DKC1,* and *TINF2*, have been identified. It has also been shown that the presence of a common gene polymorphism involving the *MUC5B* promoter is a major risk factor for FPF and sporadic IPF.[9] Those seminal studies, along with genome-wide association studies, allowed the genetic basis of IPF to be established.[10,11] More recent studies showed that this genetic basis was shared by non-idiopathic fibrotic lung disorders, such as chronic hypersensitivity pneumonitis,[12] interstitial pneumonia with autoimmune features,[13] and rheumatoid arthritis-associated interstitial lung disease (ILD).[14,15] In the present issue of the JBP, two groups of authors report their experience in the use of antifibrotic agents in IPF and in the characterization of FPF in Brazil.[16,17]

Although there is no consensus definition, FPF is usually defined by a family history of two or more relatives with ILD.[18] The prevalence of IPF is estimated to be 20 per 100,000 population,[19] and approximately 10% of the cases are FPF.[20] Adults with FPF are essentially indistinguishable from patients with sporadic IPF in terms of clinical presentation, radiographic findings, and histopathology, except that those with FPF tend to present it at earlier ages.[21]

In the current issue of the JBP, Hortense et al.[17] report their findings in a sample of 35 patients with FPF. All of the patients were diagnosed with fibrosing ILD and had at least one member in the family with fibrosing ILD. The patients were evaluated between 2014 and 2017. There was no gender predominance, and the median age was quite high (66 years). Smoking and environmental exposure were quite common, being reported in 45% and 80% of the cases, respectively. Among the patients, HRCT patterns were heterogeneous: typical usual interstitial pneumonia (UIP), in 6 (17%); nonspecific interstitial pneumonia, in 9 (26%); organizing pneumonia, in 3 (9%); and chronic hypersensitivity pneumonitis, in 2 (6%). When available, lung histology (n = 6) confirmed the heterogeneity of the HRCT findings. Notably, only 4 patients (11%) had hematological and/or liver disease suggestive of a TRG mutation.[17]

The study by Hortense et al.[17] confirms that patients with FPF can present with a wide variety of clinical features. For instance, a study involving 111 families with FPF compared 309 individuals with ILD with 360 unaffected relatives, revealing that the risk factors for developing ILD were male gender (55.7% vs. 37.2%; $p < 0.0001$), older age (68.3 vs. 53.1 years; $p < 0.0001$), and a history of smoking (67.3% vs. 34.1%; $p < 0.0001$).[21] In addition, a UIP pattern was highly prevalent, being identified in 85% of the patients. However, pathological heterogeneity was observed within individual families—two or more pathological patterns were identified within the affected individuals in 45% of those families, and there was evidence of UIP and nonspecific interstitial pneumonia histopathology in numerous families, suggesting that distinct ILD patterns involve similar pathogenetic pathways.[21] The identification of smoking and environmental exposure as risk factors for IPF illustrates the fundamental interaction between genetic susceptibility and environmental exposure in the development of lung fibrosis,[21] which might contribute to the heterogeneity of the pathological pattern.

An autosomal dominant mode of inheritance with incomplete penetrance is usually observed in FPF.[21] Mutations in TRGs are detected in approximately 30% of the families investigated. A younger age at diagnosis and the presence of hematologic or liver disease are associated with an increased prevalence of TRG mutations in FPF.[10] Such mutations are associated with a worse prognosis and a higher incidence of hematologic complications after lung transplantation in IPF.[22] Less frequently, there can be mutations in surfactant-related genes. In that case, ILD might improve with the use of steroids or azithromycin in children, although there is a lack of evidence of that in adults.[23] However, in most cases (60-70%), FPF remains genetically unexplained and might be related to unique, yet-to-be identified gene mutations or to non-Mendelian genetics associated with environmental risk factors. Hortense et al.[17] suggested that it is necessary to make a precise specific diagnosis for each patient, including pulmonary phenotyping together with the genetic diagnosis, in order to propose and evaluate the treatment. However, access to genetic analysis and genetic expertise is limited, which could be a limiting factor for patients suspected of having a genetic form of pulmonary fibrosis. Novel online

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communication tools might offer an answer to this difficult question. In France, we set up a web-based genetic multidisciplinary discussion (MDD) dedicated to all suspected or confirmed cases of inherited lung fibrosis, using the OrphaLung network of rare pulmonary diseases. That genetic MDD provides an opportunity to discuss cases of suspected genetic forms of lung fibrosis with experts in the interpretation of genetic data, in the monitoring of patients and their family, and in the treatment of those patients. Our genetic MDD is open to international participants. To date, 37 different ILD centers, in nine different countries, have participated and more than 150 cases have been discussed.

There is limited evidence concerning the effects of nintedanib and pirfenidone in FPF. A multicenter retrospective study conducted in Europe and including 33 patients with lung fibrosis and a *TERT* or *TERC* mutation was unable to show any effect of pirfenidone on lung function decline.[24] A post-hoc analysis of two trials identified 102 patients who were carriers of rare variants within one TRG.[25] Those patients had a more rapid decline in FVC than did the patients without a rare variant (1.66% vs. 0.83% per month), and pirfenidone reduced the decline of FVC in that subgroup of patients.[25] National and international guidelines recommend no specific treatment strategy in patients with FPF.[26-28] At our center, we discuss the use of antifibrotic treatment with nintedanib or pirfenidone for every patient with FPF. Various molecules, especially androgens, have the capacity to stimulate telomerase activity.[29] Danazol, a synthetic androgen, has been shown to increase blood leukocyte telomere length in patients with TRG mutations and hematological disorders.[29] Danazol is being tested prospectively in patients with TRG and lung fibrosis (NCT03710356). New molecules targeting the telomere homeostasis system are being developed in an attempt to focus on that specific subgroup of patients.[30]

International collaborative studies are absolutely needed to make further progress in the understanding of lung fibrosis, particularly FPF, an area for which there is a limited number of research centers. It is our shared responsibility to build, maintain, and develop worldwide networks of clinicians and scientists, using all of the modern tools of communication to share data and knowledge, in order to develop new research programs and offer the expertise that patients and their families need and deserve.

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Idiopathic pulmonary fibrosis: accurate diagnosis and early treatment

António Morais[1,2,a]

Idiopathic pulmonary fibrosis (IPF) poses the greatest diagnostic challenge in the general context of interstitial lung diseases and, in particular, regarding interstitial pneumonias.[1-4] That is due to the clinical, imaging and histological overlapping with other chronic fibrosing pneumonias in which the pattern of usual interstitial pneumonia (UIP) may occur, as in the case of chronic hypersensitivity pneumonitis or connective tissue diseases.[1,4] A Fleischner Society document[5] defines the imaging diagnosis of IPF in cases with the presence of typical UIP and advocates the same diagnosis in cases of probable UIP only when there is no clinical indicator regarding environmental exposure or autoimmunity that would suggest the presence of another chronic fibrosing pneumonia. In such cases, the diagnostic work-up should proceed with the performance of a pulmonary biopsy.[5] The rigor of that evaluation protocol aligns the document[5] with international guidelines published in 2011,[1] which also recommend a more interventional strategy involving BAL and surgical lung biopsy in cases of probable UIP. Within the investigation of differential diagnosis of IPF, as is shown in this issue of the JBP,[6] researching the family context is highly relevant because that type of fibrosis tends to have a different evolution and therapeutic response profile, so any family relationship should always be documented in the diagnosis of interstitial lung disease.

In 2014, the results of two clinical trials of two different medications, pirfenidone[7] and nintedanib,[8] demonstrated a positive impact on the evolution of IPF by significantly reducing the decline in pulmonary function as measured by FVC, compared with a placebo, over the period of 52 weeks. Those two publications endure to this day as the greatest milestone in the evolution of the therapeutic approach to pulmonary interstitial diseases. For many years, combination therapy with corticosteroids and azathioprine, based on the mistaken context of persistent inflammation leading to fibrosis, and the subsequent addition of N-acetylcysteine, based on the idea that oxidative stress is a component of anomalous healing after alveolar epithelial damage with consequent extracellular matrix deposition and fibrosis progression, was used indiscriminately, which invariably led to the progression of the disease and to a mean survival rate of three years after diagnosis.[9,10] Subsequently, it was shown that this therapy did not provide any benefits in patients with IPF, rather causing significant adverse effects because the triple-therapy arm of the study had to be stopped prematurely due to a significant number of hospitalizations and deaths compared with the other two therapeutic arms of the study (i.e. N-acetylcysteine and placebo).[11] Although the use of pirfenidone was approved in 2008 in Japan and 2011 in Europe, it was only after the study conducted by King Jr et al.[7] that its use was considered worldwide and approved in most countries, simultaneously with the use of nintedanib. At that time, patients finally had access to medications that could slow the progression of their disease, which resulted in longer survival with better quality of life, as well as greater preservation of their autonomy.

After the initial enthusiasm, doubts arose as to whether the combined use of pirfenidone and nintedanib would be beneficial to all patients with a diagnosis of IPF and whether they should be prescribed immediately after diagnosis, especially in patients that are still only mildly symptomatic and have preserved lung function. The data stratification from those trials[7,8] left no doubt about the benefit of either drug, regardless of patient characteristics (i.e. age and gender), as well as independently of the stage of the disease according to FVC and DLCO values.[12] Effectively, when comparing patients with an FVC > 90% of the predicted value with those with lower values, it was found that the decline in pulmonary function was similar. The same result was achieved with the use of pirfenidone in patients with FVC > 80% of the predicted value compared with those with an FVC < 80% of the predicted value. These results support the benefit of early treatment in order to decelerate the progression of the disease as early as possible, which would require an equally early diagnosis.[13,14] Similarly, regarding patients in more advanced stages of the disease (FVC < 50% of the predicted value), it was shown that they had a slower decline in pulmonary function, at a value that overlapped with that of patients at a better functional stage, after starting antifibrotic therapy.[15] After an initial period during which treated patients typically presented FVC between 50% and 80% of the predicted value, according to the inclusion criteria of some of the reported clinical trials, the results led to the current standard of prescribing antifibrotic therapy for any patient diagnosed with IPF and instituting that therapy as soon as possible.[16,17] Recent studies on the prolonged use (for up to four years) of pirfenidone and nintedanib[18,19] have reported that the effect of those medications was maintained over the study period, given that the decline in FVC per year was of equal dimension. The question at hand is mainly related to the potential effect that those two medications have on other chronic progressive fibrotic diseases, especially following the recent publication of results suggesting that they have the identical effect of decreasing the degree of functional deterioration.[20,21]

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In a real-life study published in this issue of the JBP, Pereira et al.[22] evaluated a select group of 57 IPF patients who benefited from a program providing free access to treatment with nintedanib, describing the safety and tolerability of the medication. The patients included in the study were diagnosed mainly based on imaging examinations, only 22.8% having undergone a surgical lung biopsy, which is in line with data in the literature. Regarding adverse effects, and corroborating previously published studies,[23,24] gastrointestinal symptoms, especially diarrhea, were the most frequently reported in 78.9% of patients, being considered severe in 22.2% of the patients. In contrast, an increase in liver function parameters was observed in only 1 patient. Adverse effects were largely responsible for permanent discontinuation of treatment in 20 patients (35.1%) and dosage reduction in 21 (36.8%). Continued publication of real-life studies from various geographical regions of the world, such as the present study,[22] has been central to acquiring an accurate understanding of the tolerance profile of antifibrotics.

In conclusion, in the current state of the art, the differential diagnosis of IPF should be made as accurately and as early as possible so that patients may have the benefit of antifibrotic therapy when they are still in an early stage of the disease.

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Multiple, small centrilobular nodules

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

A 55-year-old man sought outpatient treatment with a 6-year history of progressive dyspnea, which had worsened over the prior 4 months. A CT scan showed scattered small centrilobular nodules that were a few millimeters away from the pleural surface and fissures and did not touch them (Figure 1).

The patient had multiple, small interstitial nodules on CT. A nodular pattern refers to multiple, round pulmonary soft-tissue density opacities smaller than 3 cm. Small nodules (or micronodules) are those that are less than 1 cm in diameter. On the basis of their distribution in the lung parenchyma, they can be classified as perilymphatic, centrilobular, or random.[1]

A perilymphatic pattern is characterized by small nodules located predominantly along the peribronchovascular interstitium, interlobular septa, and subpleural regions (which contain the pulmonary lymphatics). This pattern of distribution is frequently found in sarcoidosis, silicosis, and lymphangitic carcinomatosis. A centrilobular distribution is characterized by nodules that are a few millimeters away from the pleural surface and fissures but do not touch them. Hypersensitivity pneumonitis, silicosis, and bronchiolitis are examples of diseases in which this pattern may occur. A random pattern is characterized by small nodules that are randomly distributed in the secondary lobule and uniformly scattered throughout the lungs. Nodular diseases that disseminate through the body via the bloodstream, such as metastases and miliary granulomatous diseases (especially tuberculosis and histoplasmosis), have a random pattern of distribution.

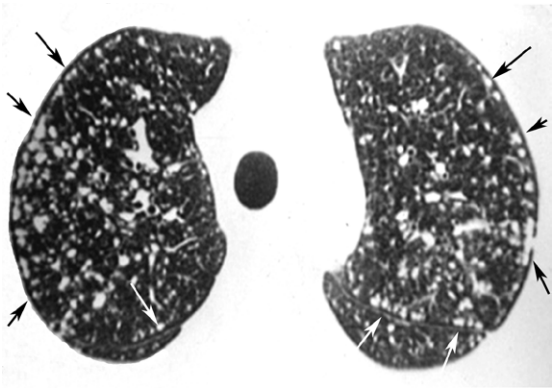

Figure 1. Axial CT scan at the level of the upper lobes, showing small soft-tissue density nodules that are distributed homogeneously throughout the lungs but do not touch the peripheral pleural surfaces (black arrows) or fissures (white arrows).

In the case described here, the nodules had a typical centrilobular distribution, sparing the pleural surfaces. This pattern is primarily seen in silicosis, hypersensitivity pneumonitis, and some forms of bronchiolitis. In most cases, the nodules found in hypersensitivity pneumonitis and bronchiolitis exhibit ground-glass attenuation. In suspected hypersensitivity pneumonitis, a history of exposure to certain antigens usually helps establish a diagnosis. In bronchiolitis, the nodules are frequently associated with a tree-in-bud pattern, which represents centrilobular branching opacities, most pronounced in the lung periphery, resembling the budding of certain plants.[2]

In suspected silicosis, it is essential to take a complete occupational history. An occupational history of silica exposure, associated with a consistent imaging pattern, is sufficient to establish a diagnosis of silicosis, there being no need for histopathological confirmation.[3] Our patient worked as a sandblaster at a shipyard, which allowed us to establish a final diagnosis of silicosis.

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Clinical practice guidelines: how do they help clinicians and patients make important decisions about health?

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PRACTICAL SCENARIO

In 2017, a clinical practice guideline (CPG) about the use of mechanical ventilation in adult patients with acute respiratory distress syndrome (ARDS), sponsored by three medical societies, recommended the use of lower tidal volumes (4-8 mL/kg of predicted body weight) and lower inspiratory pressures (plateau pressure < 30 cmH_2O). The CPG classified this recommendation as "strong" and with "moderate confidence in effect estimates".[1]

INTRODUCTION

When clinicians and patients make health-related decisions, they should consider the potential benefits and harms of diagnostic procedures and interventions, as well as patient values and preferences. When the benefits outweigh the harms, the diagnostic procedure or intervention should be recommended, or otherwise, avoided. However, in times of information abundance, how can we facilitate this decision-making process for both clinicians and patients? CPGs offer recommendations about specific clinical questions and provide a summary of the evidence—and its quality—to help the decision making of clinicians and patients.

HOW ARE RECOMMENDATIONS MADE?

In the past, recommendations were commonly based on expert opinion, but this process was often based on low quality evidence and thus may not have represented the best choice for the patient. Since then, formal systems have been created, such as the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) system, which uses rigorous methodological processes.[2] As an example, the Brazilian Thoracic Association recently adopted GRADE as a formal approach to develop Brazilian CPGs, which will be published in the JBP.

GRADE offers a systematic approach to develop CPGs, including the formulation of clinical questions aligned with patient-centered outcomes, systematic literature review, and a structured appraisal process to evaluate the quality of the evidence, which ultimately informs the recommendations. Randomized controlled trials usually provide the highest quality of evidence, but five limitations can impact on study quality: study limitations (biases), imprecision, inconsistency across studies, indirectness of evidence, and publication bias.

The process of writing CPG recommendations is rigorous. A CPG should be clearly written to avoid ambiguity and use standard approaches. The strength of a recommendation reflects the extent to which one can be confident that the desirable effects of an intervention outweigh undesirable effects. Chart 1 shows what a strong or conditional recommendation means for clinicians, patients, and policy makers. Four key factors determine the strength of a recommendation: balance between the desirable and undesirable consequences; quality of the evidence; variability in values and preferences; and costs.

In our example, the CPG makes a strong recommendation for using low tidal volumes and inspiratory pressures for patients with ARDS, because the evidence suggests that the benefits outweigh the harms. The recommendation includes a statement about the quality of the evidence, considered moderate, implying that, although the panel recommends the intervention, they acknowledge the fact that the quality of evidence is not high and that further research is likely to have an impact on our confidence in the estimate of the effect of the intervention.

Finally, it is important to remember that recommendations from CPGs are only a guide for decision making and should always be put into context, considering patient preferences, values, and perspectives, as well as local available resources.

Chart 1. Examples of recommendations that inform patients, clinicians, and policy makers for the decision making.

	Strong recommendation	Conditional recommendation
Patients	Most informed patients would choose the recommended management, and only a minority would not accept it	Most informed patients would choose the recommended management, but many would not
Clinicians	Most patients should receive the recommended course of action	Clinicians must ensure that patients' care is in keeping with their values and preferences
Policy makers	The recommendation can be adopted as a policy in most situations	There is a need for substantial debate and stakeholder involvement

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Practical challenges of diagnosing obstruction in the presence of restriction

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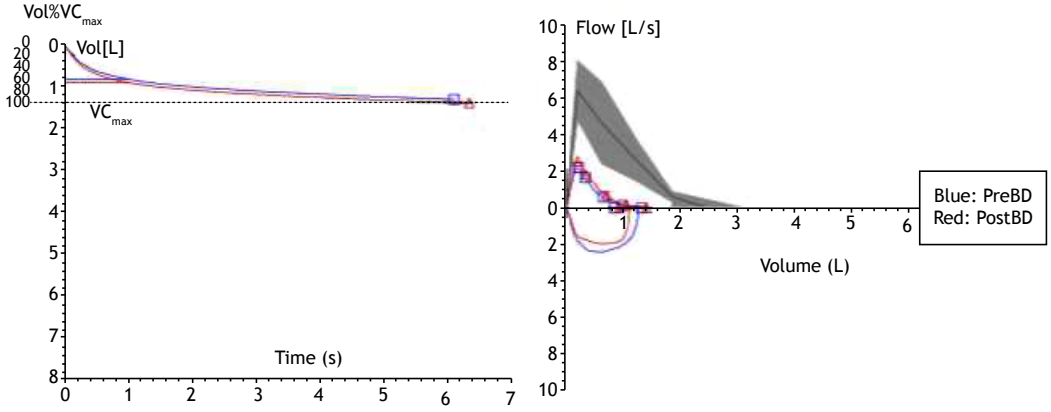
BACKGROUND

In a previous issue of this series,[1] we highlighted that fibrotic/restrictive and airway-centered/obstructive abnormalities may coexist in individual patients, leading to flows and volumes within the "normal" range. If the functional consequences of the former derangements dominate over the latter, recognizing obstruction might be even more challenging.

OVERVIEW

A 77-year-old, obese—body mass index (BMI) = 34.1 kg/m^2—woman with COPD (smoking history, 30 pack-years) was referred by her family physician to the respiratory clinic due to persistent dyspnea (modified Medical Research Council scale score = 3) despite therapy with inhaled long-acting β_2 agonist/inhaled corticosteroid (LABA/ICS). Her medical history included childhood asthma, pulmonary tuberculosis, poorly-controlled systemic hypertension, bioprosthetic aortic valve replacement due to severe stenosis, and atrial fibrillation. Spirometry showed an obstructive ventilatory defect pre- and post-bronchodilator (⇓FEV_1/FVC) with a moderate-to-severe reduction in FVC and FEV_1 (Figure 1A). Body plethysmography revealed associated restriction (⇓TLC) with a high RV/TLC ratio (Figure 1B). At the end of a six-minute walk test (100 m), she presented with severe dyspnea (Borg scale, 8/10) and high RR (32 breaths/min). Chest CT uncovered extensive fibrotic lesions and atelectasis, as well as severe cardiomegaly in association with emphysema (Figure 1C).

A



B

Spirometry		PreBD	LLN	ULN	Z-score	%pred	PostBD	%pred	ΔL	Δ%
FVC	L	1.32	1.85	3.13	-1.83	53	1.41	57	0.09	6.82
FEV_1	L	0.85	1.31	2.53	-1.76	44	0.93	48	0.08	9.40
FEV_1/FVC	%	64.13	69.27	86.27	-1.60	82	65.68	84	1.55	2.42
PEF	L/s	2.21	4.80	8.01	-2.62	34	2.54	40	0.34	15.23
MMEF25-75%	L/s	0.42	1.06	2.66	-1.80	23	0.47	25	0.005	11.07

Plethysmography										
TLC	L	2.96	3.47	5.63	-2.89	65	2.82	62	-0.14	-4.69
RV	L	1.67	1.39	2.94	-1.25	77	1.34	62	-0.32	-19.27
ITGV	L	1.76	1.54	3.66	-1.55	68	1.72	66	-0.04	-1.99
CI	L	1.20	1.09	2.00	-1.48	78	1.10	71	-0.10	-8.64
RV/TLC	%	56.20	35.38	57.38	1.75	121	47.60	103	-8.60	-15.30

Figure 1A and B. In A and B, pulmonary function test results showing a mixed ventilatory defect in a 77-year-old obese female with severe dyspnea despite pharmacological therapy for asthma/COPD. PreBD: pre-bronchodilator; PostBD: post-bronchodilator; LLN: lower limit of normality; ULN: upper limit of normality; pred: predicted; ΔL: difference between PostBD and PreBD in liters; Δ%: difference between PostBD and PreBD in %; MMEF: maximal mid-expiratory flow; ITGV: intrathoracic gas volume (functional residual capacity by plethysmography); and IC: inspiratory capacity.

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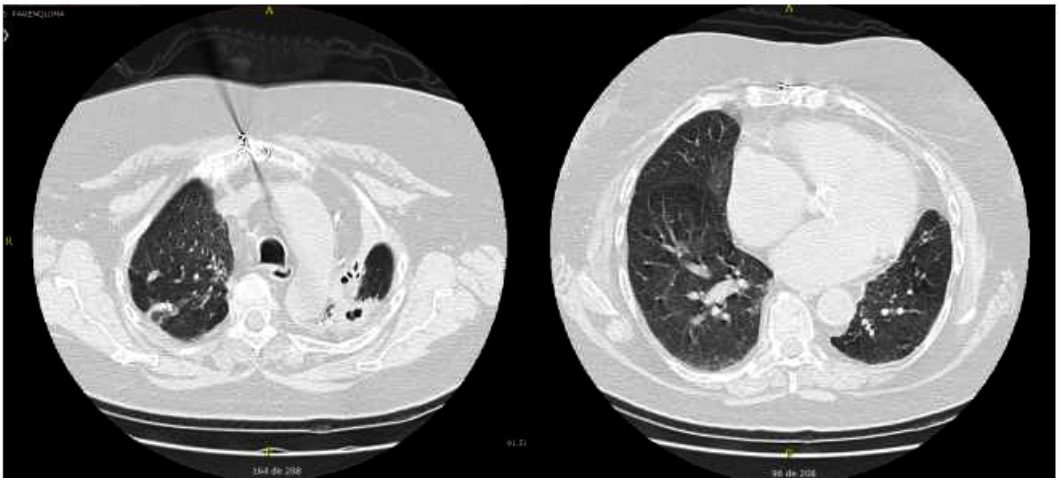

Figure 1C. In C, CT scans of the chest demonstrated centrilobular emphysema coexisting with fibrotic lesions and atelectasis, mainly in the left upper lobe (left scan), and cardiomegaly (right scan).

Low VC in a patient with airflow limitation more commonly reflects a larger increase in VC's "floor" (RV) than in VC's "ceiling" (TLC). In the appropriate clinical scenario, however, this can be ascribed to a coexistent restriction, i.e., a low "ceiling".[2] In the present case, a relatively small difference between FVC% (% of predicted) and FEV_1% (e.g., < 12%),[3] as well as an FVC% < 85% and an FEV_1/FVC ratio ≥ 55%,[4] might have raised the suspicion of associated restriction—which was confirmed by plethysmography. High BMI, chronic scarring, atelectasis, and cardiomegaly[5] might have all contributed to the restrictive defect. Care should be taken, however, that restriction *per se* may increase RV/TLC, because increased lung elastic recoil decreases TLC to a greater extent than it decreases RV. Thus, a high RV/TLC does not necessarily indicate air trapping.[2] A persistently low FEV_1/FVC ratio associated with a 320-mL decrease in post-bronchodilator RV in a heavy smoker provided further clues that, in this case, a high RV/TLC did represent air trapping.

Regardless of the etiology, patients showing a mixed defect are particularly prone to reporting exertional dyspnea: TLC minus functional residual capacity difference—i.e., inspiratory capacity (IC)—represents the limit for tidal volume (V_T) expansion on exertion. The IC of the patient was only 1.20 L (2.96-1.76 L): dyspnea ensues whenever V_T is a too large a fraction of IC (> 0.7).[6] It follows that reaching a V_T as low as ~0.8 L would be enough to elicit severe dyspnea: this explains her severe exercise intolerance and tachypnea despite the treatment with inhaled LABA/ICS..

CLINICAL MESSAGE

A decrease in VC in patients with airflow limitation might reflect air trapping or a mixed ventilatory defect. The latter is confirmed by FEV_1/(F)VC and TLC below the 5th percentile of predicted values.[2] A detailed clinical history and physical examination combined with chest imaging usually point to the underlying mechanism(s).

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Effects of the implementation of a hand hygiene education program among ICU professionals: an interrupted time-series analysis

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ABSTRACT

Objective: To evaluate the effects that a hand hygiene education program has on the compliance of health professionals in an ICU. **Methods:** This was a quasi-experimental study with an interrupted time-series design, conducted over a 12-month **period:** the 5 months preceding the implementation of a hand hygiene education program (baseline period); the 2 months of the intensive (intervention) phase of the program; and the first 5 months thereafter (post-intervention phase). Hand hygiene compliance was monitored by one of the researchers, unbeknownst to the ICU team. The primary outcome measure was the variation in the rate of hand hygiene compliance. We also evaluated the duration of mechanical ventilation (MV), as well as the incidence of ventilator-associated pneumonia (VAP) at 28 days and 60 days, together with mortality at 28 days and 60 days. **Results:** On the basis of 959 observations, we found a significant increase in hand hygiene compliance rates—from 31.5% at baseline to 65.8% during the intervention phase and 83.8% during the post-intervention phase, corresponding to prevalence ratios of 2.09 and 2.66, respectively, in comparison with the baseline rate ($p < 0.001$). Despite that improvement, there were no significant changes in duration of MV, VAP incidence (at 28 or 60 days), or mortality (at 28 or 60 days). **Conclusions:** Our findings indicate that a hand hygiene education program can increase hand hygiene compliance among ICU professionals, although it appears to have no impact on VAP incidence, duration of MV, or mortality.

Keywords: Hand disinfection; Health personnel; Pneumonia, ventilator-associated; Respiration, artificial; Guideline adherence.

INTRODUCTION

Healthcare-associated infections (HAIs) are recognized as a major problem among inpatients, prevalence rates of 6.4-8.7% having been reported in North America and Europe.[1,2] Ventilator-associated pneumonia (VAP) is one of the most common HAIs, being the most common among ICU patients.[3] VAP increases the duration of mechanical ventilation (MV) and the length of hospital stay, resulting in increased costs.[4] Mortality rates are high among patients with VAP, ranging from 20% to 50%, although it is impossible to determine the extent to which VAP alone accounts for these rates.[5,6]

Measures to prevent VAP include the use of noninvasive ventilation in an attempt to avoid endotracheal intubation; the use of protocols to evaluate the possibility of daily sedation interruption and ventilator weaning; keeping the head of the bed elevated; the use of silver nitrate-coated catheters or tubes with increased sealing capacity to allow subglottic secretion drainage; and providing oral care with chlorhexidine, selective oropharyngeal/digestive decontamination, or a combination of the two.[7,8]

Although none of the care bundles specifically designed to prevent VAP include proper hand hygiene by health care workers, it is generally recommended for infection prevention,[9] given that transmission of pathogens from one patient to another via the hands of health care workers plays an important role in the pathogenesis of HAIs (including VAP).[10] Although the importance of proper hand hygiene has been established, compliance rates remain low.[11] Studies have shown that educational measures are effective in increasing compliance rates and reducing infection rates.[12,13] However, these results are difficult to extrapolate because interventions, observation periods, ICU characteristics, and ICU staff characteristics vary across studies. In addition, few studies have evaluated the impact that a hand hygiene education program alone has on VAP incidence. We hypothesized that such a program might increase hand hygiene compliance and, consequently, reduce the incidence of VAP. To test this hypothesis, we conducted the present study in the ICU of a teaching hospital.

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METHODS

This was a quasi-experimental study with an interrupted time-series design, conducted between January and December of 2016 in the ICU of the *Hospital Universitário da Universidade Federal de Juiz de Fora* (HU-UFJF, Federal University of Juiz de Fora University Hospital), located in the city of Juiz de Fora, Brazil. The HU-UFJF is a 150-bed teaching hospital, and the HU-UFJF ICU is a 9-bed medical-surgical ICU for adult patients. The present study was approved by the Research Ethics Committee of the HU-UFJF.

Nosocomial infection control measures already in place in the HU-UFJF ICU included contact isolation (masks, caps, and gowns being worn for contact with patients from whom methicillin-resistant *Staphylococcus aureus* [MRSA], vancomycin-resistant *Enterococcus faecalis*, or multidrug-resistant gram-negative bacilli were isolated) and implementation of a VAP prevention bundle including the following: keeping the head of the bed elevated; evaluating the possibility of daily sedation interruption and ventilator weaning; providing oral care with chlorhexidine; and prophylaxis of acute gastroduodenal mucosal injury and deep vein thrombosis.

Procedures

From June to July of 2016, all health care workers and students in the HU-UFJF ICU participated in a hand hygiene education program. The program consisted of weekly sessions attended by groups of up to eight individuals. During the sessions, the following topics were discussed: the importance of HAIs; the incidence of HAIs in the HU-UFJF ICU; the importance of cross-transmission of HAIs; the role of proper hand hygiene as a preventive measure; and how often health care workers and students in the ICU performed hand hygiene, as well as when they should do it and how to do it correctly. After the first two months, monthly sessions were held from August to December of 2016). During the sessions, the aforementioned topics were discussed again and data on hand hygiene compliance and HAI incidence rates were presented and discussed with participants.

Hand hygiene compliance monitoring

Hand hygiene compliance was monitored by one of the researchers, unbeknownst to the ICU team. The following hand hygiene practices were surveyed: 1. hand hygiene before direct contact with patients (even when gloves are worn); 2. hand hygiene after direct contact with patients (including hand hygiene after glove removal); 3. hand hygiene before performing aseptic procedures (before handling an invasive device for patient care, with or without gloves); 4. hand hygiene after body fluid exposure risk (after contact with body fluids/excretions, mucous membranes, nonintact skin, or wound dressings and if moving from a contaminated body site to another body site during care of the same patient); and 5. hand hygiene after contact with inanimate surfaces and objects (including medical equipment) in the immediate vicinity of the patient. The observer recorded all hand hygiene opportunities (defined by the presence of one or more of the aforementioned indications for hand hygiene) and whether or not it was performed. Hand hygiene was performed by washing hands with soap and water or by using an alcohol-based hand rub. Compliance rates were calculated by dividing the number of times ICU personnel performed hand hygiene by the number of hand hygiene opportunities. The quality of hand hygiene (performed by washing hands with soap and water or by using an alcohol-based hand rub) was not evaluated. Hand hygiene opportunities were recorded for each staff category, including physicians, nurses, physiotherapists, nursing technicians, students, and other health care workers.

Hand hygiene compliance was monitored by one of the researchers over 2-h periods randomly distributed through the week. Hand hygiene compliance was monitored over a 12-month period: the 5 months preceding the implementation of the hand hygiene education program (baseline period); the 2 months of the intensive (intervention) phase of the program; and the first 5 months thereafter (post-intervention phase).

Outcomes

The primary outcome measure was the variation in the rate of hand hygiene compliance. A secondary outcome measure was the variation in the rate of hand hygiene compliance by staff category (physicians, nurses, physiotherapists, nursing technicians, students, and other health care workers). We also evaluated the incidence of VAP (expressed as the number of episodes per 1,000 ventilator-days), the proportion of patients who developed VAP, and the duration of MV (number of days off MV over a 28-day period), as well as 28-day and 60-day mortality rates for the baseline period and the post-intervention phase. In patients who had been on MV for at least 48 h, VAP was diagnosed on the basis of a chest X-ray finding of a new or progressive infiltrate, accompanied by at least two of the following findings: fever or hypothermia (i.e., a body temperature above 37.8°C or below 36.0°C); leukocytosis or leukopenia (i.e., leukocytes > 12,000/mm^3 or < 4,000/mm^3); and purulent tracheal secretions, confirmed by semiquantitative culture of tracheal aspirate showing growth of potentially pathogenic bacteria.[4]

Statistical analysis

Data are presented as means and standard deviations, medians and interquartile ranges, or proportions, depending on their characteristics and distribution (Shapiro-Wilk test and visual analysis of the distribution histogram). Between-group differences were assessed by the independent sample t-test, the Mann-Whitney U test, the chi-square test, or Fisher's exact test, as appropriate. Kaplan-Meier analysis was performed in order to compare mortality and VAP incidence at 60 days between the baseline period and

the post-intervention phase, distribution differences being assessed by the log-rank test.

Generalized estimating equation models adjusted for correlated data were used in order to estimate prevalence ratios, with opportunities × bed as clusters, a Poisson family distribution, and a log link function. Robust variance estimation was used, an independent correlation structure being assumed. For compliance rates by staff category and for prevalence rates (presented as a graph), the same type of model was used with an interaction term for professionals × observation period (baseline, intervention, and post-intervention). All statistical estimates and tests performed by this model are presented in graph form. All tests were performed with the Statistical Package for the Social Sciences, version 13 (SPSS Inc., Chicago, IL, USA), and MedCalc, version 17.8.6 (MedCalc Software, Mariakerke, Belgium).

RESULTS

During the study period, 324 patients were admitted to the HU-UFJF ICU: 142 at baseline, 51 during the intervention phase, and 131 during the post-intervention phase. Of those 324 patients, 130 required MV and were therefore at risk of developing VAP: 57 at baseline, 17 during the intervention phase, and 56 during the post-intervention phase. Table 1 shows the baseline demographic and clinical characteristics of the patients on MV admitted before and after the implementation of the hand hygiene education program.

A total of 959 hand hygiene opportunities were observed over the course of 42 2-h periods. Of those 959 opportunities, 419 (43.7%) were observed before the implementation of the program, 114 (11.9%) were observed during the program, and 426 (44.4%) were observed after the implementation of the program. Nursing technicians accounted for 41.2% of all opportunities; physicians, nurses, students, physiotherapists, and other health care workers accounted for 24.5%, 14.3%, 6.5%, 6.3%, and 7.3%, respectively. There was a progressive and significant increase in hand hygiene compliance rates—from 31.5% at baseline to 65.8% during the intervention phase and 83.8% during the post-intervention phase, corresponding to prevalence ratios of 2.09 and 2.66, respectively, in comparison with the baseline rate (Table 2). Although sample size was not calculated, the statistical power of the study was 100% for a significance level of 5% and an 84% increase in compliance. However, this should be interpreted with caution because of the possibility of type II errors (even with a null probability).

The same behavior was observed when we analyzed the rates for each staff category. Post-intervention compliance rates were significantly higher than baseline compliance rates for all health care workers in the ICU except physiotherapists; however, their baseline compliance rates were already high (Figure 1).

There were no significant differences between the baseline period and the post-intervention phase regarding VAP incidence, VAP at 28 days, or VAP at 60 days. In addition, there were no significant differences between the baseline period and the post-intervention phase regarding mortality at 28 days, mortality at 60 days, or the number of days off MV over a 28-day period in the ICU (Table 3). The Kaplan-Meier curves for mortality and VAP incidence showed no differences between the two observation periods (Figure 2).

DISCUSSION

Our hand hygiene education program resulted in a significant increase in hand hygiene compliance during

Table 1. Baseline and post-intervention characteristics of admitted patients.[a]

Characteristic	Baseline (n = 57)	Post-intervention (n = 56)	p
Age, years	63.0 [28.5]	57.0 [17.0]	0.73
Male sex	31 (54.4)	35 (62.5)	0.38
SAPS II	50.3 ± 19.8	51.9 ± 18.4	0.65
SOFA	9 [9]	9 [5]	0.94
Indication for ICU admission, N (%)			0.20
Clinical indication	32 (57.1)	26 (46.4)	
Elective surgery	22 (38.6)	26 (46.4)	
Urgent surgery	3 (5.3)	4 (7.2)	
Comorbidities			
Hypertension	27 (47.4)	28 (50.0)	0.78
Diabetes	13 (22.8)	8 (14.3)	0.24
COPD	7 (12.3)	8 (14.3)	0.75
Heart failure	9 (15.8)	7 (12.5)	0.62
Kidney failure	6 (10.5)	11 (19.6)	0.17
Active cancer	14 (24.6)	13 (23.2)	0.87
Immunodeficiency	13 (22.8)	12 (21.4)	0.86

SAPS: Simplified Acute Physiology Score; and SOFA: Sequential Organ Failure Assessment. [a]Values expressed as median [interquartile range], n (%), or mean ± SD.

the study period. However, it had no impact on VAP incidence, duration of MV, or mortality.

Transmission of pathogens from one patient to another via the hands of health care workers plays an important role in the pathogenesis of HAIs.[14,15] For this reason (and because hand hygiene compliance rates are low), the World Health Organization (WHO) published in 2009 guidelines for implementing and evaluating hand hygiene education programs in health care facilities.[11] The 2009 WHO guidelines recommend five strategies: availability of hand hygiene products at the bedside or for health care professionals to carry with them; educational programs for health care professionals; (verbal and written) reminders in the workplace; performance feedback; and support from the hospital administration in order to encourage staff involvement.

Table 2. Prevalence ratios for hand hygiene compliance during the observation periods.

Observation period	PR	95% CI	p
Baseline	1		
Intervention phase	2.09	2.22-3.19	< 0.0001
Post-intervention phase	2.66	1.52-2.86	< 0.0001

PR: prevalence ratio. Results obtained by a repeated-measures Poisson model.

Several studies have evaluated the efficacy of the 2009 WHO guidelines[11] or the effects of some of the guideline components on different outcomes. In 2017, Gould et al.[12] published a systematic review of 26 studies, including randomized and uncontrolled studies, examining the effects of strategies to improve adherence to hand hygiene recommendations. They concluded that programs including all five strategies recommended in the WHO guidelines[11] and those including some but not all of the recommended strategies can increase hand hygiene compliance, the level of evidence being low. Of the studies evaluating programs including all five strategies recommended in the WHO guidelines, only 1 was a randomized study, having shown a 6.3% difference in hand hygiene compliance between the intervention and control groups. Four other randomized studies evaluated programs including some but not all of the strategies recommended in the WHO guidelines, and a meta-analysis of the results of those studies showed increased hand hygiene compliance in the intervention groups (OR = 1.19; 95% CI: 1.01-1.42).

In a systematic review employing less stringent inclusion criteria, Luangasanatip et al.[13] found 6 randomized studied and 25 uncontrolled studies. Of the 6 randomized studies, 2 were included in a

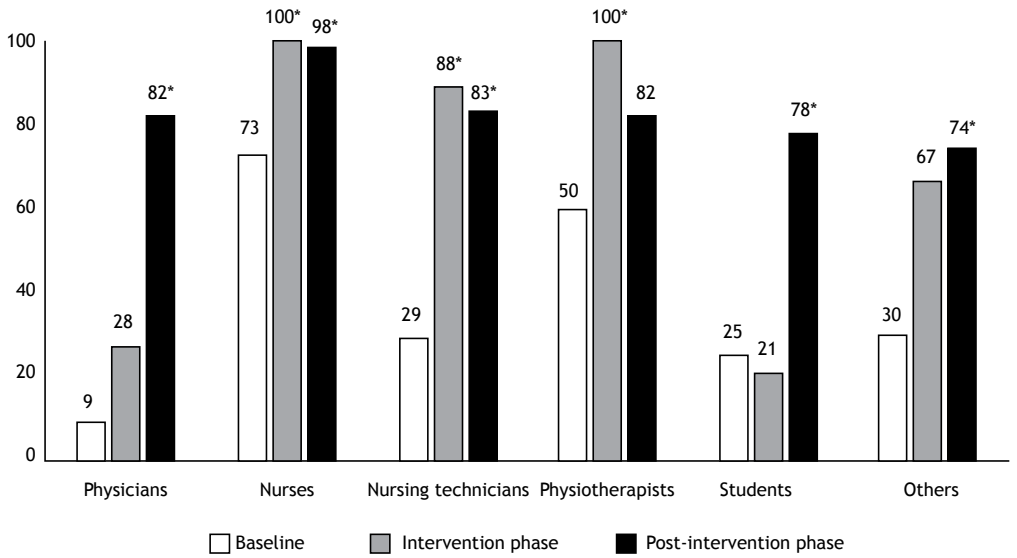

Figure 1. Prevalence rates for hand hygiene compliance in the ICU during the observation periods. *p < 0.05 vs. baseline.

Table 3. Outcomes for patients on mechanical ventilation.[a]

Outcome	Baseline (n = 57)	Post-intervention (n = 56)	p
VAP IDR	0.011	0.012	0.39
VAP at 28 days	4 (7.0)	7 (12.5)	0.33
VAP at 60 days	8 (14.0)	11 (19.6)	0.42
Mortality at 28 days	31 (54.4)	25 (44.6)	0.30
Mortality at 60 days	34 (59.6)	33 (58.9)	0.94
Days off MV over a 28-day period	5.9 [9.9]	6.1 [10.0]	0.94

IDR: incidence density rate (per 1,000 ventilator-days); VAP: ventilator-associated pneumonia; and MV: mechanical ventilation. [a]Values expressed as absolute value (proportion) or median [interquartile range].

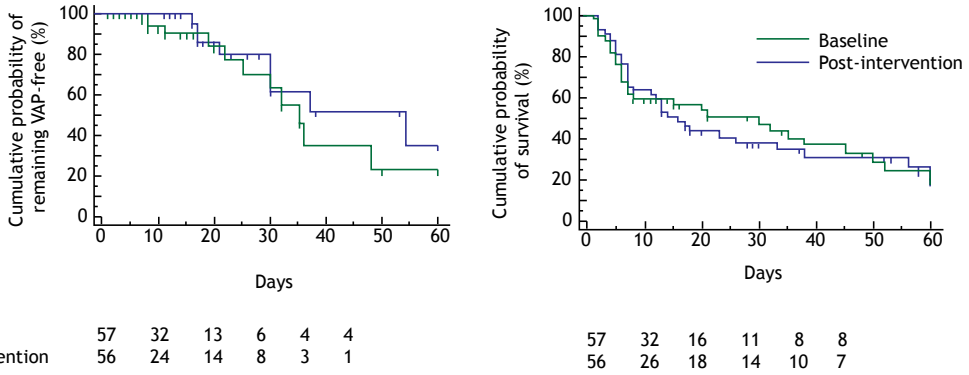

Figure 2. Kaplan-Meier curves for ventilator-associated pneumonia (VAP) and mortality at 60 days.

meta-analysis, an OR of 1.35 (95% CI: 1.04-1.76) for adherence to hand hygiene practices having been found in the intervention groups. Of the uncontrolled before-and-after studies, 18 were included in the meta-analysis, which showed a similar result, although with a wider confidence interval (OR = 1.82; 95% CI: 0.2-12.2).

Our study consisted of educational sessions, during which participants received feedback on hand hygiene compliance and ICU infection rates. One of the strategies recommended in the 2009 WHO guidelines, i.e., availability of hand hygiene products at the bedside, had been implemented in our facility before the beginning of the study. The prevalence ratios for hand hygiene compliance during and after the intervention (i.e., 2.09 and 2.66, respectively) in the present study are consistent with those found in previous studies,[16,17] which also consisted of implementing educational measures. In a randomized study conducted over the course of 12 months in 30 ICUs in Canada, implementation of an educational program resulted in an increase in hand hygiene compliance in the intervention and control groups (from 15.8% to 48.2% in the former and from 15.9% to 42.6% in the latter), corresponding to a 6.3% difference (95% CI: 4.3-8.4%).[16] In a study conducted in 100 hospitals in China and involving a hand hygiene education program, there was an absolute increase of 32.7% (95% CI: 15.6-49.7%) in the rate of compliance for hand hygiene opportunities before patient contact and of 20.4% (95% CI: 5.6-35.2%) for hand hygiene opportunities after patient contact.[17] It is difficult to compare the aforementioned results because of the specific characteristics of the ICUs evaluated in the studies, including different profiles of patients and health care professionals, with different views of hygiene practices. Therefore, interventions to increase hand hygiene compliance should be tailored to local needs and available resources. In our case, an education-based (and therefore low-cost) intervention was effective in increasing hand hygiene compliance.

Most studies evaluating clinical outcomes of strategies to increase hand hygiene compliance have found reductions in MRSA infection and colonization rates, as well as a reduction in *Clostridium difficile* infections.[18-20] Few studies have evaluated the effects of such strategies on VAP incidence. In one such study,[21] conducted in two cardiovascular surgery ICUs, an educational program combined with hand hygiene compliance monitoring and oral care resulted in a 59% reduction in VAP incidence. Although it was impossible to establish the individual impact of each measure (hand hygiene compliance monitoring and oral care), the authors found a negative correlation between hand hygiene compliance and VAP incidence ($r^2 = 0.878$; $p < 0.001$), a finding that suggests the importance of hand hygiene compliance.[21] In another study,[22] a program to increase hand hygiene compliance was implemented in 150 inpatient units in 12 hospitals. In addition to increasing compliance rates (from 58.1% to 94.7% over the course of two years), the program reduced the incidence of VAP (from 49% to 45%; $p = 0.045$).[22] Likewise, a 12-month educational program conducted in the ICU of a tertiary hospital resulted in a 75% increase in hand hygiene compliance rates and a reduction in VAP incidence (from 6.9 episodes per 1,000 ventilator-days to 3.7 episodes per 1,000 ventilator-days; $p < 0.01$).[23]

In our study, we found no association between improved hand hygiene compliance and reduced VAP incidence. This might be due to the low incidence of MRSA VAP in our ICU, hand hygiene being most effective in reducing MRSA infections. Given that gram-negative bacteria (particularly *Pseudomonas aeruginosa* and *Acinetobacter baumannii*) are the most common causes of VAP in our ICU, improved hand hygiene compliance might have had no impact on VAP incidence. Our study has limitations that might explain why improved hand hygiene compliance had no impact on VAP incidence. First, the magnitude of improvement might have been insufficient to reduce VAP incidence. Second, the periods of hand hygiene compliance monitoring and the number of patients observed might have been insufficient, resulting in limited statistical power to detect the clinical effect. Third, the observer recorded whether or not hand hygiene was performed; hand hygiene

technique was not recorded. Finally, because VAP is multifactorial, the fact that only one of the factors involved in its pathogenesis was addressed might have been insufficient to reduce VAP incidence. In addition to having had no impact on VAP incidence, improved hand hygiene compliance had no impact on mortality, duration of MV, or length of ICU stay in the present study. This might be due to the fact that our educational program had no impact on VAP incidence, as well as to the fact that the aforementioned outcomes are more closely related to the condition that led to hospitalization than to hospital-acquired infections.

The present study has other limitations that should be considered. Because our study was not a randomized controlled trial, factors other than the educational program itself might have contributed to improved hand hygiene compliance. The ICU team might have noticed the presence of the observer during the periods of hand hygiene compliance monitoring, despite the fact that the observer made an effort to go unnoticed. This might have resulted in improved hand hygiene compliance during the observation periods. Given that the present study was conducted in a single ICU, with its own epidemiological characteristics, the results obtained cannot be necessarily extrapolated to other ICUs.

In conclusion, our findings indicate that a hand hygiene education program can improve hand hygiene compliance in the ICU, although it appears to have no impact on VAP incidence, mortality, duration of MV, or length of ICU stay.

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ORIGINAL ARTICLE

Inflammatory lung injury in rabbits: effects of high-frequency oscillatory ventilation in the prone position

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ABSTRACT

Objective: To compare the effects that prone and supine positioning during high-frequency oscillatory ventilation (HFOV) have on oxygenation and lung inflammation, histological injury, and oxidative stress in a rabbit model of acute lung injury (ALI). **Methods:** Thirty male Norfolk white rabbits were induced to ALI by tracheal saline lavage (30 mL/kg, 38°C). The injury was induced during conventional mechanical ventilation, and ALI was considered confirmed when a PaO_2/FiO_2 ratio < 100 mmHg was reached. Rabbits were randomly divided into two groups: HFOV in the supine position (SP group, n = 15); and HFOV with prone positioning (PP group, n = 15). For HFOV, the mean airway pressure was initially set at 16 cmH_2O. At 30, 60, and 90 min after the start of the HFOV protocol, the mean airway pressure was reduced to 14, 12, and 10 cmH_2O, respectively. At 120 min, the animals were returned to or remained in the supine position for an extra 30 min. We evaluated oxygenation indices and histological lung injury scores, as well as TNF-α levels in BAL fluid and lung tissue. **Results:** After ALI induction, all of the animals showed significant hypoxemia, decreased respiratory system compliance, decreased oxygenation, and increased mean airway pressure in comparison with the baseline values. There were no statistically significant differences between the two groups, at any of the time points evaluated, in terms of the PaO_2 or oxygenation index. However, TNF-α levels in BAL fluid were significantly lower in the PP group than in the SP group, as were histological lung injury scores. **Conclusions:** Prone positioning appears to attenuate inflammatory and histological lung injury during HFOV in rabbits with ALI.

Keywords: Respiration, artificial/adverse effects; Prone position; Lung/physiopathology; Pneumonia; Respiratory distress syndrome, adult; Acute lung injury; Disease models, animal; Rabbits.

INTRODUCTION

Acute respiratory distress syndrome (ARDS) is a heterogeneous syndrome with complex pathology and mechanisms.[1] It is a life-threatening condition that is associated with high mortality, morbidity, and costs.[2-5] The clinical management of ARDS is essentially supportive and includes optimized protective mechanical ventilation (MV), the strategies of which should be directed at minimizing ventilator-induced lung injury, oxygen toxicity, and lung inflammation.[6] In a recent study, Amato et al.[7] found that decreases in driving pressure were strongly associated with increased survival in patients with ARDS. Therefore, high-frequency oscillatory ventilation (HFOV) is an attractive ventilatory method,[8,9] because it involves the use of a lower tidal volume (V_T, 1-3 mL/kg) with an oscillatory frequency higher than that of physiological breathing (5-10 Hz), thus avoiding volume excursions and increases in alveolar pressure. During HFOV, a constant mean airway pressure (Paw) is applied in order to achieve and maintain alveolar recruitment, even at end-expiration.[10,11]

Despite the advantages of HFOV, the results of clinical studies have not supported its routine use. The recent Oscillation for Acute Respiratory Distress Syndrome Treated Early Trial[12] was interrupted due to an increase in in-hospital mortality in the HFOV group. However, the patients in that group required more vasoactive support than did those in the control group, making it difficult to analyze the results. In two recent systematic reviews and meta-analyses, Meade et al.[13] and Goligher et al.[14] evaluated the use of HFOV in patients with ARDS. Meade et al.[13] compared HFOV with protective conventional MV (CMV) in patients with ARDS and found mortality to be greater in the HFOV group patients than in the CMV group patients, although that effect varied depending on the severity of hypoxemia, lung injury apparently being greater among patients with mild or moderate ARDS, although mortality rates seemed to be lower among patients with severe ARDS. Goligher et al.[14] also analyzed HFOV in comparison with protective CMV, one study comparing HFOV with the use of a low V_T and a high positive end-expiratory pressure (PEEP), and concluded that HFOV, used as in the studies conducted

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to date, provides no mortality benefit in comparison with protective CMV and may even be harmful in comparison with the use of a low V_T with a high PEEP.

As an adjuvant therapy, prone positioning optimizes lung recruitment and ventilation-perfusion matching.[15,16] In the prone position, lung perfusion is more evenly distributed, which improves ventilation to the dorsal areas of the lungs, thus improving perfusion.[17,18] In addition, prone positioning lessens alveolar overdistension[19] and cyclic alveolar collapse, as well as reducing ventilator-induced lung injury,[20] redirecting the compressive forces exerted by the weight of the heart on the lungs,[21] and improving the drainage of secretions.[22]

In the Prone Positioning in Severe Acute Respiratory Distress Syndrome study,[23] patients with severe ARDS who were on MV were allocated to being placed in the prone position for at least 16 consecutive hours or to remaining in the traditional supine position. The authors found that 28-day and 90-day mortality rates were lower in the prone positioning group. A subsequent meta-analysis demonstrated that, if prone positioning during MV is used for periods longer than 16 h per day and in conjunction with protective MV, it significantly reduces mortality in patients with moderate or severe ARDS.[24]

There have been few studies evaluating the effects that the combination of prone positioning and HFOV have on oxygenation, lung inflammation, and histologically confirmed damage in experimental models of acute lung injury (ALI).[25] To our knowledge, there have been no studies evaluating the regionalization of lung injury regarding histology, lung inflammation, and oxidative stress.

The hypothesis of the present study is that prone positioning combined with HFOV improves oxygenation, as well as attenuating the lung injury caused by inflammation or oxidative stress. Therefore, the objective was to compare prone and supine positioning during HFOV, in terms of the effects they have on oxygenation, lung inflammation, histological lung injury, and oxidative stress, in a rabbit model of ALI.

METHODS

Design, animals, and instrumentation

This was a prospective, randomized, in vivo animal study. Thirty male Norfolk white rabbits, weighing 2.0-3.0 kg, were obtained from the animal facilities of the São Paulo State University Botucatu School of Medicine. The rabbits were first anesthetized with intramuscular injections of ketamine (50 mg/kg) and xylazine (4 mg/kg).[26,27] Each rabbit was then ventilated with 100% inhaled oxygen during spontaneous breathing, after which the neck and thorax were shaved for placement of electrodes for heart rate monitoring. The anterior region of the neck was anesthetized with 2% lidocaine, a tracheotomy was performed, and a tracheal tube (3.0-3.5 mm diameter PORTEX tube; Smith Medical, Hythe, England) was inserted. Immediately thereafter, ventilation was initiated with a ventilator (Galileo Gold; Hamilton Medical AG, Bonaduz, Switzerland) in pressure-regulated volume control mode with the following initial parameters: FiO_2 = 1.0; V_T = 6 mL/kg; PEEP = 5 cmH_2O; and RR = 40-50 breaths/min. A 22-gauge vascular catheter (Introcan Safety; B. Braun, Melsungen, Germany) was then inserted into the common carotid artery, and a 5-French double-lumen catheter (Arrow International Inc., Reading, PA, USA) was advanced into the superior vena cava through the jugular vein. The arterial catheter was used in order to assess blood gases and arterial blood pressures with a monitoring system (LogiCal; Medex, Dublin, OH, USA) connected to a conventional physiological monitor (DX 2010; Dixtal, Manaus, Brazil). The double-lumen catheter was used for the continuous intravenous infusion of ketamine (10 mg/kg per hour) and xylazine (4 mg/kg per hour). Muscle paralysis was induced by intravenous administration of pancuronium bromide (0.2 mg/kg) and maintained with 0.1 mg/kg doses, as needed, to minimize respiratory movements and avoid disproportionate tachycardia.

During the experiment, we used continuous intravenous infusion of norepinephrine (0.5-1 μg/kg per minute) to keep the mean arterial pressure above 50 mmHg, as necessary. The need for inotropic support was determined through the use of a vasoactive-inotropic score.[28] Fluid maintenance was provided by continuous infusion of 0.9% saline solution containing 5% dextrose at 4 mL/kg per hour. Body temperature was monitored continuously by esophageal probe and was maintained at 38-39°C with electric warming pads. Continuous pulse oximetry was also performed.

The rabbits were handled with care to minimize discomfort, distress, and pain, in compliance with the Guide for the Care and Use of Laboratory Animals published by the US National Institute of Health (NIH Publication No. 85-23, 2011 revision). The study was approved by the Experimental Research and Ethics Committee of the Botucatu School of Medicine of São Paulo State University (Reference no. 795).

Lung injury induction

Lung injury was induced by surfactant lavage.[26,29] In brief, six successive lung lavages were performed with heated saline (37-38°C) in aliquots of 30 mL/kg, passed through the tracheal cannula at a maximum pressure of 30 cmH_2O, for 60 s, every 3-5 min. Drainage of the fluid was achieved by gravity, by external movements of thoracic compression, and by gentle suction. After stabilization, arterial blood samples were obtained for blood gas analysis to verify that animals were hypoxemic (PaO_2/FiO_2 ratio ≤ 100 mmHg in two analyses, 15 min apart). If the animals were still not hypoxemic, two additional lavages were performed sequentially, new blood gas analyses being performed 10 min thereafter, and so on, until the PaO_2/FiO_2 ratio reached the target value. After another stabilization period, animals were given two 30-s sustained inflations with a mean Paw of

30 cmH_2O, a dynamic maneuver intended to promote lung recruitment and normalize the volume history.[30]

Experimental groups

Using the Research Randomizer program (available at http://www.randomizer.org), we randomly divided the rabbits into two groups: ALI+HFOV in the supine position (SP group, n = 15); and ALI+HFOV with prone positioning (PP group, n = 15). At the start of the experimental period, we ventilated the animals in both groups with a SensorMedics 3100A ventilator (CareFusion, Yorba Linda, CA, USA), using the following parameters: mean Paw of 16 cmH_2O; oscillatory frequency of 10 Hz; inspiratory time of 33% of the respiratory cycle; and initial pressure amplitude of 20 cmH_2O. The pressure amplitude was modified to reach the target $PaCO_2$ range (40-45 mmHg). In both groups, the FiO_2 was maintained at 1.0 throughout the experiment.

After a 15-min stabilization period, the animals were moved into the prone position or maintained in the supine position, according to the randomization. That was designated time zero (T_0) of the experimental protocol. At 30 min, 60 min, and 90 min thereafter (T_{30}, T_{60}, and T_{90}, respectively), the mean Paw was decreased to 14, 12, and 10 cmH_2O, respectively, to avoid hemodynamic instability. At 120 min (T_{120}), all animals were returned to or remained in the supine position and were ventilated for an additional 30 min (i.e., until T_{150}). Arterial blood samples, for blood gas analysis, were obtained at baseline, after the induction of lung injury, and every 30 min throughout the 150-min observation period. Blood gas analyses were performed at the corresponding time points (baseline, ALI confirmed, T_{30}, T_{60}, T_{90}, T_{120}, and T_{150}), as shown in Figure 1.

In accordance with other studies using a similar methodology, we chose to include 15 animals in each group.[26,29] Rabbits that died before T_{150} were replaced. During the experimental period, the groups were compared regarding the mean arterial pressure (to evaluate hemodynamic stability); the PaO_2/FiO_2 ratio; and the oxygenation index—[*FiO2* × *mean Paw*] / *PaO2* × 100—expressed in cmH_2O/mmHg. At T_{150}, the rabbits were euthanized through the administration of high intravenous doses of ketamine and xylazine. The following outcome measures were then evaluated: malondialdehyde concentrations (lipid peroxidation), to quantify oxidative stress in ventral and dorsal lung tissue; proportions of neutrophils in the BAL fluid (BALF); TNF-α levels in the BALF and in lung tissue, to quantify lung inflammation; and histopathological analysis, to quantify lung tissue damage.

Tissue collection

The right lung was dissected and stored for oxidative stress analysis, and the left lung was dissected for BAL. Tissue specimens for oxidative stress study were snap-frozen in liquid nitrogen and stored at −80°C until analysis, as previously described.[26,27]

BAL

The BALF was collected, and the cells were counted in a hemocytometer. Cells were differentiated using a Romanowsky-type stain (Panótico Rápido; Laborclin, Pinhais, Brazil), and the proportion of neutrophils was assessed.

TNF-α measurement

Levels of TNF-α were measured in the BALF and lung tissue homogenates with a radioimmunoassay technique, as reported elsewhere.[31] The standards

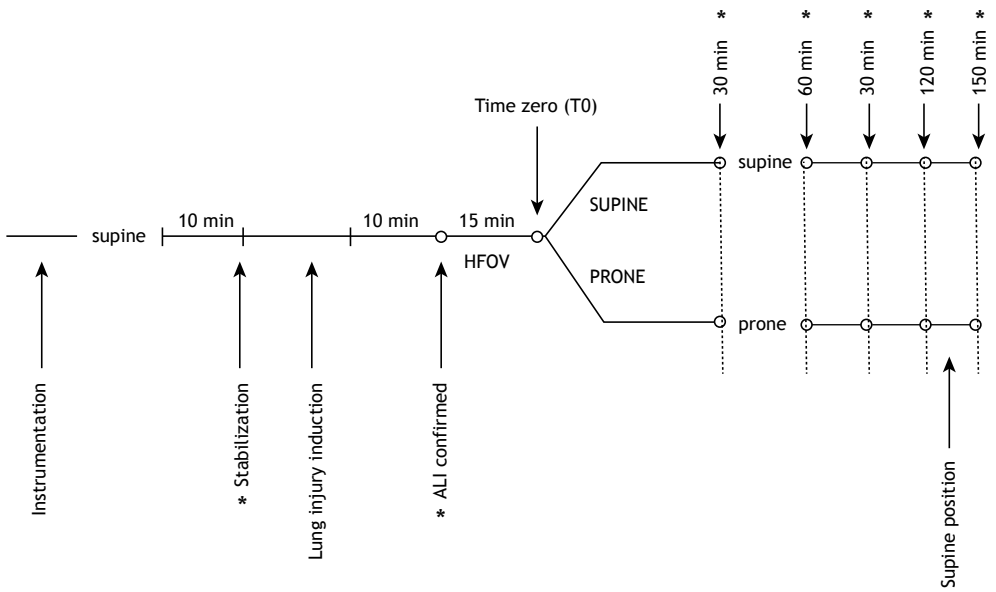

Figure 1. Experimental protocol design. ALI: acute lung injury; and HFOV: high-frequency oscillatory ventilation. *Arterial blood gas analysis.

used were a specific antiserum to human TNF-α (Caltag Laboratories, South San Francisco, CA, USA) at a dilution of 1:100,000; radiolabeled human TNF-α (New England Nuclear, Boston, MA, USA); and purified human TNF-α (Collaborative Research, Bedford, MA, USA).

Lipid peroxidation measurement

Concentrations of malondialdehyde, a marker of lipid oxidative damage, were measured in tissue homogenates by using the method devised by Esterbauer and Cheeseman.[32] Lung tissue was homogenized with 20 mM ice-cold Tris-HCl buffer, pH 7.4, at a ratio of 1 g of tissue to 10 mL of buffer. The homogenate was centrifuged at 3,000 × *g* at 4°C for 10 min. The supernatant (200 µL) was set aside and mixed with a solution containing methanol and 10.3 mM N-methyl-2-phenylindole, in acetonitrile (650 µL; Oxis International, Portland, OR, USA). The solution was acidified with 37% hydrochloric acid (150 µL) and incubated at 45°C for 60 min. Samples were again centrifuged as described above, to clarify any precipitate formed during incubation. Absorbance was measured with a spectrophotometer (DU 650; Beckman Coulter, Carlsbad, CA, USA) at 586 nm, against standard curves of 1,1,3,3-tetramethoxypropane and 4-hydroxynonenal diacetyl (Oxis International). Lung tissue measurements were indexed to lung tissue protein content.

Histopathological analysis

Lungs were filled with 10% buffered formalin, by gravity (at a maximum pressure of 30 cmH_2O), to preserve the alveolar architecture. At least 48 h after fixation, fragments were embedded in paraffin. Axial lung sections were cut, stained with H&E, and examined by two pathologists who were blinded to the groups and worked independently. For each slide, we randomly selected ten microscopic fields for examination, thus performing 20 tests per animal. Pulmonary histological damage was quantified by a score that involved seven variables: alveolar inflammation; interstitial inflammation; alveolar hemorrhage; interstitial hemorrhage; edema; atelectasis; and necrosis. For each of those seven variables, the severity was graded as follows: 0 = no injury; 1 = injury in 25% of the field; 2 = injury in 50% of the field; 3 = injury in 75% of the field; and 4 = diffuse injury. Therefore, the maximum possible score was 28.[33]

Statistical analysis

Data were analyzed with SigmaPlot, version 11.0 for Windows (Systat Software, San Jose, CA, USA). Normally distributed data were compared between the groups for the same time points by t-test or across time points by Kruskal-Wallis one-way ANOVA and are expressed as mean ± standard deviation. Data with non-normal distribution were compared by the Mann-Whitney rank-sum test and are expressed as median (range). Intragroup comparisons at different time points were performed using Friedman's repeated measures ANOVA by ranks, all pairwise multiple comparison procedures being performed by Dunn's test. Contingency tables of categorical data were compared by Fisher's exact test. Tissue analyses among groups and lung injury regions were performed through two-way ANOVA. Values of $p \leq 0.05$ were considered statistically significant.

RESULTS

There was no statistical difference between the two groups in terms of body weight ($p = 0.50$) or the number of lavages required in order to induce ALI ($p = 0.75$). The proportion of fluid recovered from the lavaged lungs was 85.7% and 86.2% in the PP and SP groups, respectively ($p = 0.49$).

There was no statistical difference in mean arterial pressure between the two groups. The animals in both groups were hemodynamically stable, the mean arterial pressure remaining above 50 mmHg due to the continuous infusion of norepinephrine, with no difference between the SP and PP groups in terms of the median vasoactive-inotropic score, which was 50 (range, 0-70) and 50 (range, 0-50), respectively ($p = 0.27$). There were three deaths during the experimental period, all of them in the SP group.

After the lavages, there was significant hypoxemia, decreased respiratory system compliance, and increased the mean Paw in the animals in both groups (Table 1), the successful induction of ALI thus being confirmed. At T_{30}, both groups showed significant improvement in oxygenation, presenting oxygenation indices similar to those seen at baseline, those indices remaining stable until T_{150} (Figure 2).

The median malondialdehyde concentrations did not differ between the PP and SP groups, whether measured in ventral lung tissue samples—8.2 nm (range, 7.7-11.4 nm) and 8.7 nm (range, 5.7-13.6 nm), respectively ($p = 0.62$)—or in dorsal lung tissue samples—7.4 nm (range, 5.9-0.8 nm) and 8.1 nm (range, 7.1-9.5 nm), respectively ($p = 0.62$). The mean proportion of neutrophils in the BALF was lower in the PP group than in the SP group (16 ± 14 vs. 25 ± 18), although the difference was not significant ($p = 0.76$). However, the TNF-α levels in the BALF and lung tissue were significantly lower in the PP group than in the SP group (Figure 3), and that difference was greater in the dorsal lung tissue samples. The histological lung injury score was also significantly lower in the PP group than in the SP group (Figure 4).

DISCUSSION

The results of the present study support those of previous studies, namely, that HFOV per se improves oxygenation and has a protective effect against histological and inflammatory lung injury. In addition, when HFOV was combined with prone positioning in this animal model of ALI, we observed better protection against the inflammatory response, as evaluated by determining TNF-α levels, as well as lower histological injury scores. Despite the lower

Table 1. Oxygenation indices, pulmonary mechanics, and hemodynamic data, at baseline and after induction of lung injury.[a]

Parameter	Group			
	Supine position		Prone position	
	Baseline	After lung injury	Baseline	After lung injury
PaO2/FiO2 (mmHg)	447.6 (364.18-492.75)	72.1 (52.08-86.18)*	481.7 (428.37-493.88)	64.5 (48.25-81.88)*
OIb (cmH2O/mmHg)	1.5 (1.41-2.06)	13.7 (11.21-21.15)*	1.44 (1.38-1.74)	14.7 (11.8-21.26)*
Crs (mL/cmH2O)	3.3 (3.1-3.68)	1.2 (1.0-1.3)*	3.8 (2.83-4.4)	1.2 (1.0-1.38)*
Mean Paw (cmH2O)	7.0 (6.9-7.1)	10.0 (9.5-11.0)*	7.04 ± 0.5	9.75 ± 0.63*

OI: oxygenation index; Crs: respiratory system compliance; and Paw: airway pressure. [a]Results expressed as mean ± SD for data with normal distribution and as median (range) for data with non-normal distribution. [b]Calculated as [*FiO2* × *mean Paw*] / *PaO2* × 100. *p < 0.05 vs. after lung injury; Kruskal-Wallis one-way ANOVA for data with normal distribution and Mann-Whitney rank-sum test for data with non-normal distribution.

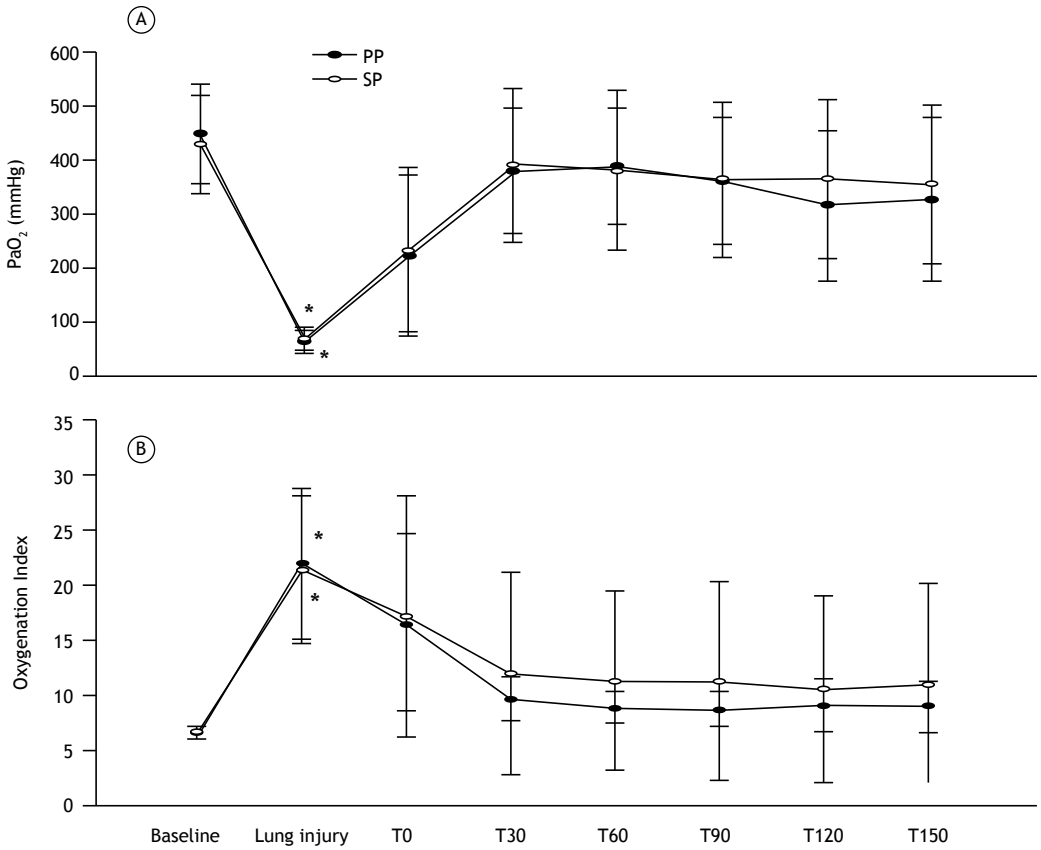

Figure 2. PaO_2 and oxygenation index[a] over time (A and B, respectively) in the experimental groups.[b] PP: prone position group (filled ovals); SP: supine position group (open ovals); T_0: time zero; T_{30}: 30 min; T_{60}: 60 min; T_{90}: 90 min; T_{120}: 120 min; and T_{150}: 150 min. [a]Calculated as [*FiO2* × *mean Paw*] / *PaO2* × 100. [b]Values expressed as mean ± SD. *p ≤ 0.05 vs. baseline.

numbers of inflammatory cells in the BALF in the PP group, the difference in comparison with the SP group was not significant.

It has been known for decades that prone positioning improves oxygenation in animal models of lung injury and in patients with severe ARDS. The mechanisms of that improvement include a more uniform pleural-pressure gradient and less compression of the lung by the heart, as well as more uniform distribution and better matching of ventilation and perfusion.[34] In addition to those physiological effects, we found that, in the prone position, there were structural changes within the lungs; that is, the dorsal lung areas were preserved regarding histological and inflammatory injury.

A previous study performed by our group showed that HFOV plays a major protective role in ALI, improving oxygenation, minimizing inflammatory processes, reducing histological damage, and attenuating oxidative lung injury, proving superior to protective CMV in those aspects.[29] Likewise, a study conducted by Liu et al.[35] showed that HFOV at a relatively high oscillatory frequency attenuated lung injury in an ovine model of ARDS. In that study, HFOV at an oscillatory frequency of 9 Hz minimized lung stress and V_T, resulting in less lung injury and lower levels of inflammatory mediators

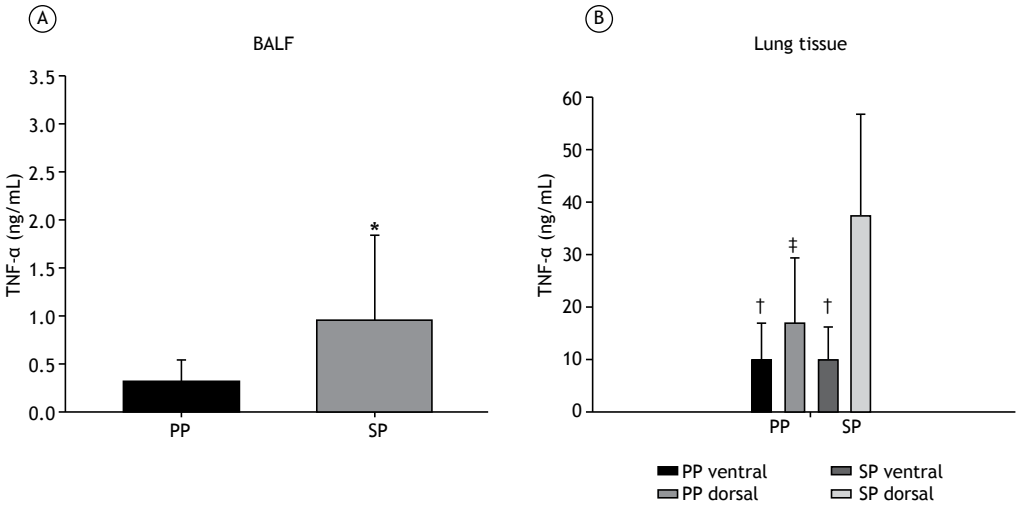

Figure 3. TNF-α levels in BAL fluid (BALF) and lung tissue (A and B, respectively),[a] the latter comparing ventral and dorsal lung tissue samples, in the prone position (PP) and supine position (SP) groups. [a]Values expressed as mean ± SD. *p ≤ 0.05 vs. PP group. †p > 0.05 vs. dorsal lung tissue in the PP group. ‡p ≤ 0.05 vs. dorsal lung tissue in the SP group.

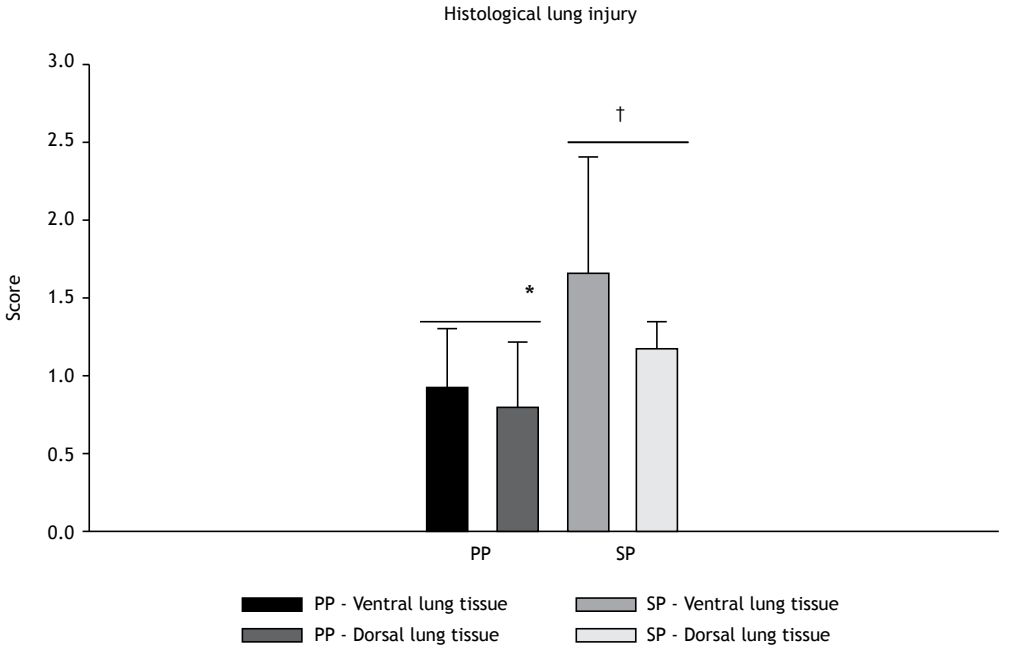

Figure 4. Histological lung injury scores in the supine position (SP) and prone position (PP) groups, including comparisons between scores for ventral and dorsal lung tissue samples.[a,‡] [a]Values expressed as median (range). *p < 0.05 vs. ventral lung tissue (Mann-Whitney rank-sum test). †p < 0.05 vs. PP group (Mann-Whitney rank-sum test). ‡p > 0.05 for interactions among lung regions and positioning (Kruskal-Wallis ANOVA, followed by Dunn's test).

than those observed when HFOV at an oscillatory frequency of 3 Hz or CMV was employed.

In a prospective randomized clinical study involving patients with ARDS,[36] the authors analyzed oxygenation by calculating the PaO_2/FiO_2 ratio and oxygenation index, analyzing lung inflammation by determining serum and BALF levels of cytokines, as well as by cytological examination of the BALF cytology. The authors concluded that prone positioning during CMV or HFOV improved oxygenation in comparison with supine positioning throughout HFOV. In addition, they found that prone positioning during HFOV reduced serum levels of IL-8 and the proportion of neutrophils in the BALF, indicating decreased lung inflammation. Those data were confirmed by our findings, which showed that, in the dorsal lung tissue, the inflammatory response, as evaluated by determining TNF-α levels, was less pronounced in the PP group than in the SP group.

In the present study, the proportion of neutrophils in the BALF did not differ significantly between the

two groups, although there was a trend toward lower values in the PP group. It is possible that the proportion of neutrophils was higher in the SP group because of greater damage occurring in the dorsal lung tissue during ALI induction. That suggests that prone positioning was protective against inflammatory lung injury. The fact that our findings did not reach statistical significance was likely due to the short MV period. Regarding the assessment of lung inflammation, we found that TNF-α levels in the BALF were lower, probably indicating less inflammatory injury, in the PP group than in the SP group, as were TNF-α levels in homogenates of lung tissue samples from the ventral and dorsal regions. However, TNF-α values for the ventral and dorsal regions were comparable within the PP group. Similar results were observed by Fu et al.,[37] who induced ALI in newborn piglets that were subsequently ventilated for 24 h. The authors observed that, among the piglets with ALI, histological lung injury was more severe in the gravity-dependent region than in the non-gravity-dependent region, as well as that different ventilation strategies resulted in different effects on the injured lungs. Despite improving oxygenation, HFOV with a high lung volume strategy was found to attenuate lung injury by reducing pulmonary infiltration by polymorphonuclear cells, hemorrhage, alveolar edema, and hyaline membrane formation, to a greater degree than did CMV.[37]

In a study involving patients with severe community-acquired pneumonia and ARDS on protective CMV, Chan et al.[38] showed that oxygenation was better and levels of IL-6 were significantly lower in the patients who were ventilated in the prone position than in those who were ventilated in the supine position. Similarly, in an early study of ARDS, Rival et al.[39] found that a recruitment maneuver and prone positioning probably have combined effects, as well as showing that the recruitment maneuver probably improved PaO_2 to a greater degree when the patients were in the prone position, especially if they remained in that position for an extended period of time.

Our study has some limitations. One is the fact that it was an experimental study, given that animal models cannot replicate all of the characteristics of ALI/ARDS in humans.[40] In addition, because of the risk of hemodynamic instability, ventilation time is limited in rabbit models of ALI. In the present study, rabbits were ventilated for only two hours, and it was therefore difficult to apply the ideal HFOV and time in the prone position to achieve the anti-inflammatory effect and decrease the lesion. Furthermore, we evaluated prone positioning only during HFOV. There is a need for longer-term studies involving groups of healthy, nonventilated animals (controls) and groups of animals ventilated with CMV, as well as for clinical studies evaluating outcomes in patients treated with these combination strategies.

In conclusion, our findings corroborate those of previous studies showing that HFOV improves oxygenation and has a protective effect against the inflammatory response and histological lung damage in models of lung injury. In addition, our data underscore the major protective role played by prone positioning. In this model of ALI in rabbits subsequently undergoing HFOV, in which we compared gravity-dependent and non-gravity-dependent lung regions, prone positioning was found to minimize inflammatory processes and histological damage.

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Familial pulmonary fibrosis: a heterogeneous spectrum of presentations

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ABSTRACT

Objective: To describe the clinical, functional, and radiological features of index cases of familial pulmonary fibrosis (FPF) in Brazil. **Methods:** We evaluated 35 patients with FPF - of whom 18 (51.4%) were women - with a median age of 66.0 years (range, 35.5-89.3 years). All of the patients completed a standardized questionnaire, as well as undergoing pulmonary function tests and HRCT of the chest. In 6 cases, lung tissue samples were obtained: from surgical biopsies in 5 cases; and from an autopsy in 1 case. **Results:** A history of smoking and a history of exposure to birds or mold were reported in 45.7% and 80.0% of the cases, respectively. Cough and marked dyspnea were reported by 62.8% and 48.6% of the patients, respectively. Fine crackles were detected in 91.4% of the patients. In 4 patients, the findings were suspicious for telomere disease. The median FVC and DLCO, as percentages of the predicted values, were 64.9% (range, 48.8-105.7%) and 38.9% (range, 16.0-60.0%), respectively. Nine patients had reduced DLCO despite having normal spirometry results. Regarding HRCT, patterns typical of usual interstitial pneumonia were found in 6 patients (17.1%). In 25 cases (71.5%), the HRCT features were consistent with a diagnosis other than idiopathic pulmonary fibrosis. In 11 cases (31.4%), the radiological patterns were uncharacteristic of interstitial lung disease. Of the six lung tissue samples analyzed, four showed interstitial pneumonia with bronchiolocentric accentuation, and, on the basis of the clinical and radiological data, the corresponding patients were diagnosed with hypersensitivity pneumonitis. **Conclusions:** Patients with FPF can present with a wide variety of clinical features. Most HRCT scans of these patients exhibit patterns not typical of usual interstitial pneumonia. The family history of fibrotic lung diseases should be investigated in all patients under suspicion, regardless of their age.

Keywords: Idiopathic pulmonary fibrosis; Respiratory function tests; Tomography, X-ray computed.

INTRODUCTION

Familial pulmonary fibrosis (FPF) occurs when at least two members of the same biological family are affected by a fibrosing interstitial lung disease (ILD).[1] Although some studies have used more stringent criteria for FPF, including the presence of at least two cases of fibrosing ILD in individuals related within three degrees, the aforementioned definition is widely accepted.[2,3] It should be noted that the affected family members do not necessarily have to have the same ILD.[1,2]

FPF has classically been described as rare. According to an official American Thoracic Society (ATS)/European Respiratory Society (ERS)/Japanese Respiratory Society (JRS)/*Asociación Latinoamericana de Tórax* (ALAT, Latin American Thoracic Association) statement, familial forms of idiopathic pulmonary fibrosis (IPF) account for less than 5% of all IPF cases.[4] However, in a study in which relatives of individuals diagnosed with IPF were screened for fibrosing ILD by trained health professionals, the prevalence of familial disease was found to be as high as 20%.[5] Therefore, FPF might be much more common than previously thought, its prevalence varying according to the screening methods used.

There has been increasing interest in FPF in recent years because genetic mechanisms involved in familial forms of fibrosing ILD might also be involved in the pathogenesis of sporadic forms of fibrosing ILD, particularly IPF. One such genetic mechanism is the rs35705950 polymorphism in the promoter of the *MUC5B* gene; when it involves two alleles, it increases the risk of FPF and sporadic IPF by more than 20-fold.[6] Mutations in telomere-related

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genes have also been associated with sporadic and familial forms of fibrosing ILD.[7,8]

Although it is important to investigate the genetic aspects of FPF, it is equally important to investigate clinical, radiological, and pathological features of the disease because of the large diversity of phenotypes in patients with FPF.[1-3] To the best of our knowledge, there have been no studies of FPF in the Brazilian population. In view of this, the objective of the present study was to describe the clinical, functional, and radiological features of index cases of FPF in Brazil. A secondary objective was to present and discuss histological findings in patients undergoing lung biopsy.

METHODS

Patients

The present study was a case series involving index cases of FPF. Active case finding was conducted from March of 2014 to November of 2017 at the University of São Paulo at Ribeirão Preto School of Medicine *Hospital das Clínicas*, located in the city of Ribeirão Preto, Brazil. The inclusion criteria were as follows: being over 18 years of age, having been diagnosed with fibrosing ILD, and having at least one member of the same biological family affected by fibrosing ILD. Only patients whose chest X-rays/HRCT scans and those of at least one affected relative were available for analysis by our research group were included in the study. All participants gave written informed consent, and the study protocol was approved by the local research ethics committee (Protocol no. 883,203).

Clinical and laboratory evaluation

A standardized form was used in order to record clinical information on all identified index cases. The following data were collected: demographic data; age at onset of symptoms; age at diagnosis of fibrosing ILD; degree of relatedness to the closest affected relative; environmental exposure history; manifestations consistent with collagen vascular disorders; upper gastrointestinal symptoms; degree of dyspnea, as assessed by the modified Medical Research Council scale[9]; severity of cough; presence of expectoration, wheezing, fine crackles, and digital clubbing; resting SpO_2; and room-air SpO_2.

Participants underwent spirometry with ATS-approved spirometers, lung capacities, lung volumes, and DLCO being measured in accordance with the Brazilian Thoracic Association guidelines for pulmonary function testing.[10] Normal lung function values were calculated on the basis of reference equations for the Brazilian population.[11-13]

Chest HRCT scans were performed on multidetector scanners, volumetric images being acquired during inhalation and exhalation without iodinated contrast medium.

All HRCT scans were blindly reviewed by two thoracic radiologists, who categorized the findings into four patterns, in accordance with criteria proposed by the Fleischner Society[14]: (i) typical usual interstitial pneumonia (UIP); (ii) probable UIP; (iii) indeterminate UIP; and (iv) findings consistent with a diagnosis other than IPF. In the case of HRCT findings consistent with a diagnosis other than IPF, an attempt was made to identify a specific pattern of ILD, such as nonspecific interstitial pneumonia (NSIP), hypersensitivity pneumonitis (HP), and organizing pneumonia (OP).[15,16] In cases in which it was impossible to establish a definitive diagnosis, the findings were classified as constituting an uncharacteristic pattern. Disagreements were resolved by consensus.

All available pathological data were reviewed by the same pathologist (specializing in pulmonary pathology), in accordance with histomorphological criteria established by the ATS/ERS and the Pulmonary Pathology Society.[15,17]

The results are presented as category frequencies and, given the nature of the distribution of most of the data, as medians and ranges.

RESULTS

The case series comprised 35 patients, whose clinical characteristics are presented in Table 1. There was a slight predominance of women (51.4%) in the study. The median age at screening was 66.0 years (range, 35.5-89.3 years). The median age at onset of symptoms was 63.2 years (range, 34.0-84.0 years). The median age at diagnosis of lung disease was 64.0 years (range, 35.3-85.0 years). Evidence of fibrosing ILD affecting at least one family member was obtained by reviewing HRCT scans in 22 cases (62.9%); by reviewing HRCT scans and pathological data in 3 cases (8.6%); and by reviewing conventional chest X-rays in 10 (28.6%). More detailed information on the available data regarding affected family members can be found in the online supplement of the JBP (Chart S1, available at http://www.jornaldepneumologia.com.br/detalhe_anexo.asp?id=64).

A history of smoking was reported by 45.7% of the study participants, and other relevant environmental exposures were reported by 80.0%. A history of exposure to birds was reported by 57.1%. Cough was reported by 62.8%, and grade 2, 3, or 4 dyspnea (as assessed by the modified Medical Research Council scale) was reported by 48.6%. Wheezing and expectoration were uncommon findings. Fine crackles were found in 91.4%, whereas digital clubbing was found in only 20.0%. Manifestations consistent with collagen vascular disorders were reported by or found in none of the study participants. The median room-air SpO_2 was 96% (range, 70-98%). An SpO_2 of ≤ 90% was found in 6 patients.

In 4 patients (11.4%), the clinical findings were suspicious for telomere disease: myelodysplastic syndrome, in 2, and chronic liver disease, in 2 (1 with liver cirrhosis only and 1 with liver cirrhosis and a history of hair graying before the age of 25 years).

Table 1. Clinical characteristics of 35 index cases of familial pulmonary fibrosis.

Characteristic	n (%)
Sex	
Male	17 (48.6)
Female	18 (51.4)
Age at screening, years	
≤ 30	0 (0.0)
30-39	2 (5.7)
40-49	2 (5.7)
50-59	5 (14.3)
60-69	12 (34.3)
70-79	10 (28.6)
≥ 80	4 (11.4)
Age at symptom onset, years	
≤ 30	0 (0.0)
30-39	2 (5.7)
40-49	3 (8.6)
50-59	9 (25.7)
60-69	14 (40.0)
70-79	5 (14.3)
≥ 80	2 (5.7)
Age at diagnosis, years	
≤ 30	0 (0.0)
30-39	3 (8.6)
40-49	2 (5.7)
50-59	6 (17.8)
60-69	14 (40)
70-79	8 (22.9)
≥ 80	2 (5.7)
Degree of relatedness to closest affected relative	
First degree	34 (97.1)
Second degree	1 (2.9)
Smoking status	2 (5.7)
Current smoker	14 (40.0)
Former smoker	19 (54.3)
Never smoker	
Current or past environmental exposures	
No exposure	7 (20.0)
Mold	8 (22.9)
Birds	20 (57.1)
Cough	
No cough or mild cough	13 (37.2)
Daily, mild cough	16 (45.7)
Daily, severe cough	6 (17.1)
Degree of dyspnea, mMRC scale	
0	6 (17.1)
1	12 (34.3)
2	6 (17.1)
3	4 (11.5)
4	7 (20.0)
Expectoration	
Absent	23 (65.7)
Present	12 (34.3)
Bloody sputum	2 (5.7)

mMRC: modified Medical Research Council.

Table 1. Continued...

Characteristic	n (%)
Wheezing	
Absent	23 (65.8)
During airway infections	10 (28.6)
Common but mild	2 (5.7)
Digital clubbing	
Absent	28 (80.0)
Present	7 (20.0)
Fine crackles	
Absent	3 (8.6)
Present	32 (91.4)
SpO_2, %	
≥ 96	20 (57.1)
91-95	9 (25.7)
86-90	1 (2.9)
81-85	3 (8.6)
≤ 80	2 (5.7)

mMRC: modified Medical Research Council.

Median percent predicted TLC, FVC, FEV_1, FEV_1/FVC, and DLCO were 68.0% (range, 41.3-102.4%), 64.9% (range, 48.8-105.7%), 69.3% (range, 49.1-117.9%), 108.5% (range, 84.0-124.0%), and 38.9% (range, 16.7-60.0%), respectively (Table 2). Supranormal expiratory airflow, defined as an FEV_1/FVC ratio > 105% of predicted, was found in 77.1% of the study participants. Of the 35 study participants, 22 (62.8%) had restrictive lung disease; 7 (20.0%) had normal lung function; 5 (14.3%) had indeterminate lung disease; and 1 (2.9%) had mild obstructive lung disease. DLCO was found to be reduced in all of the patients in whom it was measured (n = 30).

HRCT findings consistent with typical UIP and indeterminate UIP were found in 6 patients (17.1%) and 4 patients (11.4%), respectively. HRCT findings were consistent with a diagnosis other than IPF in most of the patients (n = 25; 71.4%). Of those 25 patients, 11 (31.4%) had HRCT findings that were uncharacteristic of ILD; that is, they were inconsistent with previously described radiological features of ILD. Of the remaining 14 patients, 9 (25.7%) had HRCT findings that were consistent with NSIP, 3 (8.6%) had HRCT findings that were consistent with OP, and 2 (5.7%) had HRCT findings that were consistent with chronic HP (Table 3 and Figure 1).

Lung tissue samples were obtained from 6 patients for pathological examination. Of those 6 samples, 1 was obtained from autopsy and 5 were obtained from surgical biopsies. Of those 6 patients, 1 had HRCT findings that were initially suggestive of NSIP. However, the patient subsequently presented with extensive areas of ground-glass opacities and consolidations. Pathological examination of the autopsy tissue revealed diffuse alveolar damage and OP at different stages of organization. In another patient, HRCT findings were consistent with indeterminate UIP, and surgical biopsy showed unclassifiable cellular and fibrosing interstitial pneumonitis with multiple lymphoid aggregates (Figure 2A). The patient had no clinical manifestations suggestive of collagen vascular disorders, and autoantibody testing was negative. In the 4 remaining patients, HRCT findings were suggestive of NSIP (in 2) and chronic HP (in 2). Histological examination showed interstitial pneumonitis with bronchiolocentric accentuation in all 4, patchy areas of OP being observed in 3 (Figure 2B). Although none had any relevant gastrointestinal symptoms, all 4 reported exposure to birds and were therefore diagnosed with HP after a multidisciplinary discussion.

DISCUSSION

Ours is the first study to describe the clinical features of index cases of FPF in Brazil. It is of note that FPF has a wide variety of clinical and radiological manifestations.

Although the onset of the clinical manifestations of FPF occurred between the ages of 50 and 69 years in 65.7% of the patients in the present study, the onset of symptoms can be as early as age 34 years and as late as age 84 years. Of the 35 FPF patients in the present study, 14.3% were diagnosed before the age of 50 years and 5.7% were diagnosed after the age of 80 years. The presence of fibrosing ILD in a patient younger than 50 years of age is suggestive of familial disease.[1,5] However, this is not usually the case for older individuals, particularly those older than 80 years of age. Therefore, the results of the present study indicate that there is a need for careful screening of family members for other ILDs, independently of patient age at symptom onset or diagnosis.

In the present study, 97.1% of the participants had at least one first-degree relative (father, mother, or brother) who also had a fibrosing ILD. A maternal uncle was the closest affected relative in only one

Table 2. Lung function parameters in 35 index cases of familial pulmonary fibrosis.[a]

Parameter	n (%)
TLC[b]	
≥ 80	12 (38.7)
70-79	3 (9.7)
60-69	6 (19.4)
50-59	6 (19.4)
40-49	4 (12.9)
≤ 39	0 (0.0)
FVC	
≥ 80	8 (22.9)
70-79	6 (17.1)
60-69	8 (22.9)
50-59	11 (31.4)
40-49	2 (5.7)
≤ 39	0 (0,0)
FEV_1	
≥ 80	11 (31.4)
70-79	6 (17.1)
60-69	13 (37.1)
50-59	4 (11.4)
40-49	1 (2.9)
≤ 39	0 (0.0)
FEV_1/FVC	
≥ 110	16 (45.7)
100-109	14 (40.0)
90-99	4 (11.4)
80-89	1 (2.9)
≤ 79	0 (0.0)
DLCO[c]	
≥ 60	0 (0.0)
50-59	8 (26.7)
40-49	5 (16.7)
30-39	10 (33.3)
20-29	4 (13.35)
≤ 19	3 (10.0)

[a]All results are expressed as percentages of the predicted values. [b]Data available for 31 patients. [c]Data available for 30 patients.

case. This underscores the relevance of the results of the present study.

Of the 35 study participants, 45.7% reported being smokers or former smokers, and 80.0% reported exposure to mold or birds. It is widely accepted that FPF cannot be attributed to genetic factors alone; rather, it is caused by an interaction between genetic factors and harmful environmental exposures resulting in an additional intracellular and interstitial microenvironment that modulates molecular pathways dependent on single nucleotide polymorphisms, alternative splicing, small RNAs, enzymatic activity, and epigenetic mechanisms promoting a favorable environment for fibrosis onset. [18-20] In other words, individuals are born with a predisposition to FPF and may or may not develop the disease depending on environmental exposures. Our findings corroborate this hypothesis. In addition, the prevalence of risk factors for HP in patients in Brazil was found to be extremely high. This might be due to the fact that the study sample consisted almost exclusively of patients living in the countryside of the state of São Paulo, Brazil (91.4%). In FPF patients living in larger urban areas, exposure to birds and other animals might be less common.

As expected in ILD patients, dyspnea and dry cough were the most common clinical complaints, in 82.9% and 61.8% of the patients, respectively.[21] In addition, auscultation revealed fine crackles in 91.4%, a finding that shows the importance of screening for fine crackles in patients suspected of having fibrosing ILD.[22,23]

In 4 of our patients, FPF was clinically attributed to telomere disease on the basis of the combined presence of hematological abnormalities, chronic liver disease, and premature graying of hair.[24,25] Although the aforementioned findings are not specific for telomere disease, they should be screened for in patients and their relatives because they are an indication for the use of molecular biology testing to measure telomere length in peripheral blood and for specific gene sequencing in younger generations.[26]

With regard to pulmonary function tests, most of the patients in the present study had results that were consistent with restrictive lung disease, a finding that was expected in view of the nature of the lung diseases under study. The only patient who was found to have (mild) obstructive lung disease had a smoking history of 50 pack-years. It is of note that DLCO was substantially reduced in all of the patients in whom it was measured, a finding that underscores the high diagnostic sensitivity of DLCO measurement in patients with fibrosing ILD.[27] The fact that 9 patients had reduced DLCO despite having normal spirometry results is further evidence of the importance of DLCO measurement in patients with FPF.

In the present study, only 6 patients (17.1%) had HRCT findings consistent with typical UIP. The vast majority of patients (n = 25; 71.4%) had CT findings that were consistent with a diagnosis other than IPF. Of those 25 patients, only 14 (40.0%) had specific CT findings. Therefore, a large number of patients (n = 11; 31.4%) had CT findings that were uncharacteristic of ILD.

Although at least one study has shown a high frequency of CT findings consistent with UIP in patients with FPF,[2] the results of the present study are similar to those of a study involving a large number of FPF patients (n = 289), 160 (55%) of whom had CT findings consistent with unclassifiable ILD.[28] In that study, those who had CT findings consistent with definite or probable ILD were diagnosed with UIP (22%), NSIP (12%), HP (6%), or OP (2%).[28] The

Table 3. CT patterns in 35 index cases of familial pulmonary fibrosis.

CT pattern	n	%
Typical UIP	6	17.1
Probable UIP	0	0.0
Indeterminate UIP	4	11.4
Consistent with a diagnosis other than IPF	25	71.4
Inconsistent with fibrosing ILD	11	31.4
Consistent with NSIP	9	25.7
Consistent with organizing pneumonia	3	8.6
Consistent with hypersensitivity pneumonia	2	5.7

UIP: usual interstitial pneumonia; IPF: idiopathic pulmonary fibrosis; ILD: interstitial lung disease; and NSIP: nonspecific interstitial pneumonia.

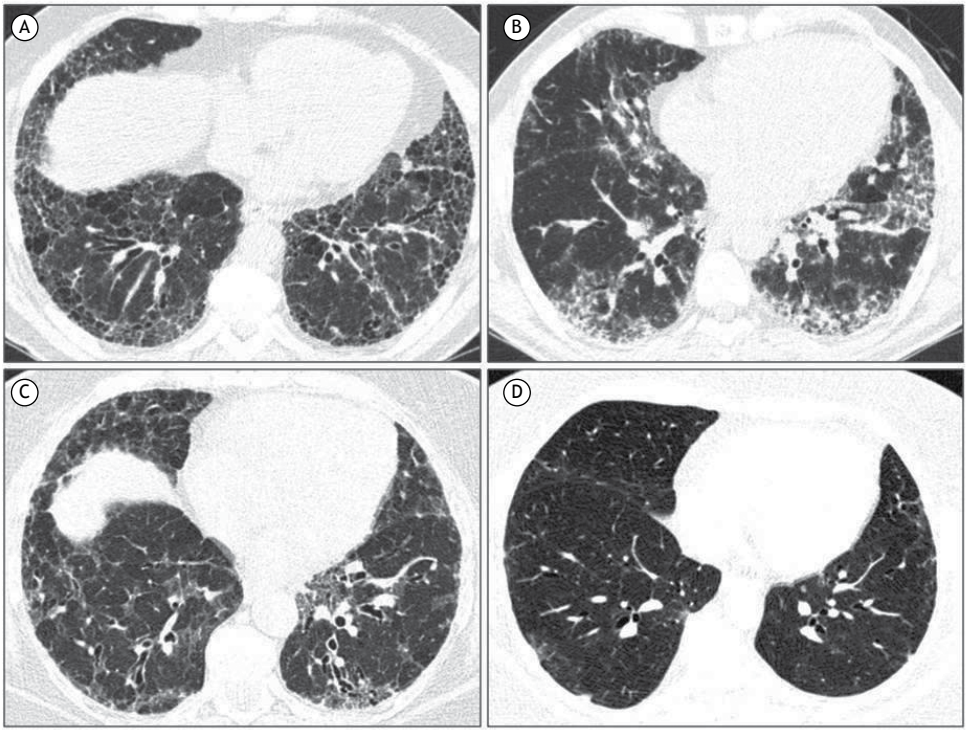

Figure 1. Axial HRCT scans (lung window) of patients with familial pulmonary fibrosis. In A, CT findings consistent with typical usual interstitial pneumonia. In B, CT findings consistent with a diagnosis other than idiopathic pulmonary fibrosis, i.e., consistent with nonspecific interstitial pneumonia. In C, CT findings consistent with a diagnosis other than idiopathic pulmonary fibrosis, i.e., consistent with chronic hypersensitivity pneumonia. In D, CT findings consistent with indeterminate usual interstitial pneumonia.

study in question was conducted by renowned experts and appears to have involved a thorough review of previously published data. Therefore, our results are consistent with previous evidence suggesting that a typical UIP pattern is found in only a minority of patients with FPF. Unlike what was observed in the aforementioned study,[28] UIP was less common than NSIP in the present study, a finding that might be due to local characteristics. Nevertheless, the present study reinforces the notion that CT findings consistent with unclassifiable ILD are the most common.

It can be argued that CT findings consistent with unclassifiable ILD indicate incipient disease that will later progress and result in findings that are more specific; in particular, findings that are consistent with UIP. Well-designed longitudinal studies are needed in order to confirm this possibility. However, in the present study, even elderly patients had findings that were uncharacteristic of ILD. In a study reviewing CT scans of 26 FPF patients on two occasions, separated by a median of 1,049 days, a typical UIP pattern was observed only in those patients in whom initial CT findings were consistent with possible UIP.[29] Therefore, although CT findings of unclassifiable ILD in patients with FPF have yet to be fully understood, it appears that they do not necessarily correspond to an early stage of UIP.

Lung tissue samples were available for review in only 6 cases, having been obtained from surgical

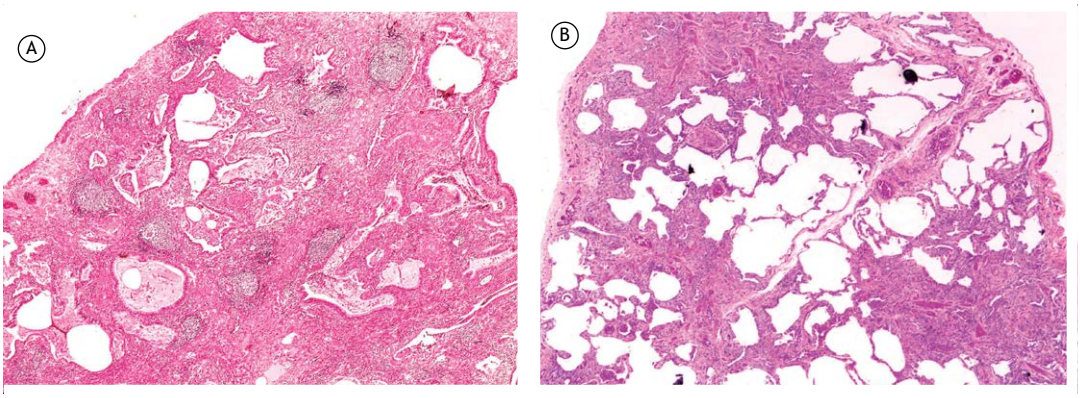

Figure 2. Representative histopathological findings of familial interstitial lung disease. In A, findings consistent with unclassifiable ILD. Note diffuse fibroplastic architectural distortion with cyst formation and lymphoid aggregates. In B, findings consistent with interstitial pneumonia with bronchiolocentric accentuation. Note the predominance of fibroplastic peribronchiolar involvement and delta-shaped subpleural extension associated with organizing pneumonia. Note also that the interlobular septum and the remaining pleura have a normal appearance (H&E; magnification, ×5 for both).

biopsies in 5 and from an autopsy in 1. Pathological examination of the autopsy tissue revealed diffuse alveolar damage and areas of OP at different stages of organization, findings that indicate terminal events related to a fatal acute exacerbation, a systemic infection, or prolonged mechanical ventilation.[30] The five lung tissue samples obtained from elective surgical biopsies provided information that was more relevant. Those samples were obtained in an unsystematic way, the decision to request a biopsy having been made by the attending physicians on the basis of their own health care practices.

The fact that 1 patient was diagnosed with unclassifiable cellular and fibrosing interstitial pneumonitis is not surprising, given that 43.3% of biopsy samples from FPF patients in a previous study were diagnosed as such.[31] In that study,[31] a definite UIP pattern was identified in only 40% of cases. According to the authors,[31] although most biopsy samples from patients with FPF exhibit individual histopathological features that are commonly associated with UIP, current diagnostic criteria for UIP are not met in most cases.

Of the six lung tissue samples analyzed in the present study, four showed interstitial pneumonitis with bronchiolocentric accentuation. Of those four samples, three also showed areas of OP. Of the patients who reported exposure to birds, 2 reported current exposure to birds, 1 reported current exposure to birds and goose feathers (in a pillow), and 1 reported past exposure to birds. CT findings were consistent with HP in 2 and with NSIP in 2. Findings of interstitial pneumonitis with bronchiolocentric accentuation can be challenging to interpret.[32,33] After a multidisciplinary discussion, 3 patients were diagnosed with HP, whereas 1 was diagnosed with probable HP because of a history of occupational exposure to substances involved in the tire vulcanization process.

It is difficult to establish a diagnosis of HP in a family setting because it can be argued that HP in this context is due to simultaneous exposure to antigens in individuals living in the same environment. However, even in this context, only a few will develop HP. Therefore, if two or more family members develop HP when exposed to the same environmental conditions, it can be assumed that they share a genetic predisposition to the disease. A review of the available information on the relatives of the 4 patients who had interstitial pneumonitis with bronchiolocentric accentuation did not suggest simultaneous cases of HP. In addition, lung tissue samples were obtained from only 5 of the 29 patients without a typical UIP pattern, either because of the presence of significant comorbidities or because the patients declined to undergo biopsy. Therefore (and given the high prevalence of HP in Brazil), the prevalence of HP was likely underestimated in the present study.

The present study has several limitations, one of which is the fact that we did not collect information on the characteristics of relatives of the index cases. Although an effort was made to investigate as many (symptomatic or asymptomatic) family members as possible, few families were properly investigated, the vast majority of which had insufficient data for analysis. However, the fact that the study was limited to index cases ensured the homogeneity of the inclusion criteria. Another limitation is that interstitial pneumonia with autoimmune features might have gone undiagnosed in some cases because no autoantibody testing was performed in several patients. Likewise, because upper gastrointestinal endoscopy and esophageal pH monitoring were not routinely performed, it was impossible to identify cases in which gastroesophageal reflux might have contributed to the pathogenesis of the disease. A final limitation is the absence of genetic study results, which were still pending at this writing.

The phenotypic heterogeneity of FPF in the present study could be due to the various molecular genomic and epigenetic mechanisms involved in the pathogenesis of the disease. However, this does not seem to be the case, because previous studies have

shown that a single genetic disorder can have different presentations, and vice versa.[1,7,34] In view of this and of the findings of the present study, we propose that term FPF be replaced with the term familial ILD, which more accurately reflects the complexity of the disease.

In conclusion, pulmonologists should be aware of the various clinical presentations of familial ILD. It appears that clinicians tend to associate familial ILD with IPF. This has implications, including therapeutic implications. Even in a family setting, the initial treatment of HP should consist of removal of exposure and the use of corticosteroids rather than antifibrotic agents, which should be reserved for patients with HRCT or biopsy findings consistent with UIP. In the near future, therapeutic decisions for patients with familial ILD will ideally be based on an appropriate characterization of individual integrated molecular patterns.[35]

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Accuracy of chest auscultation in detecting abnormal respiratory mechanics in the immediate postoperative period after cardiac surgery

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ABSTRACT

Objective: To investigate the accuracy of chest auscultation in detecting abnormal respiratory mechanics. **Methods:** We evaluated 200 mechanically ventilated patients in the immediate postoperative period after cardiac surgery. We assessed respiratory system mechanics - static compliance of the respiratory system (C_{st},rs) and respiratory system resistance (R,rs) - after which two independent examiners, blinded to the respiratory system mechanics data, performed chest auscultation. **Results:** Neither decreased/abolished breath sounds nor crackles were associated with decreased C_{st},rs (≤ 60 mL/cmH_2O), regardless of the examiner. The overall accuracy of chest auscultation was 34.0% and 42.0% for examiners A and B, respectively. The sensitivity and specificity of chest auscultation for detecting decreased/abolished breath sounds or crackles were 25.1% and 68.3%, respectively, for examiner A, versus 36.4% and 63.4%, respectively, for examiner B. Based on the judgments made by examiner A, there was a weak association between increased R,rs (≥ 15 cmH_2O/L/s) and rhonchi or wheezing ($\varphi = 0.31$, $p < 0.01$). The overall accuracy for detecting rhonchi or wheezing was 89.5% and 85.0% for examiners A and B, respectively. The sensitivity and specificity for detecting rhonchi or wheezing were 30.0% and 96.1%, respectively, for examiner A, versus 10.0% and 93.3%, respectively, for examiner B. **Conclusions:** Chest auscultation does not appear to be an accurate diagnostic method for detecting abnormal respiratory mechanics in mechanically ventilated patients in the immediate postoperative period after cardiac surgery.

Keywords: Diagnostic tests, routine; Physical examination; Respiratory sounds; Respiratory mechanics; Data accuracy; Respiration, artificial.

INTRODUCTION

Chest auscultation performed with a traditional (acoustic) stethoscope is a practical, inexpensive method of diagnosing and monitoring abnormalities of the respiratory system in clinical practice.[1-3] Although routinely used by health care professionals for the evaluation of patients with cardiopulmonary disorders, chest auscultation has some important limitations: it is a subjective tool; it requires good hearing acuity and a high level of experience on the part of the health care professional in order to detect adventitious sounds[4]; the nomenclature for respiratory sounds is not standardized[5]; acoustic stethoscopes are not ideal instruments to detect respiratory sounds because they can modify sounds within the spectrum of clinical interest[6]; and there is significant interobserver variability.[7] Despite those limitations, chest auscultation is presently applied to assess the respiratory function of mechanically ventilated patients and the findings are therefore employed in the decision-making process for patient care. However, abnormal respiratory sounds might not reflect impaired respiratory function or abnormal respiratory mechanics, and abnormalities in respiratory mechanics do not necessarily translate into audible sounds. Therefore, chest auscultation might not provide accurate information about the mechanical properties of the respiratory system.

We hypothesized that chest auscultation findings would not show an association with the mechanical properties of the respiratory system in mechanically ventilated patients. Therefore, the aim of this study was to investigate the accuracy of chest auscultation as a diagnostic method to detect abnormalities in respiratory mechanics in mechanically ventilated patients in the immediate postoperative period after cardiac surgery.

METHODS

This was a cross-sectional study conducted at the Cardiac Surgery ICU of the *Instituto de Cardiologia do Distrito Federal*, in the Federal District of Brasília, Brazil. The local research ethics committee approved the

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study protocol, and all of the patients evaluated gave written informed consent prior to undergoing surgery.

From among consecutive adult patients undergoing cardiac surgery between January of 2013 and December 2013, we recruited 200 to participate in this study. We applied the following inclusion criteria: undergoing cardiac surgery for definitive or palliative treatment of heart disease, with or without cardiopulmonary bypass; having a Ramsay sedation scale score of 6; requiring continuous mechanical ventilation (volume- or pressure-controlled modes); and not receiving any vasoactive medication at the time of data collection. Patients who declined to participate in the protocol were excluded, as were those who were sent to the ICU with an open chest and those in whom the ventilator weaning process had already begun. The study design is shown in Figure 1.

Protocol

After the first 20 min of the immediate postoperative period, beginning at the arrival of the patient in the ICU, we assessed the mechanical properties of the respiratory system, after which we performed chest auscultation. The mechanical properties of the respiratory system were evaluated by end-inspiratory occlusion,[8] with patients in the supine position and without triggering the mechanical ventilator (Evita 2 or Evita 4; Dräger Medical, Lübeck, Germany). The following ventilator settings were used for the assessment of respiratory system mechanics: volume controlled continuous mandatory ventilation; a constant inspiratory flow rate (60 L/min); a tidal volume of 8 mL/kg (of the ideal weight); a positive end-expiratory pressure (PEEP) of 8 cmH_2O; an FiO_2 sufficient to maintain peripheral oxygen saturation above 95%; and an end-inspiratory pause of 3 s. To detect auto-PEEP, end-expiratory occlusion was performed.[9] Static compliance of the respiratory system (C_{st},rs) was obtained by the following formula:

tidal volume / elastic recoil pressure − [*PEEP* + *auto-PEEP*]

To obtain the respiratory system resistance (R,rs), we used this formula:

[*peak inspiratory pressure* − *elastic recoil pressure*] / *flow rate*

Reference values for C_{st},rs and R,rs[10] were adopted, a C_{st},rs < 60 mL/cmH_2O being considered below normal and an R,rs ≥ 15 cmH_2O/L/s being considered above normal.

After the assessment of respiratory system mechanics had been completed, chest auscultation was performed by two highly experienced ICU health care professionals (a physician and a physiotherapist), both of whom were blinded to the mechanics data and were working independently. The auscultation was performed with patients in the same position

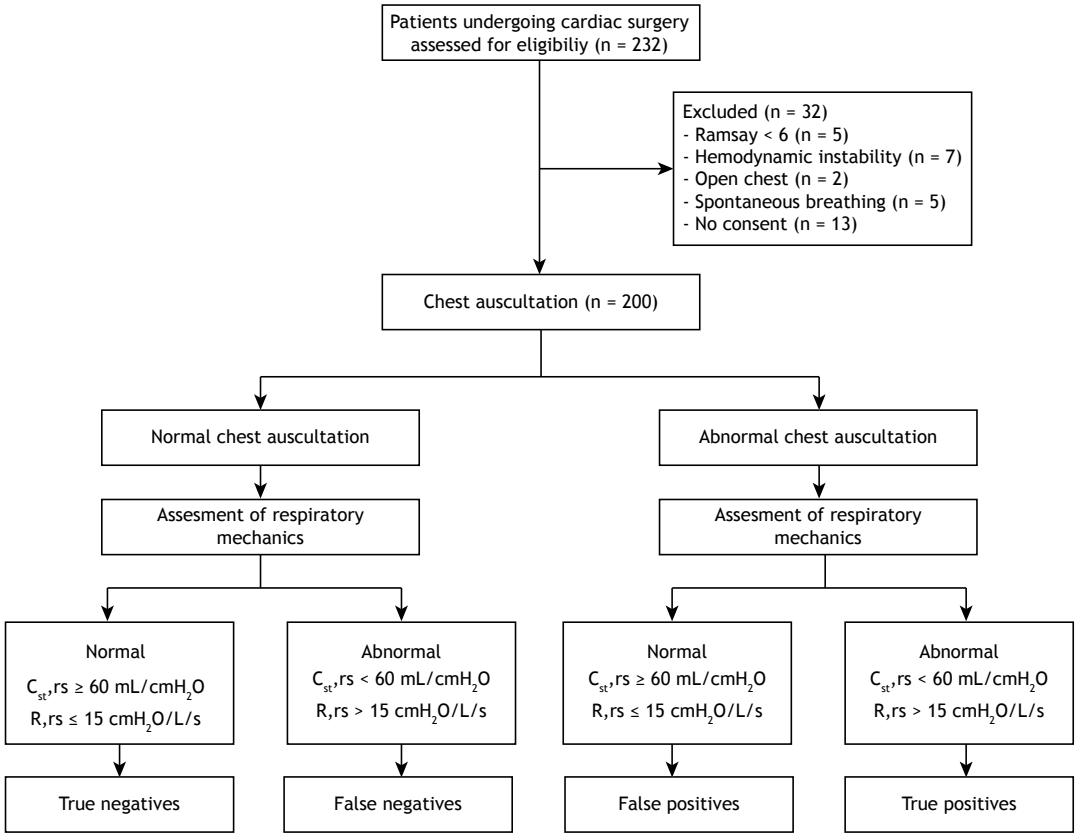

Figure 1. Study design. C_{st},rs: static compliance of the respiratory system; and R,rs: respiratory system resistance.

and with the same ventilator settings used in the previous assessment of the mechanical properties of the respiratory system (without the end-inspiratory pause), and both professionals used the same stethoscope (Littmann Classic II; 3M, St. Paul, MN, USA). To ensure consistency between the examiners, the skin was marked, on both sides, at the following sites: on the upper chest in the second intercostal space, along the midclavicular line; on the lateral chest between the fourth and fifth intercostal spaces, along the midaxillary line; and on the lower chest between the seventh and eighth intercostal spaces, along the midaxillary line.[11] Abnormal chest auscultation findings were defined as any abnormal sound (decreased breath sounds, crackles, rhonchi, or wheezing) heard at one or more of the six sites marked. Because the waveform analysis of the mechanical ventilator could influence examiner impressions, thereby skewing the chest auscultation results, examiners were instructed not to look at the mechanical ventilator display while they performed chest auscultation. Normal or decreased breath sounds and crackles were considered to be related to the lung parenchyma or chest wall, whereas rhonchi and wheezing were considered airway-related sounds.

Statistical analysis

The sample size calculation was performed by using PASS software, version 11.0 (NCSS, LLC, Kaysville, UT, USA), with the following parameters: diagnostic test sensitivity of 80%; a diagnostic test specificity of 90%; a 5% probability of a type I error; a diagnostic test power of 80%; and a 60% prevalence of abnormal respiratory system mechanics in the immediate postoperative period after cardiac surgery. Thus, the minimum sample size necessary was determined to be 178 subjects.

Student's t-tests for independent samples were used in order to determine whether C_{st},rs and R,rs were abnormal depending on how they were classified by each examiner on the basis of the chest auscultation findings. Chi-square tests or Fisher's exact tests were used in order to identify associations between chest auscultation variables and those related to respiratory mechanics. The accuracy of chest auscultation in representing alterations of the mechanical properties of the respiratory system was expressed as sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio. Cohen's kappa statistic (κ) was determined in order to assess the interobserver agreement in chest auscultation, and the phi coefficient (φ) was calculated in order to test the strength of the correlations between the auscultation findings and the respiratory mechanics. Continuous variables are expressed as mean ± standard deviation, and categorical variables are expressed as absolute and relative values unless otherwise stated. Statistical analyses were performed with the SPSS Statistics software package, version 17.0 (SPSS Inc., Chicago, IL, USA), and the significance level was set at 5%.

RESULTS

We evaluated 200 patients (116 men) in the immediate postoperative period after cardiac surgery. Among the patients evaluated, the mean age was 56.9 ± 11.7 years and the mean body mass index was 26.8 ± 4.1 kg/m^2. The cardiac surgery procedures and patient respiratory comorbidities are shown in Table 1.

In the study sample, the mean C_{st},rs was 50.1 ± 18.3 mL/cmH_2O, and 41 (20.5%) of the 200 patients had a C_{st},rs value ≥ 60 mL/cmH_2O. According to examiner A, 147 (73.5%) of the patients had normal sounds related to the lung parenchyma or chest wall and C_{st},rs did not differ between the patients in whom such sounds were classified as normal and those in whom they were classified as abnormal (49.6 ± 18.3 mL/cmH_2O vs. 50.9 ± 22.7 mL/cmH_2O; p = 0.65). Examiner B categorized 127 (63.5%) of the patients as having normal sounds related to the lung parenchyma or chest wall and observed no significant difference in C_{st},rs, regardless of whether those sounds were classified as normal or abnormal on chest auscultation (49.7 ± 18.8 mL/cmH_2O vs. 50.3 ± 17.5 mL/cmH_2O; p = 0.82). The C_{st},rs data related to examiner A and examiner B are shown in Figures 2A and 2B, respectively.

In the study sample, the mean R,rs was 9.3 ± 3.8 cmH_2O/L/s and the R,rs was increased in 20 (10.0%) of the 200 patients. Examiner A found that the R,rs was significantly lower in the patients with normal auscultation than in those in whom there was rhonchi or wheezing (9.1 ± 3.6 cmH_2O/L/s vs. 12.5 ± 4.9 cmH_2O/L/s; p < 0.01). Examiner B categorized 187 (93%) of the patients as presenting no airway-related sounds and observed no significant difference in R,rs, regardless of whether those sounds were classified as normal or abnormal on chest auscultation (9.3 ± 3.8 cmH_2O/L/s vs. 8.4 ± 3.7 cmH_2O/L/s; p = 0.35). The R,rs data related to examiner A and examiner B are shown in Figures 2C and 2D, respectively.

Regarding C_{st},rs, the false-positive rates were 31.7% and 36.5% for examiners A and B, respectively, compared with 74.8% and 63.5%, respectively, for

Table 1. Cardiac surgery procedures and patient respiratory comorbidities.

Variable	(N = 200)
Cardiac surgery procedures, n (%)	
Myocardial revascularization	139 (69.5)
Heart valve replacement	50 (25.0)
Aortic repair	5 (2.5)
Atrial septal repair	3 (1.5)
Heart valve repair	2 (1.0)
Intracardiac tumor resection	1 (0.5)
Respiratory comorbidities, n (%)	
None	141 (70.5)
Nicotine addiction	52 (26.0)
COPD	5 (2.5)
Tuberculosis sequelae	2 (1.0)

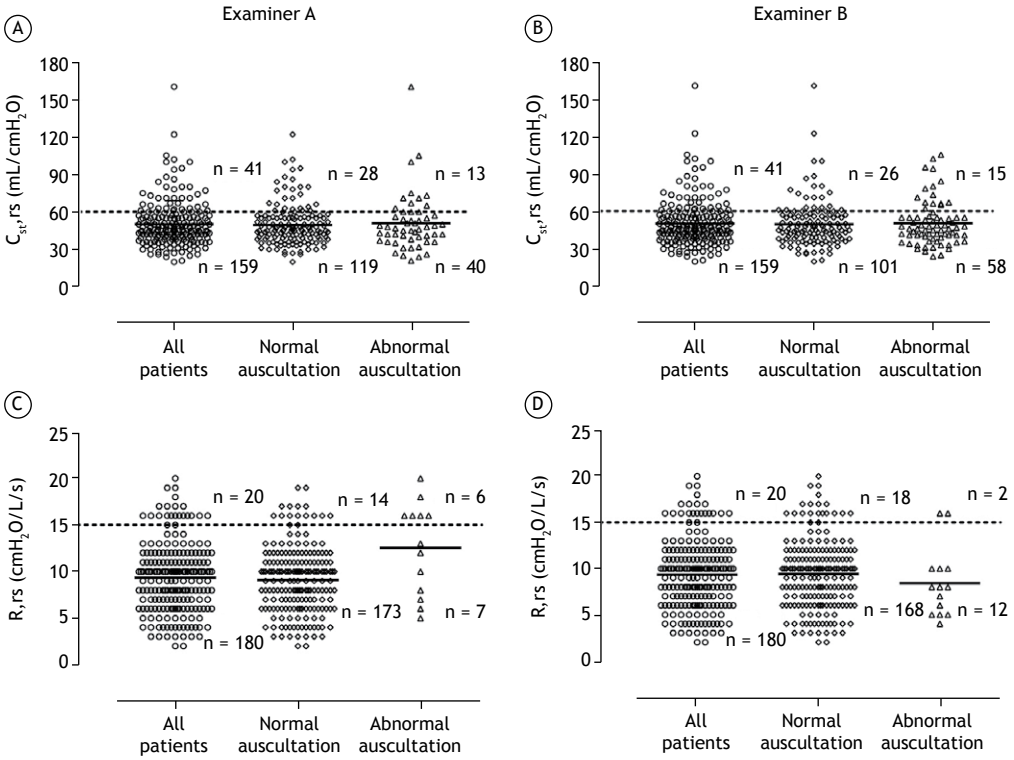

Figure 2. A and B: static compliance of the respiratory system (C_{st},rs); C and D: respiratory system resistance (R,rs). Open circles represent individual values of C_{st},rs and R,rs; open diamonds represent individual values of C_{st},rs and R,rs when examiners classified chest auscultation as normal; open triangles represent individual values of C_{st},rs and R,rs when examiners classified chest auscultation as abnormal; dotted horizontal lines mark the cut-off values for C_{st},rs (≥ 60 mL/cmH$_2$O) and R,rs (≤ 15 cmH$_2$O/L/s); and solid horizontal lines are the mean C_{st},rs and R,rs values for each chest auscultation classification.

Table 2. Association between sounds related to the lung parenchyma or chest wall and static compliance of the respiratory system.

Variable		C_{st},rs (mL/cmH$_2$O) < 60 (n)	C_{st},rs (mL/cmH$_2$O) ≥ 60 (n)	p	φ	φ p
Decreased breath sounds, abolished breath sounds, or crackles			Examiner A			
	Yes	40	13	0.39	0.03	0.66
	No	119	28			
			Examiner B			
	Yes	58	15	0.99	0	0.99
	No	101	26			

C_{st},rs: static compliance of the respiratory system; and φ: phi coefficient.

the false-negative rates. decreased/abolished breath sounds nor crackles were associated with decreased C_{st},rs, regardless of the examiner (Table 2). When diminished breath sounds and crackles were analyzed separately, decreased C_{st},rs was not associated with either (p = 0.71 and p = 0.37, respectively, for examiner A; and p = 0.39 and p = 0.86, respectively, for examiner B).

For R,rs (Table 3), examiners A and B had false-positive rates of 3.8% and 6.6%, respectively, and false-negative rates of 70% and 90%, respectively. As can be seen in Table 3, there was a weak positive association between rhonchi/wheezing, as reported by examiner A, and increased R,rs (φ = 0.31; p < 0.01), although no such association was observed for examiner B (φ = 0.03; p = 0.63). In addition, airway-related sounds were not associated with the presence of auto-PEEP (p = 0.41 and p = 0.46 for examiners A and B, respectively).

When performed by examiner A, chest auscultation had a sensitivity and specificity of 25.1% and 68.3%, respectively, for the detection of abnormal sounds related to the lung parenchyma or chest wall and of 30.0% and 96.1%, respectively, for the detection of abnormal airway-related sounds. When performed by examiner B, chest auscultation had a sensitivity and specificity of 36.4% and 63.4%, respectively, for the detection of abnormal sounds related to the lung

parenchyma or chest wall, compared with 10.0% and 93.3%, respectively, for the detection of abnormal airway-related sounds. Other values related to the accuracy of chest auscultation in detecting abnormal respiratory mechanics are shown in Table 4.

In 177 patients, the two examiners agreed that there were no airway-related sounds, whereas they agreed that there were airway-related sounds in 4 patients. However, examiner A categorized 9 patients as presenting airway-related sounds, whereas examiner B categorized those same patients as not presenting such sounds. Similarly, examiner A categorized 10 patients as not presenting airway-related sounds, whereas examiner B categorized those same patients as presenting such sounds. For airway-related sounds, there was fair agreement between the two examiners (κ = 0.245; 95% CI: 0.040 to 0.512; p < 0.01). For sounds related to the lung parenchyma or chest wall, the two examiners agreed regarding the detection of normal sounds in 94 patients and regarding the detection of abnormal sounds in 20 patients. However, in 33 patients, the sounds related to the lung parenchyma or chest wall were classified as abnormal by examiner A and normal by examiner B. In another 53 patients, such sounds were classified as normal by examiner A and abnormal by examiner B. For sounds related to the lung parenchyma or chest wall, there was no agreement between the two examiners (κ = 0.015; 95% CI: −0.123 to 0.164; p = 0.82).

DISCUSSION

Here, we have provided data on the utility of chest auscultation for detecting mechanical abnormalities of the respiratory system in mechanically ventilated patients in the immediate postoperative period after cardiac surgery. We showed that neither the presence nor the absence of abnormal respiratory sounds was associated with mechanical abnormalities of the respiratory system, and that chest auscultation failed to accurately identify patients with abnormal respiratory mechanics.

Less than one third of the patients evaluated in the present study had lung disease or were addicted to nicotine prior to undergoing surgery. Such patients could present some degree of abnormality in respiratory mechanics. In fact, in the immediate postoperative period, C_{st},rs was decreased in 79.5% of those patients and R,rs was increased in 10.0%.

Mechanical abnormalities of the respiratory system are well established in patients undergoing cardiac surgery.[12,13] A reduction in C_{st},rs can be attributed to surgery-related events affecting the elastic recoil pressure of the respiratory system, such as cardiopulmonary bypass and an inflammatory reaction to extracorporeal circulation[14]; the effects

Table 3. Association between airway-related sounds and respiratory system resistance.

Variable		R,rs (cmH_2O/L/s) ≥ 15 (n)	R,rs (cmH_2O/L/s) < 15 (n)	p	φ	φ p
Rhonchi or wheezing			Examiner A			
	Yes	6	7	< 0.01[a]	0.31	< 0.01
	No	14	173			
			Examiner B			
	Yes	2	12	0.63[a]	0.03	0.57
	No	18	168			

R,rs: respiratory system resistance; and φ: phi coefficient. [a]Fisher's exact test.

Table 4. Accuracy, sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio for chest auscultation in detecting abnormal respiratory mechanics.

Examiner Variable	Accuracy (%)	Sensitivity % (95% CI)	Specificity % (95% CI)	LR+ Ratio (95% CI)	LR− Ratio (95% CI)
A					
Decreased breath sounds, abolished breath sounds, or crackles	34.0	25.2 (21.5-28.3)	68.3 (54.1-80.6)	0.8 (0.4-1.4)	1.1 (0.9-1.4)
Rhonchi or wheezing	89.5	30.0 (13.9-46.7)	96.1 (94.3-98)	7.7 (2.4-22.8)	0.7 (0.5-0.9)
B					
Decreased breath sounds, abolished breath sounds, or crackles	42.0	10.0 (1.8-28.6)	93.3 (92.4-95.4)	0.9 (0.6-1.7)	1.0 (0.7-1.3)
Rhonchi or wheezing	85.0	79.5 (71.2-86.2)	20.5 (15.7-24.7)	1.5 (0.2-6.2)	0.9 (0.7-1.0)

LR+: positive likelihood ratio; and LR−: negative likelihood ratio.

of muscle paralysis and anesthesia[15]; sternotomy, small airway closure, and lung volume reduction[16]; and the effects of pulmonary circulation on lung parenchyma stability.[17] The increase in R,rs may be due to several factors, such as secretion or fluid accumulation in the airway, airway edema, and time constant inequalities.[18]

The main finding of the present study was that chest auscultation has low accuracy in detecting abnormal respiratory mechanics in mechanically ventilated patients in the immediate postoperative period after cardiac surgery. Although examiner A had 89.5% accuracy in detecting increased R,rs, the mean R,rs among the patients in whom examiner A classified the airway-related sounds as abnormal was 12.5 ± 4.9 $cmH_2O/L/s$ (below the cutoff value for increased R,rs), which could therefore be a false-positive result.

The lack of an association between respiratory mechanics and chest auscultation could be attributed to technical and physiological factors. From a technical point of view, the respiratory sound spectrum can be modulated along its path from the sound source to the auditory cortex of the health care professional. That phenomenon is related to the unsuitability of acoustic stethoscopes as instruments for detecting respiratory sounds, because they can amplify and attenuate sound transmission within the spectrum of interest,[6] as well as to the fact that the chest wall can reduce the amplitude of sound transmission.[19] From a physiological perspective, respiratory sounds are generated in the large airways and in the tissues of the lung parenchyma/chest wall, being dependent on the airflow pattern, large airway patency, lung tissue stiffness/stability, permeability of the small airways, and the propensity of the airways to collapse.[20] Although the mechanisms of airway-related sound generation have yet to be fully elucidated, they clearly involve the movement of secretions, vibration of the airway walls,[21] and airflow limitation.[22,23] During the assessment of respiratory mechanics and the chest auscultation protocols, we administered air at a high flow rate (60 L/min), which could have favored the generation of sounds in the large airways. It can be argued that chest auscultation is still useful for detecting certain mechanical abnormalities of the respiratory system, such as airflow limitation. Kress et. al.[24] found that inspection/palpation and auscultation of the chest had a sensitivity, specificity, positive predictive value, and negative predictive value of 51%, 95%, 96%, and 46%, respectively, for detecting intrinsic PEEP (i.e., auto-PEEP) in mechanically ventilated patients. The difference between the findings of those authors and our findings, regarding the sensitivity of chest auscultation in detecting abnormal airway mechanics on the basis of airway-related sounds, could be explained by a number of factors: differences in the ventilator modes and settings employed; different levels of PEEP administered; and the fact that those authors instructed examiners to listen for specific sounds related to airflow limitation, whereas we did not.

Crackles are likely generated by sudden opening and closing of airways.[25] Therefore, the examiners heard crackles whenever critical airway opening and closing pressures were reached. In cases of unstable lung parenchyma with time constant inequalities, some airways can be completely or partially open while others remain closed. If critical opening and closing pressures are not reached, there will be increases in peak inspiratory pressure and in the dissipation of pressure against the viscoelastic components of the respiratory system, whereas C_{st},rs will probably decrease. In that situation, neither inspiratory nor expiratory crackles will be heard because the closed airways will remain closed and air will flow only through the open airways. In addition, whenever the critical opening pressure of a closed airway is reached, the pressure propagates deeper into the respiratory tree and the subsequent airway will open if its critical opening pressure is reached. This phenomenon leads to an avalanche of airway openings involving a large number of alveolar units. Because that process will increase the lung volume, the pressure will decrease.[26] Consequently, there will be tidal recruitment, which can lead to overestimation of the C_{st},rs. That might explain, at least in part, the lack of an association between crackles and low C_{st},rs in the present study. We should also consider that by applying a PEEP of 8 cmH_2O, we could have, at least to some degree, increased C_{st},rs and stabilized the lung parenchyma in some patients. Nevertheless, given that the PEEP was not titrated but was applied as a protocol, mechanical abnormalities in the lung periphery were still present in the majority of the patients evaluated.

In the present study, we found fair interobserver agreement in the evaluation of airway-related sounds and no interobserver agreement regarding sounds related to the lung parenchyma or chest wall. These results are in accordance with those reported in infants and adults during spontaneous breathing.[27,28] In another study of individuals evaluated during spontaneous breathing, Sapiteri et al.[29] demonstrated moderate interobserver agreement for wheezing, reduced breath sounds, and crackles, although the authors did not provide the 95% confidence interval values for the kappa statistics.

Many factors can influence the characteristics of breath sounds in mechanically ventilated patients (e.g., auscultation sites, subject positioning, body size, airflow waveform, and breathing pattern), thus modifying examiner perception of respiratory sounds. Because the two examiners in the present study performed chest auscultation under essentially the same conditions (same auscultation sites, same stethoscope, and same ventilator settings) and in rapid succession, we believe that the lack of agreement is inherent to the chest auscultation technique itself; low-to-moderate agreement in chest auscultation occurs even among the most experienced examiners.[30]

This study has some limitations. First, we evaluated patients only in the immediate postoperative period after cardiac surgery. Therefore, it would be interesting to assess the accuracy of chest auscultation in a population of individuals showing different degrees of mechanical abnormalities of the respiratory system. In addition, we did not analyze the subgroup of patients with respiratory disease prior to surgery separately, because they represented only a small proportion of our study sample. Furthermore, it is well known that the mechanical properties of the respiratory system, including the lungs and chest wall, are modified by the inspiratory flow rate, inspiratory time, and inspiratory volume.[31] Therefore, one could argue that such variables play a major role in determining the site at which respiratory sounds would be produced and therefore which type of sounds (airway-related sounds or sounds related to the lung parenchyma or chest wall) would be the predominant sounds that examiners hear. Because we did not modify the inspiratory time or the flow rate in order to evaluate chest auscultation accuracy under different inspiratory and expiratory conditions, as well as because chest auscultation can be partially modified by the manner in which mechanical ventilators are adjusted to deliver inspiratory volume, there is a need for further studies aimed at investigating the accuracy of chest auscultation in detecting abnormal respiratory mechanics with varying tidal volumes.

In summary, we found a dissociation between abnormal respiratory mechanics and respiratory sounds assessed with acoustic stethoscopes. Chest auscultation does not seem to be an accurate method for detecting abnormal respiratory mechanics in mechanically ventilated patients in the immediate postoperative period after cardiac surgery. Therefore, respiratory mechanics should be continuously monitoring at the bedside in mechanically ventilated patients. Although chest auscultation is still a mandatory component of a physical examination, breath sounds should be interpreted in conjunction with other respiratory parameters, such as the mechanical properties of the respiratory system.

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Bronchial carcinoid tumors: second primary neoplasms and outcomes of surgical treatment

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ABSTRACT

Objective: To analyze determinants of prognosis in patients with bronchial carcinoid tumors treated surgically and the potential concomitance of such tumors with second primary neoplasms. **Methods:** This was a retrospective analysis of 51 bronchial carcinoid tumors treated surgically between 2007 and 2016. Disease-free survival (DFS) was calculated by the Kaplan-Meier method, and determinants of prognosis were evaluated. Primary neoplasms that were concomitant with the bronchial carcinoid tumors were identified by reviewing patient charts. **Results:** The median age was 51.2 years, 58.8% of the patients were female, and 52.9% were asymptomatic. The most common histology was typical carcinoid (in 80.4%). Five-year DFS was 89.8%. Ki-67 expression was determined in 27 patients, and five-year DFS was better among the patients in whom Ki-67 expression was ≤ 5% than among those in whom it was > 5% (100% vs. 47.6%; p = 0.01). Concomitant primary neoplasms were observed in 14 (27.4%) of the 51 cases. Among the concomitant primary neoplasms that were malignant, the most common was lung adenocarcinoma, which was observed in 3 cases. Concomitant primary neoplasms were more common in patients who were asymptomatic and in those with small tumors. **Conclusions:** Surgical resection is the mainstay treatment of bronchopulmonary carcinoid tumors and confers a good prognosis. Bronchial carcinoid tumors are likely to be accompanied by second primary neoplasms.

Keywords: Carcinoid tumor/diagnosis; Carcinoid tumor/surgery; Neoplasms, second primary; Lung neoplasms.

INTRODUCTION

Carcinoid tumors are rare malignant neoplasms originating from neuroendocrine cells. The bronchopulmonary system is the second most common site, harboring 20-25% of carcinoid tumors. Bronchial carcinoid tumors account for 1-5% of all cases of lung cancer.[1-3] Slow growth and a low metastasis rate characterize carcinoid tumors. Histologically, pulmonary carcinoid tumors are classified as typical or atypical according to some characteristics, such as number of mitoses and presence of necrosis.[4] It has been suggested that the classification be changed to well- to moderately differentiated neuroendocrine tumors; however, the World Health Organization classification of tumors maintains the terms typical and atypical carcinoid for bronchial tumors.[4]

Principles of staging and surgical treatment of carcinoid tumors are the same as for other types of lung cancer. However, since carcinoid tumors have a less aggressive behavior, various aspects of clinical and surgical management remain controversial. The most common prognostic determinants are histological classification, tumor size, and Ki-67 expression. However, because most case series are small, there is no consensus regarding determinants of clinical outcomes.[5,6] Another controversial aspect related to carcinoid tumors is their association with second primary neoplasms. Carcinoid tumors from different primary sites have been associated with second primary neoplasms in approximately 20% of cases.[1,7-9]

The objective of the present study was to analyze determinants of prognosis in patients with bronchial carcinoid tumors treated surgically and the potential concomitance of such tumors with second primary neoplasms.

METHODS

This was a retrospective study of data collected from medical charts of patients with a histological diagnosis of bronchial carcinoid tumor submitted to surgical resection at the A.C. Camargo Cancer Center, located in the city of São Paulo, Brazil, between 2007 and 2016. During the study period, pulmonary resections were performed in 1,623 patients, and carcinoid tumor resections were identified in 60. Of those, 3 were excluded because they had not been submitted to complete surgical resection and 6 were excluded because of missing data. Therefore, 51 patients (3.1%) were submitted to complete surgical resection due to bronchial carcinoid tumor and were included in the present study.

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Chest CT and bronchoscopy were performed in all patients. Tumors were classified as central, when they were directly visualized during bronchoscopy, or peripheral, when they were not. Staging workup was based on chest CT, bronchoscopy, positron emission tomography-CT, brain magnetic resonance imaging, and scintigraphy with radiolabeled octreotide, at the discretion of the attending physician.

Pathologists reviewed all paraffin blocks in order to define the histological diagnosis and classify them as typical or atypical carcinoid tumors in accordance with the criteria established by the World Health Organization.[10,11] Final histological diagnosis and classification were established after analysis of the surgical specimens.

The compiled data included age, gender, smoking history, symptoms, diagnostic method, tumor location, clinical stage, type of surgical resection, tumor size, number of resected mediastinal lymph nodes, histological classification, Ki-67 status, presence of second primary neoplasms, and status in the last follow-up evaluation. Tumor staging was in accordance with the 7th edition of the TNM classification of malignant tumors.[12]

Primary neoplasms that were concomitant with bronchial carcinoid tumors were identified by reviewing patient charts. Depending on when they were diagnosed, concomitant neoplasms were classified as previous to, synchronous with, or subsequent to bronchial carcinoid tumors. Synchronous diagnosis was defined as diagnosis of a second primary tumor within 3 months of the diagnosis of bronchial carcinoid tumor.

All statistical analyses were performed with the IBM SPSS Statistics software package, version 20.0 (IBM Corporation, Armonk, NY, USA). Continuous variables were expressed as median (minimum-maximum) in order to describe patient characteristics. Differences between categorical variables were assessed by the chi-square test or Fisher's exact test, as appropriate. Survival rates were calculated by the Kaplan-Meier method, and groups were compared by the log-rank test. A p-value < 0.05 was considered statistically significant for all tests.

The study was approved by the local research ethics committee (Protocol no. 1.607.727).

RESULTS

During the study period, 51 patients were identified and included in the analysis. Ages ranged from 16.6 years to 86.1 years (median, 51.2 years). Most of the patients were asymptomatic (52.9%). Among those presenting with clinical manifestations (n = 24), the most common symptoms were pneumonia, in 16; wheezing, in 7; hemoptysis, in 6; dyspnea, in 3; and cough, in 1. Tumor size ranged from 0.4 cm to 7.5 cm (median, 2.5 cm). Other clinicopathological characteristics are shown in Table 1.

All patients were submitted to complete surgical resection. Lobectomy was performed in 43 cases (84.3%); wedge resection, in 4 (7.8%); and pneumonectomy, in 4 (7.8%). In 9 patients (17.6%), a bronchoplastic procedure or a sleeve resection was associated with lobectomy, and pulmonary arterioplasty was performed in 1. The median number of removed lymph nodes was 6 (range, 0-31), lymph node metastasis being found in 3 patients (5.8%). Postoperative length of hospital stay ranged from 3 days to 20 days (median, 6 days). Postoperative complications were identified in 11 patients (21.6%): prolonged air leak, in 3; pleural effusion, in 2; hemothorax, in 1; chylothorax, in 1; pleural empyema, in 1; chronic pain, in 1; wound infection, in 1; and acute abdomen caused by obstruction, in 1. No postoperative mortality occurred.

The follow-up period ranged from 0.3 months to 115.4 months (median, 37.6 months). Systemic recurrence was observed in 3 patients (lung, bone, adrenal gland, and pleura). No local recurrence was observed, and there were no cancer-related deaths.

Five-year disease-free survival (DFS) was 89.8% (Figure 1). Determinants of 5-year DFS are shown in Table 2. Only a high level of Ki-67 expression was related to worse DFS (Figure 2). Patients with Ki-67 expression ≤ 5% showed higher DFS than those with Ki-67 expression > 5%. However, Ki-67 expression was determined in only 27 patients. Although DFS was higher in patients with typical carcinoid tumors than in those with atypical carcinoid tumors (92% vs. 82%), the difference was not significant (p = 0.55).

Second primary neoplasms were observed in 14 patients (27.5%). Of those, 11 were diagnosed with

Table 1. Clinicopathological characteristics of the study patients (N = 51).

Characteristic	n	%
Gender		
Female	30	41.2
Male	21	58.8
Smoking		
Yes	16	31.4
No	35	68.6
Clinical manifestation		
No symptoms	27	52.9
Clinical symptoms	24	47.1
Histology		
Typical	41	80.4
Atypical	10	19.6
Affected side		
Right	33	64.7
Left	18	35.3
Location		
Central	34	66.7
Peripheral	17	33.3
Lobe of origin		
Upper	22	43.1
Middle	08	15.7
Lower	21	41.2

typical bronchial carcinoid tumor. Only 5 patients were smokers. Of the 14 patients with second primary neoplasms, 11 (21.5%) had malignant neoplasms and 3 (6.0%) had benign neoplasms. The most common malignant neoplasms were lung adenocarcinoma, in 3, and ovarian carcinoma, in 2. The characteristics of second primary neoplasms are presented in Table 3.

Second primary neoplasms were classified as previous to, synchronous with, and subsequent to bronchial carcinoid tumors in 6 (11.8%), 5 (9.8%), and 3 (5.9%) of the patients, respectively. The median time between the diagnosis of previous primary neoplasms and that of bronchial carcinoid tumors was 20.6 months (range, 7.8-196.8 months), whereas the median time between the diagnosis of subsequent primary neoplasms and that of bronchial carcinoid tumors was 34.7 months (range, 17.8-42.6 months).

Correlations between different characteristics of bronchial carcinoid tumors and concomitant primary neoplasms are shown in Table 4. Concomitant primary neoplasms were found to be most common in asymptomatic patients and in those with small (T1 or T2) bronchial carcinoid tumors (Table 4).

DISCUSSION

Carcinoid tumors comprise 0.5% of all malignant neoplasms, and only 20-25% of those arise from the bronchopulmonary system.[1] Because it is a rare neoplasm, most of the studies on carcinoid tumors are retrospective in nature and include a small number of patients recruited over a long period of time.[5,6] Our study included 51 patients over a period of 10 years, similar to or even greater than other series that reported cases in a single institution.[6,13,14]

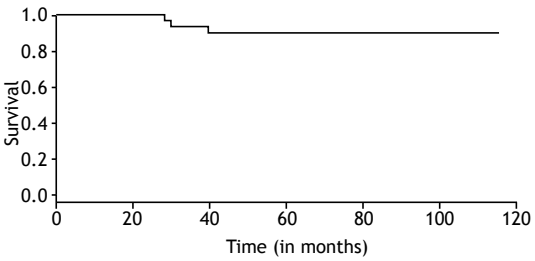

Figure 1. Disease-free survival of patients with bronchial carcinoid tumors submitted to complete surgical resection.

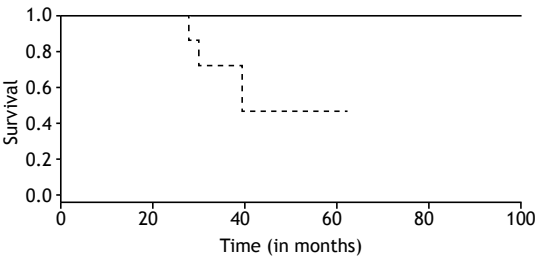

Figure 2. Disease-free survival and Ki-67 expression. Continuous line: Ki-67 ≤ 5%. Dashed line: Ki-67 > 5% (p = 0.01).

Table 2. Univariate analysis of determinants of five-year disease-free survival.

Variable	n	Five-year DFS, %	p
Age, years			
≤ 55	28	88.2	0.64
> 55	23	93.7	
Gender			
Male	21	93.3	0.56
Female	30	85.9	
Smoking status			
Smoker	16	90	0.82
Nonsmoker	35	89.5	
Histology			
Typical	41	92	0.55
Atypical	10	80	
Clinical presentation			
Asymptomatic	27	92.9	0.48
Symptomatic	24	86.7	
Location			
Central	31	88.2	0.64
Noncentral	20	91.7	
T Stage			
T1 and T2	32	90.5	0.95
T3	19	90	
Ki-67 expression			
≤ 5%	19	100	0.01
> 5%	08	47.6	

DTS: disease-free survival; and T: tumor.

In the present study, most of the carcinoid tumors were classified as typical, with no clinical manifestations, and the size of the tumor was small. The same characteristics have been described in different studies, suggesting that carcinoid tumors have an indolent clinical behavior.[5,14] Clinical manifestations have been reported in 40-50% of cases,[2,7,15] the most common being recurrent pneumonia, hemoptysis, wheezing, dyspnea, and cough, as in our study.

Surgical resection is the mainstay curative treatment of bronchial carcinoid tumors; however, there are some questions regarding the extent of resection and the role of mediastinal lymphadenectomy.[16,17]

Table 3. Characteristics of second primary neoplasms in patients with bronchial carcinoid tumors.

Primary site and type	n
Benign neoplasms	
Parotid adenoma	1
Bronchial neurofibroma	1
Parathyroid adenoma	1
Malignant neoplasms	
Lung, adenocarcinoma	3
Ovarian, serous carcinoma	2
Colorectal, adenocarcinoma	1
Melanoma	1
Palate, squamous cell carcinoma	1
Thyroid, papillary carcinoma	1
Testis, germ cell tumor	1
Cervix, squamous cell carcinoma	1

Some authors have suggested sublobar resection as an appropriate surgical approach for peripheral typical bronchial carcinoid tumors. Nevertheless, other authors recommend lobectomy/pneumonectomy regardless of the histological type.[18-20] Given that all of the aforementioned studies were retrospective in nature and compared heterogeneous groups of patients, it is difficult to draw any definitive conclusions about the extent of surgical resection to treat bronchial carcinoid tumors.[16] Sublobar resection could be an adequate procedure for small peripheral typical bronchial carcinoid tumors. In addition, pneumonectomy should be avoided when performing bronchoplasty or arterioplasty.[1,19-21]

There are no definitive studies addressing the role of mediastinal lymphadenectomy in long-term survival. One group of authors found mediastinal lymph node metastases in 11.1% of cases, and most of the cases classified as N2 (83.3%) were not identified during preoperative evaluation.[22] Because mediastinal lymph node metastases appear to be a determinant of prognosis, resection of mediastinal lymph nodes could be important for adequate pathological staging and treatment.

As in other studies,[13,17,18] lobectomy was the most common type of surgical intervention performed (in 84.3% of cases) in the present study. In order to avoid pneumonectomy, a bronchoplastic procedure was performed in 9 cases (17.6%), and arterioplasty was necessary in 1 patient. Mediastinal lymphadenectomy is our standard approach for all lung cancers. However, in our series of bronchial carcinoid tumors, no lymph

Table 4. Correlation of clinicopathological variables between patients with bronchial carcinoid tumors with and without second primary neoplasms.

Variable	Second primary neoplasms		p
	Yes	No	
Age, years			
≤ 55	5 (17.9%)	23 (82.1%)	0.09
> 55	9 (39.1%)	14 (60.9%)	
Gender			
Male	8 (38.1%)	13 (61.9%)	0.15
Female	6 (20.0%)	24 (80.0%)	
Smoking status			
Smoker	5 (31.2%)	11 (68.8%)	0.68
Nonsmoker	9 (25.7%)	26 (74.3%)	
Histology			
Typical	13 (31.7%)	28 (68.3%)	0.25
Atypical	1 (10.0%)	9 (90.0%)	
Clinical presentation			
Asymptomatic	10 (30.3%)	23 (69.7%)	0.05
Symptomatic	4 (22.2%)	14 (77.8%)	
Location			
Central	7 (22.6%)	24 (77.4%)	0.33
Noncentral	7 (35.0%)	13 (65.0%)	
T Stage			
T1 and T2	12 (37.5%)	20 (62.5%)	0.05
T3	2 (10.5%)	17 (89.5%)	

T: tumor.

nodes were removed in 3 patients. Those patients were older and underwent sublobar resection of small and peripheral tumors. Metastases were found in only 3 (5.8%) of the patients submitted to mediastinal lymphadenectomy. Despite these controversial aspects, we believe that lobectomy associated with mediastinal lymphadenectomy should be performed in all patients with adequate clinical performance, regardless of histological type and absence of lymph node metastases in clinical staging. We recommend this approach because sometimes complete histological classification is only obtained after complete resection and analysis of an entire specimen. The possible presence of clinically unsuspected lymph node metastases demands lymphadenectomy.

Since bronchial carcinoid tumors usually have a less aggressive biological behavior, the overall survival is good. Various studies have reported low rates of recurrence and 5-year overall survival higher than 80%.[5,18,21]

Some prognostic factors can help predict more aggressive biological behavior among bronchial carcinoid tumors. Atypical carcinoid tumors and lymph node metastasis are described as factors associated with a worse prognosis.[5,15,21,23] Histology is considered to be an independent prognostic factor in most studies.[2,5,15,19,21,24] Contrary to what has been described in most studies,[5-7,11,21] 5-year DFS was not significantly different between typical (92%) and atypical (80%) carcinoid tumors in our study. According to Cardilo et al.,[24] histology is not an independent determinant of survival. Kornerup et al.[25] evaluated 68 patients with carcinoid tumors and found no differences in overall survival between typical and atypical tumors. With regard to histology, our results are inconsistent with those of other studies.[5-7,11,21] This might be due to the fact that there were few (only three) recurrent events and the median follow-up period was short (i.e., 37.6 months) in our study.

In our study, Ki-67 expression was the only variable associated with prognosis. Because determination of Ki-67 expression is not routinely performed at our institution, data on Ki-67 expression were available for 27 patients only, and any statistical analysis of a small group of cases should be cautiously interpreted. Nevertheless, DFS was significantly higher in patients with Ki-67 expression < 5% in our sample. Kornerup et al.[25] also found that the histological classification (typical or atypical tumors) had no influence on the outcomes, but Ki-67 expression was an important prognostic factor. Similarly, Zahel et al.[26] questioned the reliability of that histological classification to determine the biological behavior of pulmonary carcinoid tumors. They concluded that Ki-67 expression and mitotic count are better predictors of the clinical behavior of these tumors.[25,26] Because of those controversies, prognostic factors in patients with bronchial carcinoid tumors should be continuously evaluated.

The occurrence of second primary neoplasms in patients with carcinoid tumors has been described over the years. Berge and Linel[8] were the first to describe it, in 1976; they found second primary neoplasms in 40.7% of the patients in their retrospective study. However, neoplasms were incidentally found in 44.5% of autopsies, a proportion that is similar to that reported for second primary neoplasms in patients with carcinoid tumors and suggests that the incidence of second primary malignant neoplasms in patients with carcinoid tumors is no higher than that reported for patients with other cancers.[8] Nevertheless, other, more recent studies have shown that the prevalence of patients with carcinoid tumors and second primary neoplasms ranges from 18% to 25%.[9,27-29]

Our study found a strong association between bronchial carcinoid tumors and other primary neoplasms (27.5%). Most of the bronchial carcinoid tumors were identified after detection of other neoplasms and were small and asymptomatic. These findings suggest that bronchial carcinoid tumors constituted incidental findings in patients with previous neoplasms. This remains to be explained. It might be a simple association, or, as some authors have suggested,[30] the high frequency of concomitant neoplasms might be the result of mitogenic activity of growth factors secreted by carcinoid tumors.

The present study has some limitations that should be considered: its retrospective nature, the small number of cases over a long period of time, the small number of recurrent events, and the short follow-up period.

In conclusion, the present study showed that bronchial carcinoid tumors are rare neoplasms and that complete surgical resection offers a good prognosis. Although additional studies are needed in order to identify determinants of prognosis, mitotic activity, as measured by Ki-67 expression, seems to be an important prognostic factor. Bronchial carcinoid tumors are likely to be accompanied by second primary neoplasms. The reasons for this association remain unclear, and additional studies are needed to address this question.

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Translation and cultural adaptation of the King's Brief Interstitial Lung Disease health status questionnaire for use in Brazil

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ABSTRACT

Objective: To translate the King's Brief Interstitial Lung Disease (K-BILD) questionnaire to Portuguese and culturally adapt it for use in Brazil. The K-BILD quantifies the health status of patients with ILD. **Methods:** The process involved the following steps: authorization from the author of the original (English-language) questionnaire; translation of the questionnaire to Portuguese by three translators, working independently; merging of the translations by a committee of specialists; back-translation of the questionnaire to English; revision and readjustment of the back-translation by the committee of specialists; evaluation by the original author; revision of the back-translation; cognitive debriefing (verification of the clarity and acceptability of the Portuguese-language version in the target population—i.e., patients with ILD); and finalization of the Portuguese-language version. **Results:** In the cognitive debriefing step, 20 patients with ILD were interviewed. After the interviews, the clarity and acceptability index of each question was ≥ 0.8, which is considered acceptable. **Conclusions:** The Portuguese-language version of K-BILD appears to be easily administered to and understood by patients with ILD in Brazil. To our knowledge, this is the only instrument in Brazilian Portuguese that is designed to evaluate the impact that ILD has on the various aspects of the lives of those it affects.

Keywords: Lung diseases, interstitial; Pulmonary fibrosis; Surveys and questionnaires.

INTRODUCTION

Interstitial lung disease (ILD) is a term that refers to a group of chronic and progressive conditions characterized by inflammation and fibrosis of the lung parenchyma, directly associated with mortality.[1] According to a study from 1994, the incidence of ILD in New Mexico, USA, was 26-32 cases per 100,000 population per year.[2] In Brazil, a survey conducted by the Department of Informatics of the Unified Health System showed that, in 2010 alone, the incidence of idiopathic pulmonary fibrosis was 4.84 cases per 1,000,000 population.[3]

As described in the literature, patients with ILD often present with dyspnea symptoms that limit their physical activity levels.[4] The quality of life of those patients depends on various factors, such as the symptoms of the disease itself, the side effects of drug therapy, the natural progression of respiratory dysfunction, and morbidity-related functional limitations.[5] ILDs are characterized by symptoms such as dyspnea, reduced lung volume, reduced gas exchange, reduced tolerance to exercise, diaphragmatic weakness, expiratory muscle fatigue after maximal exercise, and impaired peripheral muscle function. The condition also reduces patient quality of life and survival.[6-9]

ILDs are often diagnosed late,[10] mainly because of the limited knowledge of health care professionals and the lack of local resources. Different ILDs have different prognoses and treatments, and it is difficult to establish accurate prognoses for patients with newly diagnosed ILD, because the natural history of the disease can vary.[11-13] The treatment of ILD aims to improve patient health in a broad sense. The impact of treatment can be measured by means of the support of specific questionnaires (disease-specific instruments), which are more responsive than generic instruments.[14]

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There is a shortage of specific instruments to measure the health status of patients with ILD. With the objective of developing a brief, easy-to-administer, validated tool, Patel et al.[4] developed ILD-specific instruments. One of those is the King's Brief Interstitial Lung Disease (K-BILD) health status questionnaire, which was originally written in English but has already been translated into several languages and adapted for use in different countries. The lack of specific instruments and objectives for certain diseases affects their diagnoses, as well as the choice of therapies and interventions.[15,16] The process of developing such instruments is thorough and time-consuming. Therefore, translating and culturally adapting a questionnaire that has already been validated in another language for use in different countries and cultures can be extremely valuable for the evaluation, follow-up, and diagnosis of the patients for whom it was developed.[15,17]

In this context, the need for translating and culturally adapting this specific instrument (K-BILD), which measures the health status of patients with ILD, to Brazilian Portuguese is justified. The objective of the present study was to translate and culturally adapt the K-BILD questionnaire to Brazilian Portuguese.

METHODS

Our study focuses on the cultural adaptation and translation of a specific instrument (K-BILD) that measures the health status of patients with ILD for use in Brazil. The study was approved by the Human Research Ethics Committee of the *Universidade do Sul de Santa Catarina* (protocol no. 2.296.776/2017). The study is in accordance with the ethical precepts on research involving humans of the Brazilian National Health Council (Resolution 466/2012).

A process of translation and cultural adaptation should always evaluate the clarity, acceptability, comprehensibility, and reproducibility of the instrument in its target population. This is the step we denominate cognitive debriefing. To this end, all ILD patients who were undergoing treatment and having routine appointments at the Pulmonology Outpatient Clinic of the *Hospital Universitário Polydoro Ernani de São Thiago* of the *Universidade Federal de Santa Catarina*, located in the city of Florianópolis, Brazil) between October of 2017 and March of 2018 were invited to participate in the study.

The inclusion criteria were having a clinical diagnosis of ILD; being older than 18 years of age; being literate; and having given written informed consent for participation.

For the interview with the study participants, we used version 4 of the K-BILD questionnaire, already translated and adapted, to assess the comprehensibility and acceptability of each question. All the comments made by the participants were registered. The participants also completed a clinical survey covering the following topics: sociodemographic data, age, gender, ethnicity, marital status, level of education, ILD diagnosis, comorbidities, the modified Medical Research Council Dyspnea Scale classification,[18] and CT and spirometry findings for the diagnosis of ILD. Participation in the study did not incur in any expenses for participants, nor did it change the proposed treatment.

The methodology for translating and culturally adapting a questionnaire to a foreign language, different from the one in which the instrument was originally written, encompasses several steps. The steps of the protocol used in the present study were: 1) preparation: author's authorization for the study (rights to use, translate, and culturally adapt the instrument); 2) translation of the K-BILD from English to Brazilian Portuguese: three people performed a blind translation of the questionnaire (two native speakers of Portuguese with fluency in English and one native speaker of English with fluency in Portuguese); 3) merging: comparison and merging of the three Portuguese translations to create one single version in Portuguese, designated version 1; 4) back-translation: a literal back-translation of version 1 into English by a native speaker of English who was fluent in Portuguese and who was blinded to the original questionnaire. This version was designated version 2 (in English); 5) revision and readjustment of the back-translation: comparison of the back-translation with the original English version. Because the two English versions were very similar, no changes had to be made; 6) evaluation by the original author: version 2 was sent to the author of the K-BILD for analysis. The author made comments about items 3 and 6 of the questionnaire. Based on these observations, a new version was created: version 3 (in English); 7) revision of version 3: analysis of version 3 by the review committee and preparation of version 4 (in Portuguese); 8) cognitive debriefing: in this step we applied the questionnaire to 20 patients with ILD who agreed to participate in the study; the objective was to assess the clarity of the instrument as a whole so as to enhance it and improve its comprehensibility. All items were analyzed according to the instrument's Likert scale, and all comments made by the participants were registered; and 9) preparation of the final version: meeting of the review committee for the production of the final version of the instrument adapted for use in Brazil. Figure 1 illustrates the steps of the process.

RESULTS

During the study period, 95 patients with ILD were seen at the pulmonology outpatient clinic of the institution. Of those, 20 were included in the cognitive debriefing step of the study. The age of the participants ranged from 32 to 77 years, whereas the level of education ranged from complete primary education (50%), to complete secondary education (40%), and complete higher education (10%). The most common complaint was shortness of breath when exercising and performing activities of daily living—mentioned by 17 participants (85%), who had scores > 2 in the modified Medical Research Council scale.[18] Table

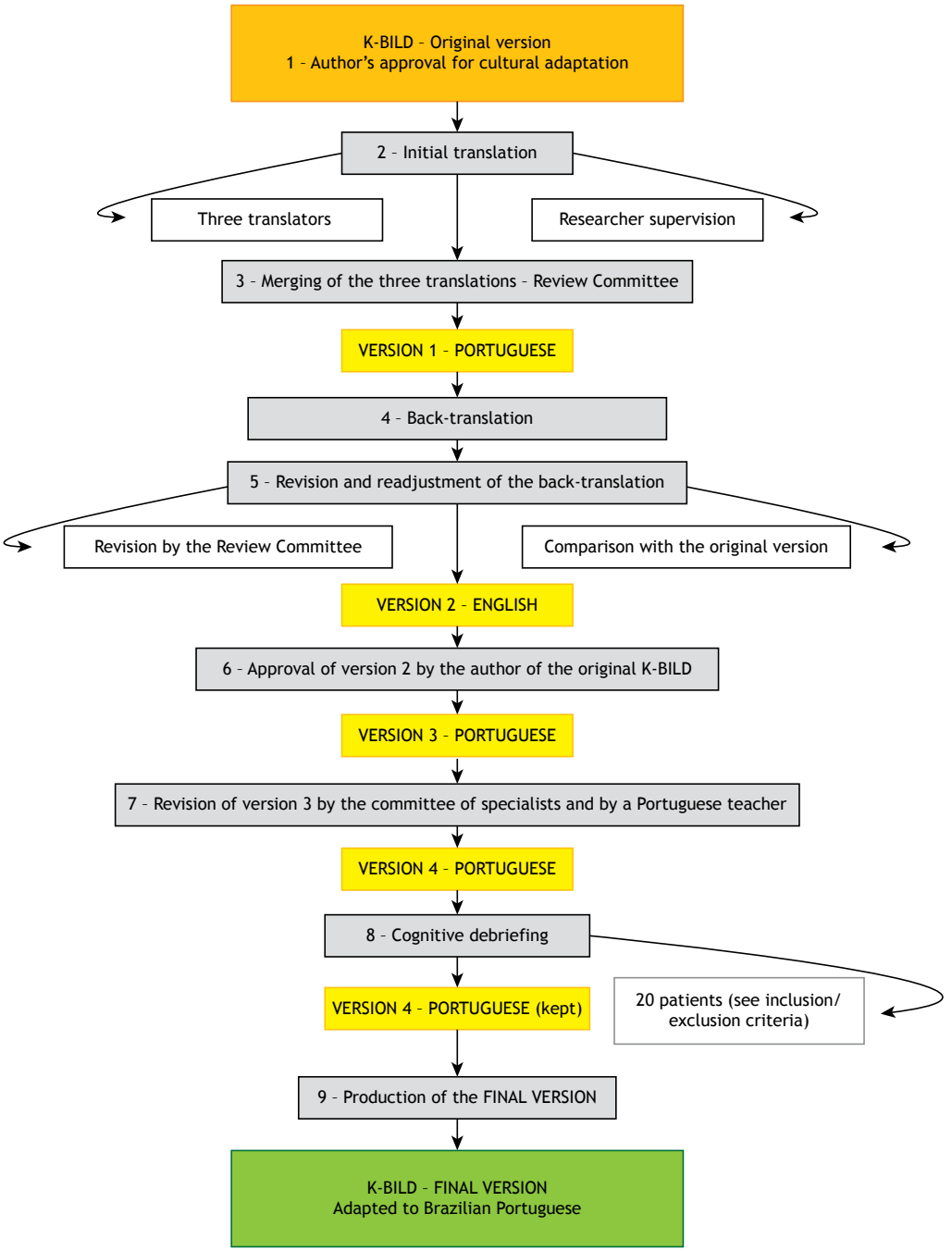

Figure 1. Summary of the process of translation and cross-cultural adaptation of the King's Brief Interstitial Lung Disease (K-BILD) questionnaire to Brazilian Portuguese.

1 describes the clinical and functional status of the study participants.

The versions produced by the translators generated no doubts or corrections. A back-translation of the K-BILD was done and sent to the author for evaluation, who responded with the following remarks: 1) in item 3: the original term "severe" had been back-translated as "severity". The committee gave the author a complete explanation of the concept in Portuguese and he decided that the term "*gravidade*" or "severity" be kept; 2) in item 6, the author questioned the use of the word "tired" or "*cansado*" in Portuguese clarifying that the term should refer to a feeling of low self-esteem related to depression or, in his words, "feeling low in mood, like depression". The committee, then, suggested replacing the term "*cansado*" or "tired" with "*incomodado*", which means "annoyed", "bothered". The suggestion was well received by the author, who considered the semantics of the term equivalent to that of the original version. The committee of specialists' revision conducted

Table 1. Characteristics of the participants in the study (N = 20).[a]

Characteristic	Result
Age, years[b]	59 (32-77)
Gender	
Female	14
Male	6
Ethnicity	
White	16
Brown	3
Indigenous	1
Level of education	
Primary education	10
Secondary education	8
Higher education	2
Diagnosis of ILD	
Interstitial lung disease secondary to collagen disease	3
Idiopathic pulmonary fibrosis	5
Nonspecific interstitial pneumonia	6
Chronic hypersensitivity pneumonitis	3
Alveolar proteinosis	2
Sarcoidosis	1
mMRC scale score	
0	3
2	9
3	5
4	3
Associated morbidities	
Systemic arterial hypertension	12
Dyslipidemia	6
Chronic kidney disease	2
Gastroesophageal reflux disease	1
Diabetes mellitus	1
Pulmonary function[c]	
FEV_1, % of predicted	65.5 (56.2-76.7)
FVC,% of predicted	66.5 (57.7-83.7)
FEV_1/FVC % of predicted	98.5 (92.5-108.5)

ILD: interstitial lung disease; and mMRC: modified Medical Research Council scale. [a]Values expressed in n, except where otherwise indicated. [b]Values expressed in median (minimum-maximum). [c]Values in median [interquartile range]. Reference values according to Crapo et al.[19] Patients evaluated while using their control medication, prior to the use of bronchodilators.

after this step showed no grammatical errors; the formatting of the questionnaire with a horizontal Likert scale was kept.

In the cognitive debriefing step, we asked about the participants' understanding of each statement and how appropriate they thought it was. We gave a clarity score between 1 and 10 for each item based on participants' understanding of the wording of that statement. On that occasion, we defined that scores between 1 and 4 would indicate a confusing statement that should be rewritten; scores between 5 and 7 would indicate an unclear statement that should be clarified; and scores between 8 and 10 would indicate a clear statement. To assess the clarity, acceptability, and comprehensibility of the instrument, each participant was asked to comment on each item with a score below 8.[20,21] Questions with a clarity index above 80% were accepted without further corrections.

The clarity index was defined by calculating the mean of the sum of the item scores given by the participants. The clarity index of each question was: 1) 9.50; 2) 9.15; 3) 9.50; 4) 9.60; 5) 9.05; 6) 9.15; 7) 8.80; 8) 9.30; 9) 9.65; 10) 9.40; 11) 9.45; 12) 9.20; 13) 9.30; 14) 9.25; and 15) 9.45. All means were above 8.0; therefore, we did not need to modify any of the terms, and version 4 in Portuguese was kept as the final version.

All data were registered in a separate record (available to those involved in the study) and will be kept for 15 years. All the study data will be filed in the archives of the pulmonology outpatient clinic of the institution and kept confidential, in accordance with the national and international good clinical research practice guidelines.

DISCUSSION

In the present study we described the process of translating the K-BILD—an instrument for the assessment of the health status and quality of life of patients with ILD[4]—to Brazilian Portuguese and its cultural adaptation for use in Brazil. The Portuguese version of the K-BILD that we developed (Supplement S1) is technically and semantically equivalent to the original version.[4] The challenges of culturally adapting an instrument are manifold, and, given Brazil's huge territory, there are many regional and sociocultural differences to be taken into consideration, in addition to the problem of the significant illiteracy rates in certain regions, which makes it even more difficult to adapt instruments like this and make sure they are comprehensible and relevant in the entire country. During the process of cultural adaptation, the committee of specialists analyzed the different domains addressed by the original instrument in terms of their relevance and appropriateness to the new cultural context and concluded they were all pertinent.[22] In this process, words of common usage in oral register were chosen, aiming to facilitate the understanding of the questions. It is widely known that the level of education as well as reading and interpreting skills are very important variables in this type of population studies, which they may affect the results.[15] Therefore, simple vocabulary words and shorter sentences were used to facilitate the reading by people with limited vocabulary and lower levels of education. Region-specific terms commonly found in oral and written Brazilian Portuguese were avoided.

After translating and back-translating the original instrument, we asked the target population about their understanding of the concepts addressed by the questionnaire. Their inputs enabled the committee of specialists to have a more comprehensive approach to their considerations and gave them more confidence in the semantic equivalence of the final version, decreasing the likelihood of it including inappropriate or ambiguous terms and, thus, creating a version that would be a good fit to the socioeconomic background of the target population. This process enabled us to achieve semantic (actual meaning of words) and idiomatic (interpretation of colloquialisms) equivalence. By adopting a strict methodology to reduce regionalism and, at the same time, making the most of this myriad of aspects that make up the Brazilian culture, the present study contributes to the efforts to provide the scientific community with a useful tool for assessing the health status of patients with ILD.

We expect that, with the validation of the K-BILD questionnaire in Portuguese, it can be used as a reference by multidisciplinary teams in Brazil providing ILD patients with follow-up and treatment, and contribute to the improvement of their quality of life. This questionnaire will also enable further studies on ILD, as it is an appropriate and effective instrument for assessing the health status of patients with this condition.

In conclusion, the K-BILD questionnaire has been successfully translated to Brazilian Portuguese and culturally adapted for use in Brazil. To our knowledge, it is the only instrument available in Portuguese to assess the impact of ILD on different aspects of life in patients with the disease.

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Factors related to the use of hookah among medical students

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ABSTRACT

Objective: This study evaluated the factors related to the use of hookah among medical students, the level of knowledge about the involved harms, and their relationship with the use and intention to stop using it. **Methods:** Students of the 1st and 6th year of medical school were evaluated. A multivariate logistic regression model was used to evaluate the association between the outcome (use of hookah in the last 30 days) and demographic, subjective psychosocial data and level of knowledge about the harms of hookah use. **Results:** The experimentation rate of hookah and current use was high (59.6% and 27.7%, respectively), with no difference between the 1st and 6th year groups (p=0.70). The 6th grade students were more knowledgeable about the harm of using hookah when compared to the 1st year students (p <0.0001), and there was no association between the use of hookah in the last 30 days and the knowledge about its harms. Cigarette smoking and the use of alcoholic beverages were associated with the use of hookah in the last 30 days, with unadjusted Odds Ratio (OR) of 11.3; 95% CI 4.62-27.7; p <0.0001 and OR 8.74; 95% CI 3.78-20.2; p <0.0001; respectively. **Conclusion:** There is a high experimentation, current use of hookah and cigarettes among medical students. Sixth year students are more knowledgeable about the harms involved. There was no association between the use of hookah in the last 30 days and the knowledge about its harms. Smoking and the use of alcoholic beverages are independent predictors of use of hookah.

Keywords: Water pipe smoking; Tobacco for water-pipe; Smoking; Medical education.

INTRODUCTION

An estimated number of 100 million people in the world use hookah for tobacco consumption. In the last decades its consumption has increased considerably in the Americas,[1] reaching experimentation rates of up to 50% among high school students in the North Caroline (USA).[2]

The way tobacco is consumed through hookah is completely different from the cigarette. Hookah fans get together to share the device, what could predispose the user to acquire bacteria, viruses and fungi contamination, as shown in literature.[3] Flavored bar tobacco is placed inside the hookah and submitted to high temperatures through coal combustion, which is used for burning. The inhalation sends the smoke through a recipient containing water, which is located in the lower part of the hookah and which cools the smoke, apparently smoothing the inhalation, according to users. Each hookah section lasts between 45 and 60 minutes, which represents one exposition equivalent to 100-200 cigarettes, thus offering higher levels of nicotine and higher exposition to carbon monoxide.[4]

The use of hookah is associated to a higher risk of developing lung diseases, periodontal disease, lung cancer[5] and nicotine addiction.[3]

A study performed in 2013 with 1,203 university students in the United States estimated an experimentation frequency of 46.4% and of continuous use in the last year of 28.4%.[6] Another study with 744 students at the University of Virginia found a hookah experimentation rate of 48.4%, and 20.4 declared having used it in the last 30 days.[7]

In Brazil, the general prevalence of hookah tobacco consumption is still little known. Data from the health national research of Brazilian students in 2015, counted with a sample of 102,301 students from the ninth grade of elementary school, found that around 6.1% used other tobacco products (cigarillo, hookah or snuff) on the 30 days prior to the research, and that the greatest prevalences were found in the Mid-West region (10%) and South region (9.6%).[8] Meanwhile, another study performed with 586 university students in Brazil found a prevalence of 47.32% of hookah use.[9]

The present study aims to evaluate the Hookah use frequency among students of the beginning and end of the medical course and relate psychosocial, demographic and level of knowledge factors about the hazards of Hookah use with frequency use and intention of stopping using it.

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METHODS

It is a transversal study, performed in a single meeting, with students from the 1st and 6th grade of the medical course of Pontifícia Universidade Católica de Goiás. We used an investigative and structured data collection tool, without identification and self-filling. More detailed information can be found in the online supplement of the JBP (Chart S1, available at http://www.jornaldepneumologia.com.br/detalhe_anexo.asp?id=70). Data related to psychosocial aspects were approached with objective questions copied from PENSE study,[8] containing the following questions: 1) Do you practice sports regularly (more than 2x week)?; 2) Are you overweight?; 3) Do you frequently feel sad or depressed (more than 2x week)?; 4) Are you engaged in any remunerated activity in your spare time?; 5) Do you consume alcoholic drinks at least 2x/week?

The particularities on Hookah use were evaluated with the following questions copied from Smith et al.[10] study questionnaire: Do you smoke or have already smoked? (comprising the consumption not only of regular cigarettes but also of other devices of tobacco use); 2) Have you ever smoked Hookah? (question that identifies Hookah experimentation);[11] 3) In the last 6 months, did you smoke Hookah?; 4) In the last 30 days, how many times did you smoke Hookah? (question that identifies current consumers/prevalence of Hookah current use);[11] 5) If you smoke Hookah, or other tobacco products, do you intend to stop?

In order to check the knowledge about the cigarette and Hookah hazards, we asked the following questions: 1) Compared to a regular cigarette, which, do you think, is more harmful?; 2) Which has more nicotine?; 3) Which is more carcinogenic?; 4) Which produces more carbon monoxide?; 5) Which produces more heavy metals? Such questions were elaborated from studies previously published in Brazil[12] and from the GTSS[13] data collection instrument.

We submitted to the approval of the Ethics Committee on Human Beings Research of the Pontifícia Universidade Católica, with opinion number 2313290 and CAAE number 73375517400000037. The questionnaire was applied after the students had signed the Informed Consent Form. We distributed 172 questionnaires, corresponding to the number of students that met the inclusion criteria (to be a student from the 1st or 6th grade of the medical course and to be present at the activity performed at the moment of the data collection). A total of 155 students agreed with the study, and from these 141 questionnaires were filled up correctly and selected for participation.

The results were analyzed with the program Stata version 13.1 (StataCorp, Texas, USA), and the level of significance was 5% ($p < 0.05$). Data normality was evaluated with the Shapiro-Wilk test. As the continuous variables did not present regular distribution, they were described using median and interquartile interval. The qualitative variables were described using absolute values and proportions. The qui square test was used to analyze the categorical variables and were calculated the non-adjusted relative risk estimates (Odds ratio) of the association between Hookah use in the last 30 days and each variable studied with confidence interval of 95%. All possible predictive variables were included in a multivariate logistic regression model to evaluate the association between the outcome (Hookah use in the last 30 days) and each independent variable while it was done the control of co-variables included in the model.

RESULT

A total of 172 students from 1st and 6th grades of the medical course, who were present at the moment of the data collection, were invited to participate in the study. From these, 155 (90%) were included and answered a self-applied questionnaire. The final sample consisted of 141 students, 72 (51.1%) from the 1st year and 69 (48.9%) from the 6th. A number of 14 individuals were excluded due to incomplete forms or with erasures (Figure 1).

The studied sample was predominantly formed by female individuals (54.6%), white (68.8%), average age of 23 years old (IQR 20-24 years), who lived with their parents or relatives (81.6%) and practiced sport with frequency ≥2x/week (68.1%). We verified that the students of the 6th year were older ($p<0.0001$), lived alone in higher proportion ($p=0.02$) and considered themselves overweight too in higher proportion ($p=0.01$) when compared to the 1st year ones.

Hookah experimentation rate was of 59.6% and did not differ from the groups of the 1st and 6th grades ($p=0.70$), and the same was observed regarding current smoking (40.4%, $p=0.32$).

From the 141 individuals, 39 (27.7%) reported having consumed Hookah more than 5 times in the

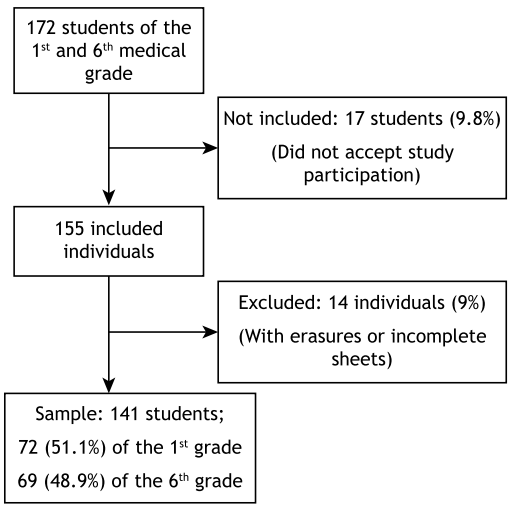

Figure 1. Research flowchart.

last 30 days, and this proportion was similar between the groups of the 1st and 6th grade (p=0.68).

When asked if Hookah would be more harmful and presented higher exposition to nicotine compared to cigarette, we observed higher proportion of correct answers in the 6th grade when compared to the 1st (p<0.0001, to both questions). However, there was no difference between the groups regarding the knowledge of Hookah generating more cancer and providing more exposition to heavy metals or to CO. We did not observe association between Hookah consumption and greater or lesser knowledge about its harms (Table 1)

Most participants that used cigarettes or Hookah (85%) reported that they intended to stop using it, and we did not observe significant differences between the groups regarding that intention (Table 2).

Cigarette smoking and the use of alcoholic drinks were associated to Hookah use in the last 30 days (current consumption) (Table 1), with unadjusted Odds Ratio of 11.3; IC95% 4.62-27.7; p<0.0001 and OR 8.74; IC95% 3.78-20.2; p<0.0001; respectively. The multivariate analysis confirmed that both smoking and alcoholic drinks use are independent predictors of Hookah, adjusted OR of 7.74; IC95% 2.99-19.99; p<0.0001 and OR 5.62; IC95% 2.25-14.0; p<0.0001; respectively.

DISCUSSION

From the 141 students of medical course that correctly answered the applied questionnaire, there was a high Hookah experimentation index (59.6%), which did not differ between the groups of the 1st and 6th grade (p=0.70). Comparatively, this frequency was above the values found among students of medical schools in Canada (40%),[14] South Africa (43.5%),[15] England (51.7%),[16] however very similar to what was observed at a former study among university students of the medical course in the city of São Paulo, where Hookah experimentation rates got to 47.32%.[17]

We observed a prevalence of 27.7% current use, which was higher than the one found in another study. In the latter one, Hookah experimentation levels got to approximately 40% and the current use corresponded to 17% of the interviewed (considering the use in the last 30 days among the ones who reported the initial date of consumption prior to these 30 days).[2] Also higher than another study that found experimentation of 33% and a prevalence of current consumption of 10.2%, considering the use of at least once in the last 30 days.[18] Hookah use usually occurs in reunions with friends, in an intermittent way, in a social atmosphere and in a recreational way,[10] what could explain the differences between the experimenters' frequencies and the regular users. It is also observed in the literature, a wide variation of current consumers' definitions and the experimentation in the different studies. A standardization on the current users' definition and the experimentation definition would favor a comparison of these findings in different populations.

A study with 486 students, from a private university in New York (USA), evaluated predisposing and protector factors for onset of Hookah consumption did not find a correlation among factors described as protectors, such as: self-esteem sensation, religiosity and high

Table 1. Characteristics and psychosocial factors associated to Hookah use in the last 30 days among medical students in Goiânia, Goiás, (n=141individuals).

	No n=102	Yes n=39	p
Age, years, average (IQR)	23 (19-24)	23 (20-24)	0.95
Male gender, n (%)	47 (46.1)	17 (43.6)	0.79
Color, n (%) white	66 (64.7)	31 (79.4)	
brown	30 (29.4)	7 (18)	0.23
black	6 (5.9)	1 (2.6)	
Lives alone n (%)	21 (20.6)	5 (12.8)	0.29
Smoking in activity, n (%)	26 (25.5)	31 (79.5)	<0.0001*
Sport ≥2x/week, n (%)	66 (64.7)	30 (76.9)	0.16
Above ideal weight n (%)	27 (26.5)	11 (28.2)	0.84
Depressed ≥2x/week n (%)	35 (34.3)	14 (35.9)	0.86
Remunerated activity, n (%)	9 (8.8)	6 (15.4)	0.26
Alcohol ≥2x/week, n (%)	23 (22.6)	28 (71.8)	<0.0001*
Hookah more harmful (hits), n (%)	62 (60.8)	17 (43.6)	0.07
Hookah more nicotine (hits), n (%)	44 (43.1)	12 (30.8)	0.18
Hookah more cancer (hits), n (%)	48 (47.1)	22 (56.4)	0.32
Hookah more CO (hits), n (%)	65 (63.7)	26 (66.7)	0.74
Hookah more heavy metals, (hits), n (%)	59 (57.8)	17 (43.6)	0.24
Total n° of hits, average (IQR)	2 (2-4)	2 (2-3)	0.24

Sample with data from n: 141 individuals, n: 102 individuals who were not used in the last 30 days and n: who were used in the last 30 days. Values expressed as median (IQR: interquartile range) or as absolute and percentage n (%). *p values <0.05 were statistically evaluated.

Table 2. Characteristics, hookah use and knowledge among medical students Goiânia, Goiás, within the studied period (n=141 individuals).

	All individuals n=141	1st grade n=72	6th grade n=69	p
Age, years, average (IQR)	23 (20-24)	20 (18.5-21)	24 (23-27)	<0.0001*
Male gender, n (%)	64 (45.4)	33 (45.8)	31 (44.9)	0.91
Color, n (%) white	97 (68.8)	48 (66.7)	49 (71)	
brown	37 (26.2)	20 (27.7)	17 (24.6)	0.85
black	7 (5.0)	4 (5.6)	3 (4.4)	
Lives alone n (%)	26(18.4)	8 (11.1)	18 (26.1)	0.02*
Smoking, n (%)	57 (40.4)	32 (44.4)	25 (36.2)	0.32
Sport ≥2x/week, n (%)	96 (68.1)	54 (75)	42 (60.9)	0.07
Above ideal weight, n (%)	38 (27)	12 (16.7)	26 (37.7)	0.01*
Depressed ≥2x/week, n (%)	49 (34.8)	26 (36.1)	23 (33.3)	0.73
Remunerated activity, n (%)	15 (10.6)	10 (13.9)	5 (7.3)	0.20
Alcohol ≥2x/week, n (%)	51 (36.2)	30 (41.7)	21 (30.4)	0.17
Has already tried hookah, n (%)	84 (59.6)	44 (61.1)	40 (58)	0.70
Hookah in the last 6 months, n (%)	47 (33.3)	24 (33.3)	23 (33.3)	1.00
Hookah in the last 30 days, n (%)	39 (27.7)	21 (29.2)	18 (26.1)	0.68
Hookah more harmful (hits), n (%)	79 (56)	27 (37.5)	52 (75.4)	<0.0001*
Hookah more nicotine (hits), n (%)	56 (39.7)	17 (23.6)	39 (56.5)	<0.0001*
Hookah more cancer (hits), n (%)	70 (49.7)	33 (45.8)	37 (53.2)	0.36
Hookah more CO (hits), n (%)	91 (64.5)	45 (62.5)	46 (66.7)	0.61
Hookah more heavy metals, (hits), n (%)	76 (53.9)	36 (50)	40 (58)	0.43
Total n° of hits, average (IQR)	2 (2-4)	2 (2-3)	3 (2-5)	0.001*
Intends to stop using Hookah, n (%)	75 (85.2)	44 (91.7)	31 (77.5)	0.06

Values expressed as median (IQR: interquartile range) or as absolute and percentage n (%). *p values <0.05 were statistically evaluated.

academic performance and the onset of Hookah use, and among the factors described as risk factors, only the impulsive behavior was related with Hookah experimentation.[19] In our study, psychosocial data, such as regular physical exercise practice, to feel depressed, to be overweight, live alone or be engaged, work in some remunerated activity in addition to the activities of the university education, were not different among Hookah users and non-users.

We observed that the onset of Hookah use happens at a later time, after the individuals had contact with alcohol, marijuana or cigarette[2,10,20] and is frequently associated with alcoholic drinks consumption.[19,21] Our study found that alcoholic drinks consumption is around three times higher among Hookah smokers when compared to non-smokers. At a longitudinal study performed with 936 university students from the New York region (USA) and surroundings, around 96% of Hookah users reported the current use of alcohol compared to 61% of non-smokers.[19]

Some theories about psychological development suggest that both Hookah experimentation and other substances such as alcohol and marijuana would be related to a transition process from adolescence to adult age[22] and that it most frequently happens within the university student environment.[19] The closeness of university environment to bars where the use of hookah and alcohol is encouraged could be related to the higher popularity of this device in this specific population,[17] what could at least partially explain this association frequently found in the different studies.

Regarding the knowledge about the Hookah hazards, different studies demonstrated that there is a mistaken perception that Hookah could be less harmful than the cigarette, and this could reinforce the experimentation and consumption.[10] In our study, however, when we compared the groups with greater or lesser correct knowledge assessment, both Hookah experimentation and habitual use and the intention to stop using it did not relate to a higher or lower knowledge about Hookah hazards. In another study performed among university students from the medical course, the lack of knowledge was also not related to a higher use of the device.[17]

In conclusion, we verified that there is a high Hookah and cigarettes experimentation and use among medical students. The higher knowledge about the use hazard among the 6th grade was not associated with a lower use frequency or with a higher intention of interrupting its consumption. It was demonstrated that smoking and the use of alcoholic drinks are independent predictors of Hookah use. However, more studies are

necessary to elucidate additional factors related to the high frequency of Hookah use observed in this population, in order to suggest further strategies and public policies of awareness and engagement against the use of this device.

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Safety and tolerability of nintedanib in patients with idiopathic pulmonary fibrosis in Brazil

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ABSTRACT

Objective: Clinical trials have shown that nintedanib 150 mg twice daily (bid) reduces disease progression in patients with idiopathic pulmonary fibrosis (IPF), with an adverse event profile that is manageable for most patients. Prior to the approval of nintedanib as a treatment for IPF in Brazil, an expanded access program (EAP) was initiated to provide early access to treatment and to evaluate the safety and tolerability of nintedanib in this patient population. **Methods:** Patients with a diagnosis of IPF within the previous five years, forced vital capacity (FVC) ≥ 50% predicted and diffusing capacity of the lungs for carbon monoxide (DLco) 30% to 79% predicted were eligible to participate in the EAP. Patients received nintedanib 150 mg bid open-label. Safety assessments included adverse events leading to permanent discontinuation of nintedanib and serious adverse events. **Results:** The EAP involved 57 patients at eight centers. Most patients were male (77.2%) and white (87.7%). At baseline, mean (SD) age was 70.7 (7.5) years and FVC was 70.7 (12.5) % predicted. Mean (SD) exposure to nintedanib was 14.4 (6.2) months; maximum exposure was 22.0 months. The most frequently reported adverse events considered by the investigator to be related to nintedanib treatment were diarrhea (45 patients, 78.9%) and nausea (25 patients, 43.9%). Adverse events led to permanent discontinuation of nintedanib in 16 patients (28.1%). Sixteen patients (28.1%) had a serious adverse event. **Conclusion:** In the Brazilian EAP, nintedanib had an acceptable safety and tolerability profile in patients with IPF, consistent with data from clinical trials.

Keywords: Drug tolerance; Expanded access program; Interstitial lung disease; Tyrosine kinase inhibitor.

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a progressive fibrosing interstitial lung disease characterized by decline in lung function, worsening dyspnea and impaired quality of life.[1] IPF typically presents in the sixth or seventh decade of life in former smokers and is more common in men than in women.[1] IPF has a variable clinical course but a poor prognosis. Data from the US prior to the availability of approved therapies for IPF suggest that median post-diagnosis survival in patients with IPF was 3 to 5 years.[2,3] Analyses of the Brazilian National Ministry of Health Mortality Database suggest that in Brazil, mortality due to IPF rose from 0.24 per 100,000 in 1979 to 1.10 per 100,000 in 2014.[4] This increase was likely due to improved diagnosis and reporting of IPF, as well as ageing of the population. IPF likely remains significantly underdiagnosed in Brazil due to low awareness of the disease, the challenges of making the diagnosis and the small number of specialized centers.

Nintedanib is an intracellular inhibitor of tyrosine kinases involved in the pathogenesis of IPF, including the platelet-derived growth factor receptor, fibroblast growth

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factor receptor, and vascular endothelial growth factor receptor.[5] The efficacy and safety of the 52-weeks treatment with nintedanib 150 mg twice daily (bid) in patients with IPF were assessed in the Phase II TOMORROW trial[6] and in the two Phase III INPULSIS® trials.[7] These trials showed that nintedanib reduced disease progression by reducing the rate of decline in forced vital capacity (FVC). An analysis of pooled data from the INPULSIS® trials suggested that nintedanib also reduced the risk of acute exacerbations.[8] The safety and tolerability profile of nintedanib was characterized predominantly by gastrointestinal adverse events, particularly diarrhea.[9,10]

Nintedanib has been approved for the treatment of IPF in many countries, including Brazil and other countries in Latin America, as well as the US, Europe and several countries in Asia. In the latest international treatment guidelines for IPF, nintedanib received a conditional recommendation for use. This indicates that it would be an appropriate choice for the majority of patients, while acknowledging that different choices will be appropriate for different patients depending on individual values and preferences.[11]

Prior to the approval of nintedanib in Brazil in February 2016, an expanded access program (EAP) was initiated to provide early access to treatment and further information on the safety and tolerability of nintedanib in patients with IPF. Here, we report the data on the safety and tolerability of nintedanib collected in this EAP.

METHODS

Design

An EAP providing open-label treatment with nintedanib was initiated at eight medical centers in Brazil in February 2015. To be eligible to participate, patients were required to be ≥ 40 years of age, with a diagnosis of IPF based on ATS/ERS/JRS/ALAT 2011 guidelines[1] within the previous 5 years, a diffusing capacity of the lungs for carbon monoxide (DLco) of 30% to 79% predicted and FVC ≥ 50% predicted. Exclusion criteria included alanine aminotransferase (ALT), aspartate aminotransferase (AST), or bilirubin levels > 1.5 times the upper limit of normal (ULN); myocardial infarction within 6 months of screening; unstable angina within 1 month of screening; bleeding risk (e.g., requirement for fibrinolysis, full-dose anticoagulation, or high-dose antiplatelet therapy); permanent discontinuation of nintedanib due to drug-related adverse events within a clinical trial; and current or planned treatment with pirfenidone, azathioprine, cyclophosphamide, cyclosporine, or prednisone at a dose of > 15 mg/day or > 30 mg every 2 days or equivalent dose of other oral corticosteroids.

Following a 4-week screening period, patients received nintedanib 150 mg bid within the EAP until nintedanib became commercially available or until permanent treatment discontinuation. A follow-up visit took place 28 days after treatment discontinuation. Treatment interruptions for up to 12 weeks and dose reductions to 100 mg bid were allowed to manage adverse events. When dose was reduced, the dose of nintedanib could be increased back to 150 mg bid following resolution of the adverse event. The investigators were provided with recommendations for the management of diarrhea and liver enzyme elevations (Figures 1 and 2). Investigators were requested to report concomitant medications used to treat IPF or manage diarrhea on a case report form. Concomitant therapies were defined as therapies received at baseline or started between the first and last intake of nintedanib. Concomitant therapies were coded according to the WHO Drug Dictionary[12] (version 17 March).

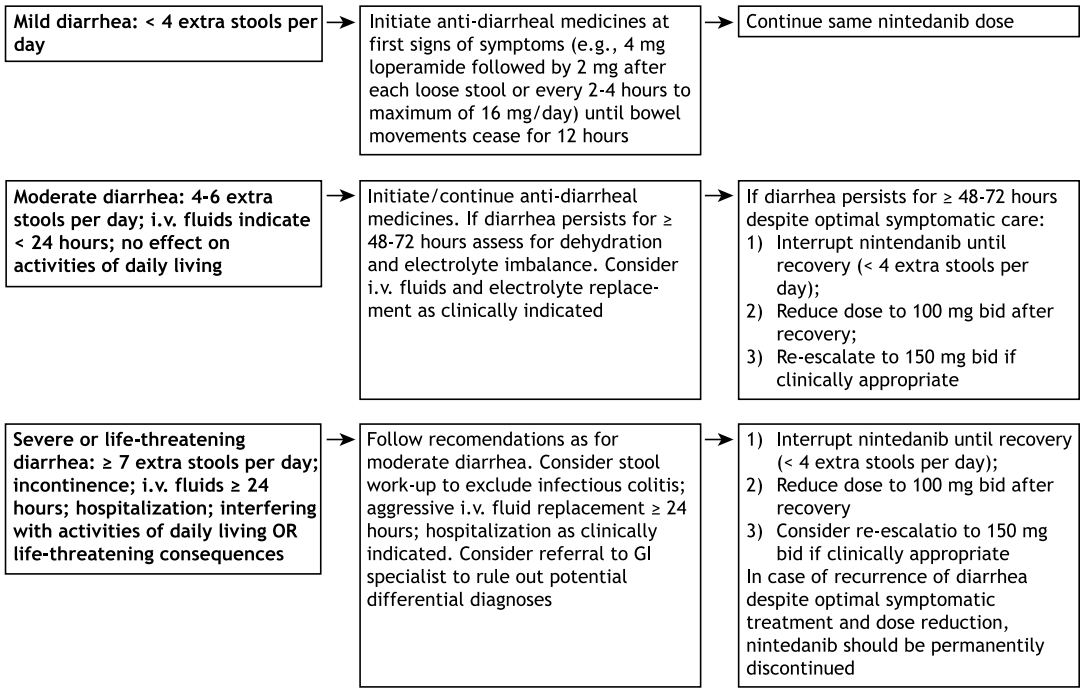
As this was an EAP, ethics committee approval of the protocol was not mandatory. However, Independent Ethics Committees of the participating centers were sent the patient information leaflet, the informed consent form and other documents for review. The program was conducted in accordance with the principles of the Declaration of Helsinki, the International Conference on Harmonization Good Clinical Practice guideline, and applicable regulatory requirements and standard operating procedures. All patients provided written informed consent before entering the program. The program was registered on www.clinicaltrials.gov (NCT02230982).

The first patient was enrolled on 23 March 2015. The last patient was screened on 3 November 2015. Nintedanib became commercially available for the treatment of IPF in Brazil on 16 February 2016. Between January 2017 and March 2017, all patients taking nintedanib in the EAP transitioned to commercially available nintedanib at the same site and with the same investigator.

Outcomes

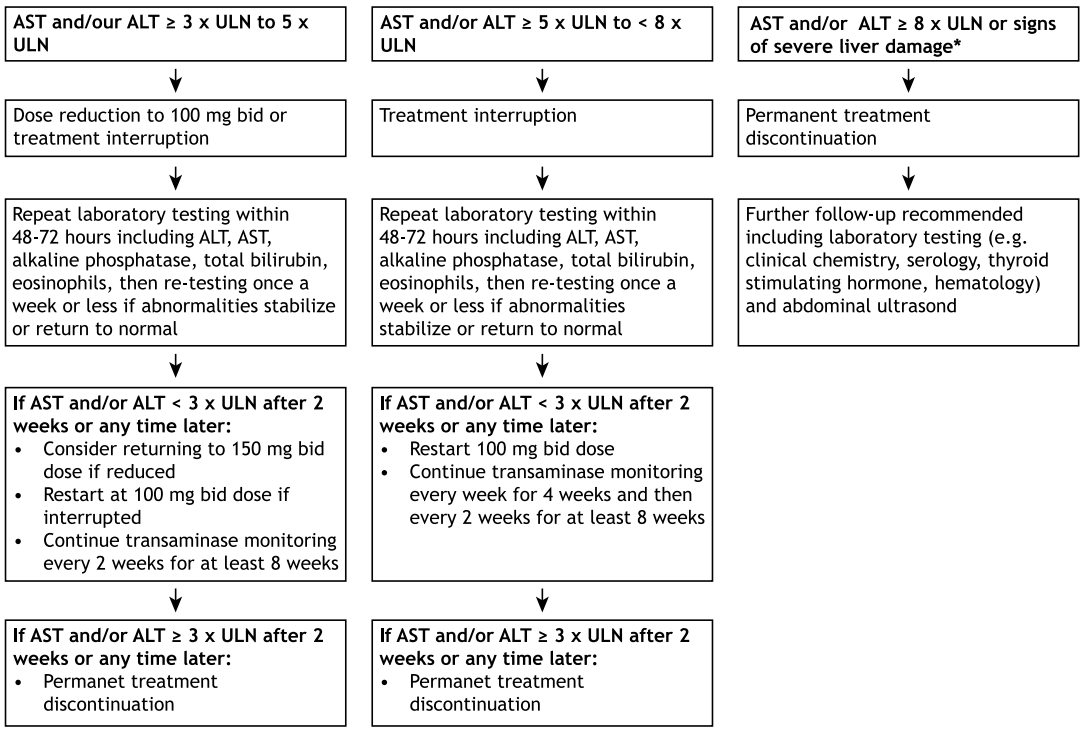
Safety was assessed in patients who received ≥ 1 dose of nintedanib. It consisted of the recording of adverse events meeting the following criteria: serious adverse events; adverse events of special interest (i.e., adverse events of liver injury [defined as AST or ALT ≥ 3 × ULN and total bilirubin ≥ 2 × ULN] or related to gastrointestinal perforation); adverse events leading to nintedanib interruption, discontinuation, or dose reduction; non-serious adverse events considered by the investigator to be related to administration of nintedanib; worsening of the underlying disease or other pre-existing conditions; changes in the results of any procedures, e.g. vital signs, physical examination, laboratory tests, that were judged clinically relevant by the investigator. Serious adverse events were defined as fatal or life-threatening adverse events, which required or prolonged hospitalization, were associated with a congenital anomaly, or resulted in a disability.

Adverse events were recorded at visits conducted at screening; at weeks 4, 8, 12, 24; every 12 weeks thereafter until the end of treatment; and at the follow-up visit 28 days after the end of treatment.



GI, gastrointestinal; i.v. intravenous

Figure 1. Algorithms for the management of diarrhea adverse events.



*Defined as increase in liver trasaminases (AST or ALT) to ≥ 3 x ULN, and i) total bilirubin > 1.5 x ULN or ii) international normalized ratio > 1.5 or iii) appearance of fatigue, nause, vomiting, right upper abdominal quadrant or tenderness, fever, rash and/or eosinophilia (> 5%).

Figure 2. Algorithms for the management of liver enzyme elevations adverse events.

They could also be recorded at any other time if the investigator became aware of them. Adverse events were coded according to preferred terms in the Medical Dictionary for Regulatory Activities (MedDRA) version 20.0. The investigator categorized the adverse events as mild (awareness of signs or symptoms which were easily tolerated), moderate (enough discomfort to cause interference with usual activity) or severe (incapacitating or causing inability to work or to perform usual activities). Safety data are presented descriptively.

RESULTS

Patients

A total of 57 patients were treated with nintedanib in this EAP. The majority of them were male (77.2%), white (87.7%) and current or former smokers (64.9%); 22.8% of patients had undergone a surgical lung biopsy (Table 1). At baseline, mean (SD) age was 70.7 (7.5) years, FVC was 70.7 (12.5) % predicted and DLco was 48.7 (13.4) % predicted. The most frequent comorbid conditions at baseline were hypertension (47.4%), dyslipidemia (21.1%), gastroesophageal reflux disease (21.1%) and diabetes mellitus (17.5%) (Table 1).

Concomitant therapies

Concomitant therapies are shown in Table 2. Anti-diarrheal therapies were the most commonly used, received by 36 patients (63.2%). Six patients (10.5%) received N-acetylcysteine and 13 patients (22.8%) received systemic corticosteroids.

Exposure

Mean (SD) exposure to nintedanib was 14.4 (6.2) months. Maximum exposure was 22.0 months. In total, 24 patients (42.1%) had ≥ 1 treatment interruption and 21 patients (36.8%) had ≥ 1 dose reduction to 100 mg bid. Most patients (70.2%) received nintedanib 150 mg bid as their last dose. Thirty-seven patients (64.9%) were still receiving nintedanib at the end of the program while 20 patients (35.1%) had permanently discontinued nintedanib. The most frequent reason for permanent discontinuation of nintedanib was adverse events (16 of 20 patients).

Safety and tolerability

Almost all patients (n = 55; 96.5%) had ≥ 1 adverse event that met the reporting criteria. The most frequently reported adverse events are presented in Table 3. Diarrhea, reported in 45 patients (78.9%), was the most common adverse event. Among patients with diarrhea, the intensity of the worst event was mild in 22 patients (48.9%), moderate in 13 patients (28.9%) and severe in 10 patients (22.2%). Nausea and vomiting were reported in 25 (43.9%) and 9 (15.8%) patients, respectively. Almost all nausea and vomiting adverse events were mild or moderate in intensity (Table 4). The majority of patients with adverse events of diarrhea (66.7%), nausea (80%) and vomiting (66.7%) continued nintedanib without dose reduction or treatment interruption.

Table 1. Baseline characteristics (n = 57).

Male, n (%)	**44 (77.2)**
Age, years mean (SD Standard Deviation)	70.7 (7.5)
Race, n (%)	
White	50 (87.7)
Black	6 (10.5)
Asian	1 (1.8)
Body mass index, kg/m^2 mean (SD)	28.0 (3.6)
Time since diagnosis of IPF, years mean (SD)	1.7 (1.2)
Smoking status, n (%)	
Current or former	37 (64.9)
Never	20 (35.1)
Lung biopsy performed, n (%)	13 (22.8)
FVC, % predicted mean (SD)	70.7 (12.5)
DLco, % predicted mean (SD)	48.7 (13.4)
Baseline conditions*, n (%)	
Hypertension	27 (47.4)
Dyslipidemia	12 (21.1)
Gastroesophageal reflux disease	12 (21.1)
Diabetes mellitus	10 (17.5)
Chronic obstructive pulmonary disease	8 (14.0)
Sleep apnea syndrome	6 (10.5)
Hypercholesterolemia	3 (5.3)
Osteoarthritis	2 (3.5)

*Conditions reported in > 10% of patients by MedDRA preferred term are shown. n = 57.

Table 2. Concomitant therapies.

	n (%) of patients
Any concomitant therapy	43 (75.4)
Anti-diarrheal	36 (63.2)
Loperamide	33 (57.9)
Loperamide hydrochloride	6 (10.5)
Antioxidant/expectorants	6 (10.5)
N-acetylcysteine	6 (10.5)
Antitussive	1 (1.8)
Codeine phosphate	1 (1.8)
Inhaled bronchodilator and/or corticosteroid	1 (1.8)
Mometasone furoate	1 (1.8)
Anti-acid (proton pump inhibitor or H2-receptor antagonist)	3 (5.3)
Omeprazole	2 (3.5)
Esomeprazole	1 (1.8)
Systemic corticoid	13 (22.8)
Prednisone	11 (19.3)
Methylprednisolone	3 (5.3)
Deflazacort	2 (3.5)

Investigators were requested to report concomitant medications used to treat IPF or manage diarrhea. Concomitant therapies are presented by Special Search Category and preferred name according to the WHO Drug Dictionary[12]. A patient may be counted in ≥ 1 category.

Table 3. Adverse events.

	n (%) of patients
Most frequent adverse events*	
Diarrhea	45 (78.9)
Nausea	25 (43.9)
Weight decreased	14 (24.6)
Decreased appetite	13 (22.8)
Vomiting	9 (15.8)
Abdominal pain	4 (7.0)
Progression of IPF†	4 (7.0)
Flatulence	3 (5.3)
Asthenia	3 (5.3)
Abdominal pain upper	2 (3.5)
Dyspnea	2 (3.5)
Influenza	2 (3.5)
Pneumonia	2 (3.5)
Urinary tract infection	2 (3.5)
Most frequent adverse events leading to permanent discontinuation of nintedanib‡	
Diarrhea	4 (7.0)
Nausea	3 (5.3)
Weight decreased	3 (5.3)
Pneumonia	2 (3.5)
Vomiting	2 (3.5)

Data shown are n (%) of patients who reported ≥ 1 adverse event; *Adverse events meeting the reporting criteria for this EAP and reported in > 3% of patients by MedDRA preferred term are shown; †Corresponds to MedDRA term 'IPF', which included disease worsening and acute exacerbations; ‡Adverse events that led to treatment discontinuation in > 3% of patients by MedDRA preferred term are shown.

Hepatic enzymes increase was reported in 1 patient. Drug-induced liver injury was reported as a serious adverse event in 1 patient. No cases of ALT and/or AST ≥ 3 × ULN and total bilirubin ≥ 2 × ULN, or adverse events related to gastrointestinal perforation were reported.

Adverse events led to permanent discontinuation of nintedanib in 16 patients (28.1%). The adverse event that most frequently led to permanent discontinuation of nintedanib was diarrhea (4 patients; 7.0%) (Table 3). Sixteen patients (28.1%) had a serious adverse

Table 4. Gastrointestinal adverse events and their consequences for nintedanib dosing.

	Patients with diarrhea adverse events (n = 45)	Patients with nausea adverse events (n = 25)	Patients with vomiting adverse events (n = 9)
Intensity of adverse event*			
Mild	22 (48.9)	17 (68.0)	6 (66.7)
Moderate	13 (28.9)	6 (24.0)	3 (33.3)
Severe	10 (22.2)	2 (8.0)	0 (0.0)
Consequence for nintedanib dosing†			
No permanent dose reduction or discontinuation	30 (66.7)	20 (80.0)	6 (66.7)
Permanent dose reduction	11 (24.4)	2 (8.0)	1 (11.1)
Permanent discontinuation	4 (8.9)	3 (12.0)	2 (22.2)

Data shown are n (%) of patients; *For patients with ≥ 1 event meeting the reporting criteria for this EAP, the intensity/consequence of the worst event is shown; †For patients with ≥ 1 event, the last consequence for dosing is shown.

event. No type of serious adverse event (based on MedDRA preferred terms) was reported in > 1 patient, except for progression of IPF (3 patients), pneumonia (2 patients) and urinary tract infection (2 patients). Three patients (5.3%) had adverse events that led to death: pneumonia (1 patient), pneumonia and progression of IPF (1 patient), and dyspnea (1 patient). None of the fatal adverse events was considered by the investigator to be related to nintedanib.

DISCUSSION

In this Brazilian EAP for nintedanib in patients with IPF, nintedanib 150 mg bid had acceptable safety and tolerability profile, consistent with data from clinical trials.[6,7,10] Gastrointestinal adverse events, particularly diarrhea, were the most frequently reported adverse events. Diarrhea is an adverse event commonly associated with inhibitors of tyrosine kinases, but the mechanism/s by which it occurs remains unclear.[13] Most patients who had diarrhea in the Brazilian EAP had events of mild or moderate intensity, and the majority continued nintedanib without a dose reduction or treatment interruption; however, almost two-thirds of patients received anti-diarrheal therapy. It is recommended that patients who experience diarrhea during nintedanib treatment should maintain adequate hydration and take anti-diarrheal therapy (e.g. loperamide) as soon as symptoms occur.[14,15]

Treatment with nintedanib may lead to elevations in liver enzymes and cases of drug-induced liver injury have been observed.[14,15] In the Brazilian EAP, drug-induced liver injury was reported as a serious adverse event in 1 patient. No cases of ALT and/or AST ≥ 3 × ULN and total bilirubin ≥ 2 × ULN were reported. It is recommended that liver function tests are conducted prior to initiation of nintedanib, at regular intervals during the first 3 months of treatment, and periodically thereafter.[14,15] Dose reductions or treatment interruptions may be necessary to manage elevations in liver enzymes.

In addition to this EAP in Brazil, data on the safety and tolerability of nintedanib have been collected through several other compassionate use/early access programs and through post-marketing surveillance. Consistent with our findings, data from these studies suggest that nintedanib has a similar safety and tolerability profile in clinical practice as was observed in clinical trials.[16-23] In post-marketing surveillance data from 6758 patients treated with nintedanib in the US in the year following the launch of nintedanib as a treatment for IPF, diarrhea, nausea and vomiting were the most frequently reported adverse events.[18] In an observational study of 94 patients with IPF in Greece, diarrhea was reported in 55% of patients treated with nintedanib over a follow-up period of 12 months, and 12% of patients discontinued nintedanib due to diarrhea.[20]

In the Brazilian EAP, 11% and 23% of patients treated with nintedanib received concomitant treatment with N-acetylcysteine and systemic corticosteroids, respectively. In a recent survey of 455 physicians from Latin America, 29% and 48% prescribed N-acetylcysteine and corticosteroids, respectively, for the treatment of IPF.[24] These findings suggest that use of these low-cost therapies remains high in Latin America despite the lack of evidence supporting their efficacy as treatments for IPF.[11,25,26]

In conclusion, in an EAP for patients with IPF in Brazil, nintedanib 150 mg bid had an acceptable safety and tolerability profile, consistent with that observed in clinical trials.

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Trends in smoking prevalence in all Brazilian capitals between 2006 and 2017

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ABSTRACT

Objective: To evaluate the trends in smoking prevalence in all Brazilian capitals between 2006 and 2017. **Methods:** This was a study of temporal trends in smoking, based on information from the Telephone-based System for the Surveillance of Risk and Protective Factors for Chronic Diseases. The trends in smoking prevalence were stratified by gender, age, level of education, and capital of residence. We used linear regression analysis with a significance level of 5%. **Results:** From 2006 to 2017, the overall prevalence of smoking in the Brazilian capitals declined from 19.3% to 13.2% among men and from 12.4% to 7.5% among women ($p < 0.05$ for both). Despite the overall decline in the prevalence of smoking in all of the capitals, the rate of decline was lower in the more recent years. There was also a reduction in the prevalence of former smoking (22.2% in 2006 to 20.3% in 2017). In contrast, there was an upward trend in the prevalence of former smoking among individuals with a lower level of education (from 27.9% in 2006 to 30.0% in 2017). In 2017, the prevalence of smoking among men was highest in the cities of Curitiba, São Paulo, and Porto Alegre, whereas it was highest among women in the cities of Curitiba, São Paulo, and Florianópolis. **Conclusions:** There have been improvements in smoking prevalence in Brazil. Annual monitoring of smoking prevalence can assist in the battle against chronic noncommunicable diseases.

Keywords: Smoking; Tobacco use disorder; Health surveys.

INTRODUCTION

Smoking is a major risk factor for chronic respiratory disease, cardiovascular disease, and various cancers.[1] Approximately 1.1 billion smokers (i.e., 80% of all smokers) live in low- or middle-income countries, where the burden of smoking-related diseases is highest.[2]

Tobacco use represents a major health care system problem because of increased socioeconomic and health care costs.[3] The total cost of smoking has been estimated at US$ 1,436 billion, which is equivalent to 1.8% of the world's annual gross domestic product.[4] Approximately 40% of this cost occurs in low- and middle-income countries, reflecting substantial losses caused by smoking.[4] In addition, the indirect cost of smoking-attributable diseases is estimated at US$ 1,014 billion.[4]

More than 7 million deaths per year are due to smoking, and approximately 890,000 are due to exposure to secondhand smoke.[5] In 2015, smoking accounted for the loss of 150 million disability-adjusted life years.[6] Smoking is associated with high morbidity and mortality; although the prevalence of smoking has steadily declined worldwide, it remains high in some regions and vulnerable groups.[3]

The reduction in smoking prevalence was primarily due to a substantial expansion and strengthening of tobacco control initiatives worldwide.[6] In Brazil, studies using data from the 1989 Brazilian National Survey on Health and Nutrition, the 2003 *Pesquisa Especial de Tabagismo* (PETab, Global Adult Tobacco Survey), the 2008 Brazilian National Household Sample Survey, and the 2013 *Pesquisa Nacional de Saúde* (PNS, Brazilian National Health Survey) have shown a reduction in tobacco use in the country.[7,8]

Regulatory measures to reduce smoking in Brazil include the implementation of the Framework Convention on Tobacco Control in 2006 and the enactment of the Smoke-Free Law in 2014.[9] The 2011-2022 Strategic Action Plan to Combat Chronic Noncommunicable Diseases (NCDs) set a goal of reducing tobacco use and implementing surveillance of smoking.[9,10] The *Sistema de Vigilância de Fatores de Risco e Proteção para Doenças Crônicas por Inquérito Telefônico* (VIGITEL, Telephone-based System for the Surveillance of Risk and Protective Factors for Chronic Diseases) is an essential tool for monitoring the frequency and distribution of major determinants of chronic NCDs and their risk factors, including smoking.[11]

The objective of the present study was to evaluate the trends in smoking prevalence in all Brazilian capitals between 2006 and 2017.

METHODS

This was a study of temporal trends in smoking between 2006 and 2017, based on data from the VIGITEL. The

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VIGITEL is a cross-sectional population-based study that annually assesses adults (≥ 18 years of age) residing in any of the 26 Brazilian state capitals or in the Federal District of Brasília. Between 2006 and 2017, 12 telephone-based surveys were conducted, a total of 54,000 interviews being conducted each year (i.e., approximately 2,000 interviews in each capital city). Details regarding the sampling and data collection process are provided elsewhere.[11]

In the present study, smoking prevalence was analyzed as follows:

a. Prevalence of current smoking: number of smokers/number of individuals interviewed. Those who answered "yes" to the question "Do you smoke?" were considered to be smokers regardless of the number of cigarettes smoked per day, frequency of smoking, or duration of smoking.
b. Prevalence of former smoking: number of former smokers/number of individuals interviewed. Nonsmokers who answered "yes" to the question "Have you ever smoked?" were considered to be former smokers regardless of the number of cigarettes smoked or the duration of smoking.
c. Prevalence of smoking ≥ 20 cigarettes per day: number of individuals smoking ≥ 20 cigarettes per day/number of individuals interviewed, the number of individuals smoking ≥ 20 cigarettes per day being assessed by the question "How many cigarettes do you smoke per day?".

As of 2009, smoking prevalence analysis included the following:

d. Prevalence of passive smoking at home: number of nonsmokers who reported living with at least one smoker who smoked inside the household/number of individuals interviewed, the number of nonsmokers who reported living with at least one smoker who smoked inside the household being assessed by the question "Do any of the people who live with you usually smoke inside the household?".
e. Prevalence of passive smoking at work: number of nonsmokers who reported having at least one coworker who smoked indoors at work/number of individuals interviewed, the number of nonsmokers who reported having at least one coworker who smoked indoors at work being assessed by the question "Do any of your coworkers usually smoke indoors at work?".

The temporal trends in smoking prevalence were stratified by gender, age group (18-24, 25-34, 35-44, 45-54, 55-64, and ≥ 65 years), level of education (0-8, 9-11, and ≥ 12 years of schooling), and capital of residence.

A linear regression model was used for trend analysis, the response variable (Yi) being the prevalence of smoking and the explanatory variable (Xi) being the year of study. A negative slope coefficient (β) indicated a reduction in smoking prevalence over the years, whereas a positive slope coefficient indicated an annual increase in prevalence. Analysis of residuals was performed in order to assess the goodness of fit of the model. The level of significance was set at 5%. The Stata statistical software package, version 14 (StataCorp LP, College Station, TX, USA) was used for data processing and statistical analysis.

The VIGITEL was approved by the Brazilian National Research Ethics Committee (Ruling no. 355,590/2013). All participants gave verbal informed consent during the telephone interview.

RESULTS

Figure 1 shows the trends in smoking prevalence in Brazil, by gender. There was a trend toward a reduction in smoking prevalence ($p < 0.001$). The prevalence of current smoking was found to be higher in males than in females (19.3% in 2006 and 13.2% in 2017 vs. 12.4% in 2006 and 7.5% in 2017). This was also true for the prevalence of former smoking, smoking ≥ 20 cigarettes per day, and passive smoking at work. In the 2015-2017 period, there was a reduction in the rate of decline in the prevalence of smoking in the general population and in males. There were reductions in the prevalence of former smoking (from 22.2% in 2006 to 20.3% in 2017; $p < 0.001$), smoking ≥ 20 cigarettes per day (from 4.6% in 2006 to 2.6% in 2017; $p < 0.001$), passive smoking at home (from 12.7% in 2006 to 7.9% in 2017; $p < 0.001$), and passive smoking at work (from 12.1% in 2006 to 6.7% in 2017; $p < 0.001$) among males and females.

The trends in smoking prevalence in Brazil were also stratified by level of education. There was a trend toward an increase in the prevalence of former smoking among individuals who had had 0-8 years of schooling (from 27.9% in 2006 to 30.0% in 2017; $p = 0.0435$; slope = 0.159); among those who had had 9-11 years of schooling, there was no significant variation ($p = 0.527$; $\beta = -0.035$); and there was a decrease in the number of former smokers among individuals who had had ≥ 12 years of schooling ($p < 0.001$; $\beta = -0.270$). There was a trend toward a reduction in the prevalence of current smoking, smoking ≥ 20 cigarettes per day, passive smoking at home, and passive smoking at work for all levels of education. The decrease in the prevalence of current smoking and smoking ≥ 20 cigarettes per day was most pronounced among individuals who had had 0-8 years of schooling ($p < 0.001$; $\beta = -0.591$ and $p < 0.001$; $\beta = -0.232$, respectively). The decrease in the prevalence of passive smoking at home and passive smoking at work was most pronounced among individuals who had had 9-11 years of schooling ($p < 0.001$; $\beta = -0.725$), followed by those who had had 0-8 years of schooling ($p < 0.001$; $\beta = -0.675$) and those who had had ≥ 12 years of schooling ($p < 0.001$; $\beta = -0.373$; Figure 2).

Table 1 shows the trends in smoking prevalence in Brazil, by age group. There was a trend toward a reduction in the prevalence of current smoking, smoking ≥ 20 cigarettes per day, passive smoking at

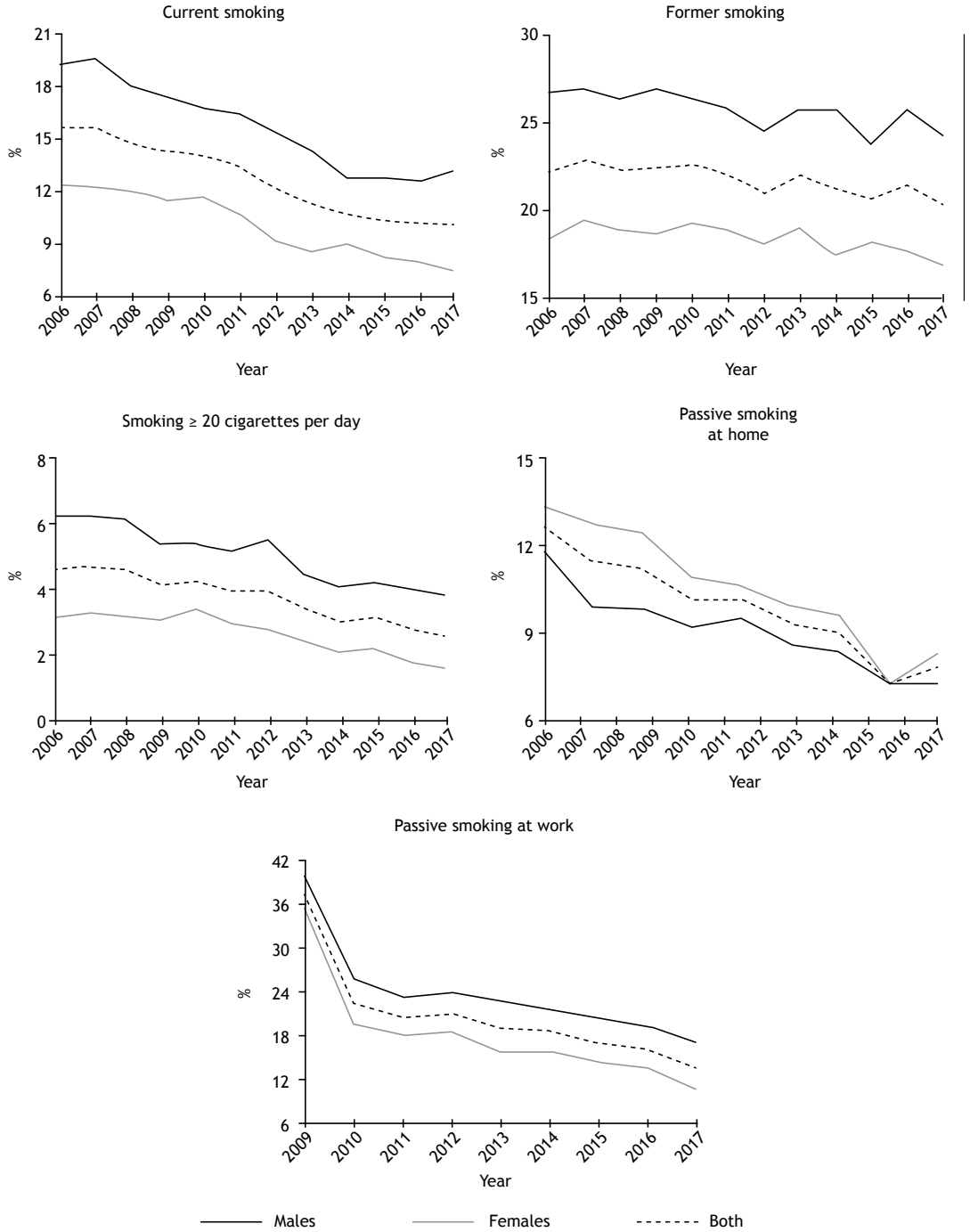

Figure 1. Trends in smoking prevalence in all Brazilian capitals, by gender. VIGITEL, 2006-2017. VIGITEL: *Sistema de Vigilância de Fatores de Risco e Proteção para Doenças Crônicas por Inquérito Telefônico* (Telephone-based System for the Surveillance of Risk and Protective Factors for Chronic Diseases).

home, and passive smoking at work in all age groups. The prevalence of smoking was highest in individuals in the 45- to 54-year age bracket between 2006 and 2014, and, as of 2015, in those in the 55- to 64-year age bracket. In all years studied, smoking prevalence was lowest in those ≥ 65 years of age. There was a trend toward an increase in the prevalence of former smoking in individuals in the 55- to 64-year age bracket ($p = 0.013$; $\beta = 0.390$). The prevalence of smoking ≥ 20 cigarettes per day was highest in those in the 45- to 54-year age bracket ($p < 0.001$; $\beta = -0.507$), the rate of increase in the prevalence of smoking ≥ 20 cigarettes per day being highest in individuals in the 55- to 64-year bracket ($p = 0.003$; $\beta = -0.271$). Although the prevalence of passive smoking at home was found to have decreased over the years, it was

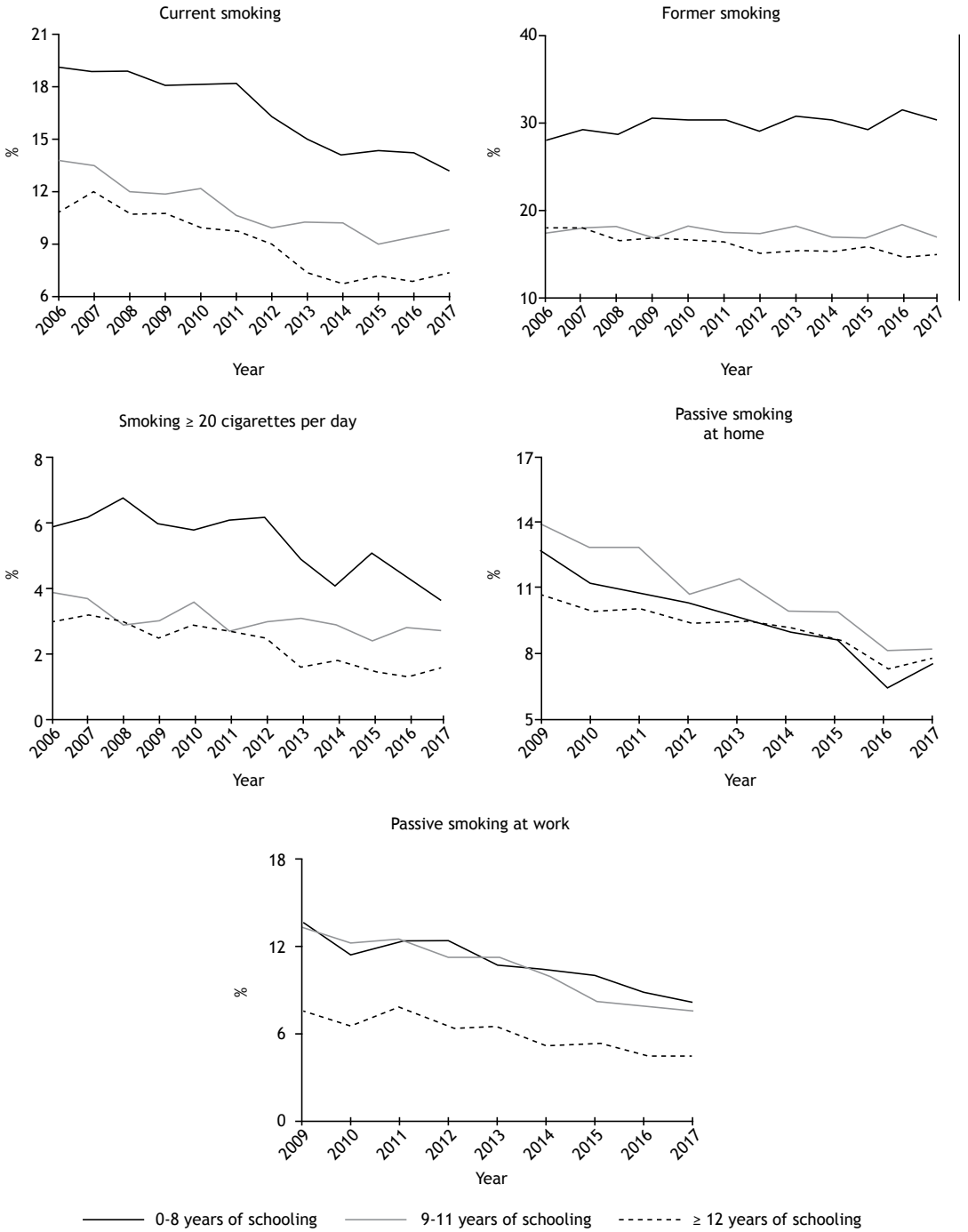

Figure 2. Trends in smoking prevalence in all Brazilian capitals, by level of education (number of years of schooling). VIGITEL, 2006-2017. VIGITEL: *Sistema de Vigilância de Fatores de Risco e Proteção para Doenças Crônicas por Inquérito Telefônico* (Telephone-based System for the Surveillance of Risk and Protective Factors for Chronic Diseases).

highest in individuals in the 18- to 24-year age bracket ($p < 0.001$; $\beta = -0.972$). The prevalence of passive smoking at work was highest in individuals in the 35- to 44-year age bracket ($p < 0.001$; $\beta = -0.975$) and in those in the 25- 34-year age bracket ($p < 0.001$; $\beta = -0.803$). Although the prevalence of passive smoking at work was lowest in individuals in the 18-24 year age bracket, the β coefficient was −0.828 in that age group, and there was no significant variation in individuals > 55 years of age.

The prevalence of smoking in males was found to have decreased in all Brazilian capitals. In 2017, smoking prevalence in males was highest in the cities of Curitiba, São Paulo, and Porto Alegre (Table 2). The prevalence of smoking in females was also found

Table 1. Trends in smoking prevalence, by age group. VIGITEL, 2006-2017.

Prevalence	Age	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	p	Slope
Current smoking	18-24	12.0	13.7	11.5	10.9	10.9	8.8	8.5	7.1	7.8	7.2	7.4	8.5	< 0.001	−0.533
	25-34	14.1	14.6	13.8	14.5	14.2	13.2	11.7	12.1	11.9	10.5	9.7	9.6	< 0.001	−0.481
	35-44	18.5	17.5	16.5	14.8	15.1	13.9	12.9	11.2	9.9	10.4	10.0	11.7	< 0.001	−0.777
	45-54	22.6	21.7	19.6	18.9	18	18.6	16.0	15.1	13.2	12.7	12.6	11.2	< 0.001	−1.033
	55-64	15.0	15.8	17.2	16.7	16.7	15.9	15.0	13.6	12.5	12.8	13.5	11.6	0.001	−0.420
	≥ 65	9.4	8.5	9.3	8.4	8.1	9.0	7.6	6.9	8.1	8.2	7.7	7.3	0.007	−0.156
Former smoking	18-24	11.9	10.7	10.1	9.6	10.2	9.2	8.7	10.3	10.3	8.7	9.3	10.4	0.103	−0.124
	25-34	14.2	14.0	14.0	14.2	13.1	13.7	13.0	13.2	12.8	12.2	12.9	12.1	< 0.001	−0.185
	35-44	22.4	23.3	20.8	20.5	19.9	19.2	16.5	17.7	15.8	16.8	16.8	14.9	< 0.001	−0.706
	45-54	34.0	33.5	33.7	33.9	33.9	33.0	30.4	30.1	30.2	27.9	26.2	24.6	< 0.001	−0.847
	55-64	31.8	36.1	36.4	36.4	37.3	37.3	39.1	39.1	37.5	36.6	39.7	37.7	0.013	0.390
	≥ 65	34.3	37.5	35.4	36.1	38.8	35.4	33.6	37.0	34.9	35.8	37.0	34.2	0.682	−0.056
Smoking ≥ 20 cigarettes per day	18-24	2.2	2.7	1.9	1.9	2.3	1.8	1.8	1.8	1.0	1.6	1.6	1.4	0.003	−0.094
	25-34	2.9	3.7	3.5	3.0	3.5	2.9	3.2	2.7	3.0	2.9	2.2	1.9	0.005	−0.108
	35-44	5.6	5.3	5.1	5.3	4.5	3.8	4.6	3.3	2.7	3.6	3.1	3.0	< 0.001	−0.261
	45-54	9.5	7.9	7.3	6.8	6.9	7.0	5.7	5.5	5.0	3.6	3.6	3.5	< 0.001	−0.507
	55-64	5.7	6.6	7.4	6.4	7.1	5.8	7.0	4.6	4.2	4.3	4.4	4.0	0.003	−0.271
	≥ 65	2.5	2.6	3.9	1.9	2.3	3.8	2.9	2.6	2.4	2.7	2.3	2.3	0.478	−0.038
Passive smoking at home	18-24	-	-	-	19.6	16.9	17.4	16.8	16.7	15.1	15.2	10.7	11.2	< 0.001	−0.972
	25-34	-	-	-	13.4	12.5	13.4	11.0	11.6	10.7	10.6	9.0	10.6	0.002	−0.460
	35-44	-	-	-	9.8	7.7	8.5	7.2	8.0	7.3	7.4	6.0	6.5	0.004	−0.340
	45-54	-	-	-	10.8	9.4	8.4	8.2	6.6	6.8	6.1	6.3	5.7	< 0.001	−0.595
	55-64	-	-	-	10.9	11.5	9.2	8.3	9.1	8.1	7.5	5.4	6.0	< 0.001	−0.692
	≥ 65	-	-	-	10.1	10.8	8.7	9.0	8.2	7.5	6.7	4.9	5.6	< 0.001	−0.687
Passive smoking at work	18-24	-	-	-	12.5	11.0	12.6	9.6	9.2	10.3	5.9	6.4	6.7	0.001	−0.828
	25-34	-	-	-	14.0	12.4	12.5	12.4	11.8	9.7	10.8	7.7	7.0	< 0.001	−0.803
	35-44	-	-	-	15.8	13.5	14.7	12.5	13.1	10.6	8.7	8.9	8.1	< 0.001	−0.975
	45-54	-	-	-	12.9	11.0	11.1	11.3	9.8	9.6	9.0	8.7	8.3	< 0.001	−0.520
	55-64	-	-	-	7.4	7.4	8.2	9.4	7.4	6.9	7.5	5.3	6.0	0.080	−0.263
	≥ 65	-	-	-	2.8	2.1	2.5	2.3	2.5	2.5	2.1	2.5	2.3	0.456	−0.023

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to have decreased in all Brazilian capitals. In 2017, smoking prevalence in females was highest in the cities of Curitiba, São Paulo, and Florianópolis (Table 3).

DISCUSSION

The present study showed a reduction in the prevalence of smoking between 2006 and 2017, as well as improvements in the prevalence of former smoking, smoking ≥ 20 cigarettes per day, passive smoking at home, and passive smoking at work. In the 2015-2017 period, there was a reduction in the rate of decline in smoking prevalence in Brazil as a whole and in some of the Brazilian capitals. The prevalence of smoking was highest in males, individuals with a lower level of education, and individuals in the 35- to 64-year age bracket. The prevalence of smoking in 2017 was highest in the capital cities of Curitiba, São Paulo, Porto Alegre, and Florianópolis.

The 2011-2022 Strategic Action Plan to Combat Chronic NCDs set a goal of reducing the prevalence of smoking by 30%.[9,10] The World Health Organization Global Action Plan for the Prevention and Control of NCDs and the United Nations 2030 Agenda for Sustainable Development have also set goals of reducing the prevalence of smoking.[12,13]

Data from the 1989 Brazilian National Survey on Health and Nutrition showed that the prevalence of tobacco use among adults was 34.8%.[14] Data from the 2003 World Health Survey showed a reduction in smoking prevalence (to 22.4%).[14] The 2008 PETab showed a smoking prevalence of 17.2%,[15] and the 2013 PNS showed a smoking prevalence of 14.7%. [8,16] These results show that Brazil has made progress in reducing the prevalence of smoking.

Brazil has set a global example on reducing smoking prevalence, and these advances have been attributed to the regulatory measures put forth by the World Health Organization Framework Convention on Tobacco Control, which came into force in 2005. Several measures have been implemented in the country, such as monitoring tobacco use and raising taxes on tobacco products.[17,18] Other measures include Decree no. 5,658, which was

Table 2. Trends in smoking prevalence among males in all Brazilian capitals. VIGITEL, 2006-2017.

Capital	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	p	Slope
Aracaju	17.2	15.4	16.3	9.9	14.2	13.6	10.6	12.7	9.9	10.4	8.2	8.7	< 0.001	−0.724
Belém	19.8	20.7	17.4	16.0	19.6	17.3	10.9	11.4	10.1	11.6	9.7	13.0	< 0.001	−0.961
Belo Horizonte	21.3	19.8	20.3	17.7	17.6	19.1	15.5	15.8	16.2	12.4	13.5	10.6	< 0.001	−0.861
Boa Vista	22.1	17.9	21.1	17.1	16.1	15.4	14.2	13.8	13.1	11.2	8.2	9.8	< 0.001	−1.119
Campo Grande	19.3	21.2	21.4	16.6	17.5	17.6	13.4	14.4	15.5	14.1	15.0	15.8	0.003	−0.575
Cuiabá	19.3	17.8	17.4	12.4	15.9	16.5	14.1	15.4	15.6	14.9	12.7	12.6	0.008	−0.437
Curitiba	21.1	19.8	20.4	23.8	17.9	20.5	15.6	15.9	14.9	14.5	17.8	18.3	0.023	−0.509
Florianópolis	20.1	23.5	18.1	19.1	17.3	1.06	16.6	14.5	14.0	10.3	11.8	13.6	< 0.001	−0.926
Fortaleza	18.7	18.0	15.8	19.4	13.9	12.6	13.0	10.0	8.6	9.0	9.8	8.8	< 0.001	−1.034
Goiânia	16.7	15.2	16.6	15.8	16.6	14.0	13.3	15.4	14.1	8.7	14.0	13.5	0.021	−0.399
João Pessoa	19.1	18.4	14.4	15.6	14.8	13.6	14.0	10.7	12.9	13.2	11.4	8.0	< 0.001	−0.765
Macapá	26.8	23.2	24.0	25.6	15.2	15.1	16.1	13.8	10.3	10.7	12.8	11.2	< 0.001	−1.531
Maceió	18.0	15.5	13.4	16.6	13.2	10.1	11.2	13.5	10.3	9.4	9.1	10.1	< 0.001	−0.706
Manaus	18.3	20.6	18.7	15.0	15.2	15.4	10.9	10.7	10.3	13.1	7.9	11.0	< 0.001	−0.963
Natal	17.4	16.5	13.9	15.1	16.5	14.4	11.4	7.9	11.6	10.6	11.5	10.4	0.001	−0.669
Palmas	17.8	17.7	14.4	14.2	13.9	15.6	11.0	7.2	10.6	9.7	10.4	12.6	0.003	−0.694
Porto Alegre	23.3	22.1	21.4	21.9	20.0	22.2	16.8	18.7	17.9	16.7	17.4	16.7	< 0.001	−0.619
Porto Velho	24.0	19.4	21.3	21.3	18.2	19.8	13.3	14.2	9.7	12.8	13.8	12.8	< 0.001	−1.083
Recife	18.7	19.2	12.3	15.2	16.9	13.0	13.4	13.4	13.3	11.1	11.4	12.2	0.002	−0.593
Rio Branco	24.1	21.2	16.5	16.5	20.1	18.9	19.0	11.7	14.8	10.9	12.6	15.0	0.002	−0.875
Rio de Janeiro	16.5	17.1	17.2	15.2	13.0	13.5	17.1	15.1	10.8	14.6	13.5	12.7	0.024	−0.365
Salvador	11.8	14.9	10.9	12.3	10.3	9.8	7.3	6.6	9.0	5.6	6.8	5.9	< 0.001	−0.717
São Luís	16.5	18.0	16.4	16.9	13.4	16.4	12.4	14.3	9.3	8.5	9.2	9.1	< 0.001	−0.892
São Paulo	22.3	22.9	21.7	19.9	21.3	21.8	20.7	17.6	15.4	15.6	14.6	17.2	< 0.001	−0.728
Teresina	21.7	20.9	17.5	19.5	15.9	17.1	16.7	11.6	11.0	10.3	9.5	7.7	< 0.001	−1.269
Vitória	17.2	17.9	15.1	14.8	15.4	14.2	11.7	10.2	11.0	10.5	10.8	12.7	< 0.001	−0.639
Brasília	18.1	20.0	15.4	17.7	15.9	10.6	13.0	16.3	12.4	13.9	14.5	14.9	0.054	−0.413
Brasil	19.3	19.6	18.0	17.5	16.8	16.5	15.5	14.4	12.8	12.8	12.7	13.2	< 0.001	−0.690

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issued in 2006 and enacted the Framework Convention on Tobacco Control, banning the advertising of tobacco products[19]; Law no. 12,546, which was issued in 2011 and established smoke-free environments[20]; and Decree no. 8,262/2014, which regulated smoke-free environments, increased the size of text and graphic warnings on the packages of tobacco products and other smoking products, prohibited the sale of tobacco products and other smoking products to minors (individuals under 18 years of age), established a minimum price for tobacco products and other smoking products, and banned smoking advertisements in the media, among other measures.[21]

In recent years, there has been a reduction in the rate of decline in smoking prevalence, a longer observation period being required in order to determine whether this trend will change. This draws attention to the need for new regulatory measures, including the use of plain packaging, enforcement of the law regulating smoke-free environments and point-of-sale advertising, control of illicit tobacco trade, and provision of support to small-scale tobacco farmers for crop diversification.[22] Other relevant issues include the impact of the current economic crisis in Brazil, the implementation of fiscal austerity measures, cuts in public spending on social welfare and health care, and the diminishing regulatory role of the Brazilian government.[23-25]

Because of historical, economic, cultural, and social issues, being male is still a determinant of smoking.[26] In addition, tobacco companies created a brand image that promoted the ideals of prestige, wealth, glamour, masculinity, athleticism, and health.[27] Data from the Global Burden of Disease 2015 study showed that, worldwide, the prevalence of smoking in 2015 was 25.0% among males and 5.4% among females.[6] Data from two Brazilian national surveys also showed a higher prevalence of smoking in males (18.9% and 21.6%) than in females (11.0% and 13.1%).[8,15]

The present study showed an upward trend in smoking cessation among individuals with a lower level of education and an increase in the rate of decline in the prevalence of smoking ≥ 20 cigarettes per day, both of which can be attributed to increased tobacco taxation and pricing. Price increases constitute the most cost-effective strategy to reduce the number of smokers and daily tobacco use, especially among younger and lower-income individuals.[28] A tax increase resulting in a 10% increase in tobacco prices can reduce

Table 3. Trends in smoking prevalence among females in all Brazilian capitals. VIGITEL, 2006-2017.

Capital	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	p	Slope
Aracaju	7.7	6.1	8.7	6.2	6.9	4.4	6.1	4.0	3.8	3.6	3.2	1.6	< 0.001	−0.517
Belém	10.8	8.3	7.8	7.6	6.9	6.3	5.6	4.6	4.3	3.2	3.0	3.1	< 0.001	−0.660
Belo Horizonte	11.0	10.9	13.2	11.5	12.9	10.8	9.9	10.3	9.2	6.0	8.7	7.1	0.002	−0.466
Boa Vista	10.7	11.6	10.5	10	8.7	7.3	3.6	4.9	5.7	3.7	4.8	3.8	< 0.001	−0.774
Campo Grande	9.8	10.4	12.4	11.3	9.0	8.1	10.3	11.1	6.3	5.4	8.6	6.6	0.016	−0.409
Cuiabá	10.7	10.4	11.0	9.7	9.4	9.6	8.7	6.5	5.5	7.2	5.8	4.4	< 0.001	−0.587
Curitiba	16.0	16.4	13.9	15.5	14.6	13.6	9.7	11.9	12.4	9.8	10.7	13.2	0.004	−0.484
Florianópolis	14.7	13.8	13.8	17.4	14.8	10.9	10.8	10.6	10.3	10.3	8.6	9.6	< 0.001	−0.614
Fortaleza	13.1	11.2	8.1	11.2	6.6	6.9	5.4	4.8	6.7	4.2	5.1	3.0	< 0.001	−0.779
Goiânia	10.2	10.6	10.0	9.0	9.4	6.9	7.0	6.0	7.1	6.7	7.0	5.5	< 0.001	−0.443
João Pessoa	10.6	9.6	6.5	6.9	8.4	6.3	7.2	4.5	4.8	4.9	3.5	5.8	< 0.001	−0.490
Macapá	8.7	10.0	9.1	8.4	7.6	8.2	4.9	6.6	4.8	5.3	5.2	3.4	< 0.001	−0.533
Maceió	10.4	10.2	7.2	7.2	8.6	6.1	8.1	5.0	4.7	5.1	5.6	3.6	< 0.001	−0.532
Manaus	8.2	9.7	7.6	6.4	6.6	6.8	6.3	3.6	6.3	4.8	3.4	4.4	< 0.001	−0.448
Natal	9.9	11.0	10.5	9.6	8.6	6.1	8.2	4.8	4.1	5.8	3.5	5.2	< 0.001	−0.660
Palmas	8.9	8.0	7.2	8.2	9.1	7.1	6.8	4.3	3.0	3.8	3.5	4.1	< 0.001	−0.552
Porto Alegre	16.9	19.4	17.1	20.9	17.7	19.0	19.3	14.7	15.1	13.4	10.5	9.0	0.002	−0.806
Porto Velho	12.9	10	13.7	12.4	9.5	9.9	10.3	9.0	6.1	7.3	4.9	3.4	< 0.001	−0.797
Recife	11.5	9.2	9.3	9.4	9.0	9.1	10.5	8.5	7.9	4.9	7.2	6.8	0.002	−0.378
Rio Branco	16.3	16.0	13.0	13.0	15.2	9.6	10.9	7.7	5.2	7.7	7.2	6.8	< 0.001	−0.983
Rio de Janeiro	13.4	14.5	14	11.4	12.1	11.8	10.5	9.0	10.2	10.8	9.2	7.9	< 0.001	−0.515
Salvador	7.2	7.3	7.6	6.0	7.3	5.5	5.4	4.0	5.4	3.8	3.7	2.6	< 0.001	−0.429
São Luís	7.7	8.1	5.0	6.6	4.7	5.8	4.2	2.9	2.5	1.5	2.3	2.2	< 0.001	−0.576
São Paulo	14.3	14.9	15.4	14.6	16.3	14.8	11.1	12.6	13.0	12.2	12.1	11.7	0.005	−0.346
Teresina	10.4	8.8	7.2	7.0	7.2	8.3	7.0	4.3	3.1	5.4	3.9	3.3	< 0.001	−0.574
Vitória	12.6	8.8	9.7	9.3	9.2	6.1	6.2	6.5	7.6	5.7	5.2	5.0	< 0.001	−0.561
Brasília	13.7	9.9	11.7	12.5	12.5	10.0	8.1	5.9	7.4	9.2	7.4	8.9	0.007	−0.490
Brasil	12.4	12.3	12.0	11.5	11.7	10.7	9.2	8.6	9.0	8.3	8.0	7.5	< 0.001	−0.496

VIGITEL: *Sistema de Vigilância de Fatores de Risco e Proteção para Doenças Crônicas por Inquérito Telefônico* (Telephone-based System for the Surveillance of Risk and Protective Factors for Chronic Diseases).

tobacco use by approximately 4% in high-income countries and approximately 8% in low- and middle-income countries. [28] Another strategy is the Protocol to Eliminate Illicit Trade in Tobacco Products,[29] the objective of which is to recoup lost taxes and reduce access to low-priced tobacco products available on the black market. Yet another strategy is the provision of universal access to smoking cessation treatment in the Brazilian Unified Health Care System, primarily at primary care clinics.[30]

With regard to the prevalence of smoking among different age groups, our results are similar to those of a study in which the prevalence of smoking was lowest in individuals in the 18- to 24-year age bracket (10.7%) and highest in those in the 40- to 59-year age bracket (19.4%).[14] In a study using data from the 2008 Brazilian National Household Sample Survey, the prevalence of smoking was found to increase with age up to the age of 59 years, decreasing among the elderly.[31]

Brazil is characterized by great cultural diversity, and there are large socioeconomic differences across individuals in the country, all of which can have an impact on tobacco use patterns.[32] The fact that the southern region of Brazil is the largest tobacco producer in the country can have a social, political, economic, and cultural impact on tobacco acceptance and use there, and might explain why smoking prevalence was highest in that region.[33] Data from the PETab and the PNS also show that smoking prevalence is highest in southern Brazil and in the state of São Paulo.[15]

In order to advance in the fight against chronic NCDs and their risk factors (particularly smoking), policy decisions and new regulatory measures conflicting with the interests of the tobacco industry are needed so that the goals of reducing the prevalence of smoking set by the Strategic Action Plan to Combat Chronic NCDs, the World Health Organization Global Action Plan for the Prevention and Control of NCDs, and the United Nations 2030 Agenda for Sustainable Development can be achieved.

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Respiratory mechanics of patients with morbid obesity

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ABSTRACT

Objective: To evaluate the different components of the resistance of the respiratory system, respiratory muscle strength and to investigate the occurrence of expiratory flow limitation (EFL) in patients with morbid obesity (MO) when seated. **Methods:** The sample was composed of MO (BMI≥40 kg/m^2) and non-obese individuals (NO) with a BMI between 18 and 30 kg/m^2. The protocol consisted of the anthropometric assessment and the following measures of respiratory function: spirometry, maximal inspiratory and expiratory pressures (MIP and MEP, respectively) and impulse oscillometry. The group comparison was performed using T-test for unpaired samples. The correlations were evaluated by the Pearson test with a significance level of 5%. **Results:** Fifty MO (age 40±10.4 years, 1.64±0.09 m, 138.8±33.6 kg and 50.7±8.9 kg/m^2), and 30 NO (age 37.6±11.5 years, 1.67±0.09 m, 65.2±10.3 kg and 23.2±22 kg/m^2) were evaluated. The MO showed higher values of total, peripheral, airways, tissue and central resistance when compared to the NO. No patient showed EFL. The waist circumference was associated with spirometric variables, MIP, and MEP The waist-to-hip ratio was correlated to respiratory mechanics and spirometric variables, MIP, and MEP. **Conclusion:** Morbidly obese patients with no obstructive spirometric pattern show increased total, airway, peripheral, and tissue respiratory system resistance when compared to nonobese. These individuals, however, do not present with expiratory flow limitation and reduced respiratory muscles strength.

Keywords: Respiratory mechanics; Obesity; Impulse oscillometry; Pulmonary resistance; Respiratory system impedance.

INTRODUCTION

Obesity is considered a public health problem around the world, presenting an important growth in the last decade.[1] Obesity is a multifactorial condition that can be related to nutritional alteration, genetic, psychological and socioeconomic factors, and sedentary lifestyle.[2] Obesity is classified by the body mass index (BMI), with intervals between 30 and 34.9 kg/m^2 considered as obesity class I; 35 to 39.9 kg/m2 considered as obesity class II; and ≥ 40 kg/m^2 considered as obesity class III also called as morbid obesity.[3,4] With the increased prevalence of obese people with BMI>50 kg/m^2, it was necessary to broaden this classification, considering intervals between 50 and 60 kg/m^2 as super obese, and > 60 kg/m^2 as super-super obese.[5]

The repercussion of obesity on the respiratory function is associated mainly with the restrictive alteration caused by the excess of adipose tissue.[6,7] The increase of fat mass in the thorax and abdomen can shift the elastic point of balance between the chest and lungs, reducing

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the functional residual capacity (FRC). This low volume of relaxation of the respiratory system (RS) favors the shift of the pressure-volume curve for its least complacent region. In addition, the reduction of the functional residual capacity is associated with the reduction of the caliber of the airway, resulting in increased resistance.[8,9]

Several methods may be used to study respiratory mechanics in individuals breathing spontaneously; however, the impulse oscillometry (IOS), which is one of the applications of the forced oscillation technique, is featured for not depending on effort, not requiring special maneuvers and for offering resistance values for central, peripheral and tissue of the respiratory system, as well as airways resistance.[10,11] Recently, Albuquerque e cols.[6] used IOS to evaluate the respiratory mechanics of patients with morbid obesity and observed an increase in the RS peripheral resistance in 5Hz. However, the authors did not investigate the mean resistances (associated to the airways resistance) and tissue resistance, as well as the occurrence or not of expiratory flow limitation in obese patients, and the respiratory muscular strength. Thus, this study aimed to evaluate the different components of the respiratory system resistance and respiratory muscular strength in patients with morbid obesity and to investigate the occurrence of expiratory flow limitation (EFL) in a seated position.

METHODS

Sample characteristics

This is a cross-sectional study using a sample composed by patients with morbid obesity (BMI ≥40 kg/m^2) from the Program of Bariatric Surgery from the Hospital Universitário Clementino Fraga Filho da Universidade Federal do Rio de Janeiro (PROCIBA / HUCFF-UFRJ), and a group of non-obese individuals, paired by age and gender, with BMI between 18 and 30 kg/m^2. All participants were volunteers and signed an informed consent form, which was approved by the Institution's Research Ethics Committee, according to Resolution 466/12 of the Brazilian National Health Council.

The following exclusion criteria were adopted: a history of pulmonary or cardiac disease, history of smoking, neurological and musculoskeletal diseases, inability to perform the proposed tests and obstructive spirometric pattern (FEV_1/FVC ≤ 70%) for both groups.

Study protocol

The study protocol was composed by an anthropometric evaluation of the body composition and respiratory function using spirometry, static respiratory pressures, and impulse oscillometry. All tests were performed in the Respiratory Physiology Laboratory of the Instituto de Biofísica Carlos Chagas Filho da Universidade Federal do Rio de Janeiro (IBCCF-UFRJ).

Anthropometric assessment

The anthropometric assessment obtained data for body mass measures, height, BMI, waist circumference (WC), hip circumference (HC) and waist-to-hip ratio (WHR). The height was verified using a stadiometer (Cardiomed, WCS-Wood, Curitiba/PR, Brazil). The WC was measured in the orthostatic position with upright posture, no clothes or shoes, in the mean point of distance between the lower costal margin and the anterior iliac crest. The HC was measured by taking the larger diameter of the gluteal region, passing over the greater trochanters of the femur, using a metallic tape measure (Sanny® SN-4010, São Paulo, Brazil), with 2m of extension and 0.1 cm precision. Finally, the WHR was calculated by dividing the waist circumference in centimeters by the hip circumference also in centimeters, according to the WHO instructions.[12]

Spirometry

Spirometry was performed according to the *American Thoracic Society*[13] and Sociedade Brasileira de Pneumologia[14] recommendations, using the computerized spirometer and its components, Lilly pneumotachograph (Erich Jaeger, Hoechberg, Germany) and flow and pressure transducers (Sensym SLP004D, Honeywell Sensing and Control, Golden Valley, MN, USA), following the manufacturer's calibration instructions. The predicted values for forced vital capacity (FVC), forced expiratory volume in the first second (VEF_1) and expiratory peak flow (PF) were calculated according to the equations of Pereira e cols.[14] In addition, the maximal voluntary ventilation (MVV)[15] was verified using the same equipment. For this variable, the predicted values were calculated according with the Brazilian reference equations described by Neder et al.[16]

Maximal Respiratory Pressures

The evaluation of the respiratory muscle strength was performed by measuring the maximal inspiratory and expiratory pressures (MIP and MEP, respectively), according to the ATS/ERS[16] recommendations. An analogical manovaccuometer (M120 – Comercial Médica, São Paulo/SP, Brazil) was used, with a 2 mm orifice on the mouthpiece to dissipate the pressure generated by the muscles of the face and oropharynx. A minimum of three acceptable measurements and a maximum of five were performed. The criteria of acceptability and reproducibility included maneuvers that did not differ in more than 10% of the highest value among themselves. An interval of one minute and thirty seconds among each verification was established. For the measurement of MIP, the individuals were instructed to take a deep breath from the RV in the manovaccuometer's mouthpiece and maintain the pressure for at least 2 seconds. For the measurement of the MEP, the participants were instructed to take a deep breath until total lung capacity (TLC), take a forced exhalation through the device and maintain the pressure for at least 2 seconds. The predicted values were calculated according to the Brazilian reference equations described by Neder et al.[17]

Impulse oscillometry

The evaluation of the respiratory mechanics was performed with an impulse oscillometer (Erich Jaeger, Hoechberg, German) and its components. After the equipment calibration, the participants remained in a seated position, with the head in a neutral position, manual support on the cheeks and nostrils occluded by a nasal clip. Five sequences of 40 seconds of respiratory signals were collected. Signals of at least 15 seconds, no artifacts, and with at least 80% of the frequency range showing a coherence function equal or higher than 0.9 were adopted as acceptability criteria. The following variables were measured: resistance in 5Hz (R5), resistance in 20 Hz (R20), inspiratory reactance in 5 Hz (X5ins), expiratory reactance in 5 Hz (X5exp), mean reactance in 5 Hz (X5), resonance frequency (f0) and integral of reactance between 5 Hz and f0 (AX). The last 3 parameters may reflect the shift of the frequency curve *vs.* reactance to the right, which is usually associated with increased peripheral resistance or respiratory system elastance.[10] In addition to the parameters directly provided by the equipment, the extrapolated resistance at 0 Hz (R0), peripheral resistance (PR=R5-R20), mean resistance (Rm), tissue resistance (TR=R5-Rm) and the derivate of the resistance over frequency (dR/dF), which is also associated with peripheral resistance, were also calculated.[11,12]

Statistical analysis

The results were presented as mean ± standard deviation (SD) or proportions (%). Since the data presented normal distribution (Kolmogorov-Smirnov), the comparison among the obtained results by the morbid obese and non-obese was performed using T-test for unpaired samples. The correlations were evaluated via the Pearson correlation test with a 5% significance level. The software SigmaStat 3.1 (Jandel Scientific, San Rafael, CA, USA) was used for all analyses.

RESULTS

The study recruited 107 subjects as shown in figure 1. After the application of the exclusion criteria, 50 morbid obese, 25 obese with BMI = 40-44.9 kg/m^2, 19 obese with BMI = 50–59.9 kg/m^2 and 6 obese with BMI ≥ 60 kg/m^2 and 30 non-obese remained. The anthropometric and demographic data of the individuals are described in table 1.

When analyzing the spirometric data obtained from morbid obese and non-obese subjects, significant differences were observed regarding the absolute values of some variables; however, no significant differences were observed among the variables regarding the percentage of the predicted values. The values of maximal respiratory pressures, MIP and MEP, did not showed significant differences among the groups (neither in absolute nor in percentage of the predicted), table 2.

As for the results of respiratory mechanics (Table 2), the morbid obese had higher values of total (R0 and R5), central (R20), airways (Rm), tissue (TR) and peripheral resistance (dR/dF and PR) when compared with non-obese. The differences observed in the AX and X5 values suggested an increased resistance or elastance of the respiratory system in the group of morbid obese. No patient showed EFL.

The WC of obese individuals was not correlated with respiratory mechanics variables; however, it was correlated with the following spirometry variables: FVC (%), FEV1 (%), PF (L/s) and MVV (L), MIP (%) and MEP (%), as shown in table 3. The non-obese subjects showed a correlation of WC with the respiratory

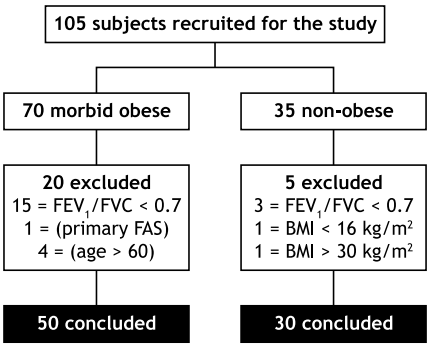

Figure 1. Flowchart for selection of the patients included in the study. FAS: Antiphospholipid Antibody Syndrome; FEV1/FVC: forced expiratory volume in the first second-forced vital capacity ratio; BMI: body mass index.

Table 1. Anthropometric and demographic characteristics of the sample components.

Variables	Morbid obese (n=50)	Non-obese (n=30)	P
Age (years)	40.0±10.4	37.6±11.5	0.2947
Female gender % (n)	79 (39)	70 (21)	0.4103
Height (m)	1.64±0.09	1.67±0.09	0.3004
Body mass (kg)	138.8±33.6	65.2±10.3	< 0.0001
BMI (kg/m^2)	50.7±8.9	23.2±2.2	< 0.0001
WC (cm)	136.3±18.8	80.5±9.9	< 0.0001
HC (cm)	143.4±17.5	97.5±5.9	< 0.0001
WHR	0.95±0.09	0.84±0.08	< 0.0001

BMI: body mass index; WHR: waist-to-hip ratio; WC: waist circumference; HC: hip circumference.

Table 2. Spirometric variables, maximal respiratory pressures and respiratory mechanics in morbid obese and non-obese.

Variables	Morbid obese (n=50)	Non-obese (n=30)	P
Spirometry			
FVC (L)	3.5±0.7	4.0±0.8	0.0275
FVC (% pred)	78.7±6.9	100.9±10.6	0.4198
FEV_1 (L)	2.8±0.6	3.2±0.6	0.0157
FEV_1 (% pred)	80.5±7.6	97.4±8.0	0.0978
FEV_1/FVC (L)	80.4±6.6	82.6±5.8	0.5384
PF (L/s)	7.0±1.9	7.8±2.0	0.0582
PF (% pred)	83.4±20.3	86.6±13.3	0.5750
MVV (L)	114.2±26.1	126.6±24.2	0.2435
MVV (% pred)	89.2±23.4	89.9±15.6	0.3236
Maximal respiratory pressures			
MIP (cmH_2O)	102.0±23.5	116.5±22.5	0.5862
MIP (% pred)	100.2±31.5	121.7±25.5	0.0572
MEP (cmH_2O)	107.5±21.2	122.7±24.4	0.3084
MEP (% pred)	107.8±30.5	102.0±11.3	0.2359
Respiratory mechanics			
R0 (kPa/l/s)	0.6±0.2	0.4±0.1	0.0001
R5 (kPa/l/s)	0.5±0.1	0.1±0.1	0.0001
R20 (kPa/l/s)	0.38±0.16	0.28±0.08	0.0010
Rm (kPa/l/s)	0.50±0.18	0.33±0.09	0.0001
PR (kPa/l/s)	0.18±0.12	0.064±0.043	0.0027
TR (kPa/l/s)	0.03±0.02	0.01±0.01	0.0002
f0 (Hz)	20.9±4.5	13.7±3.5	0.0001
AX (kPa/l*Hz)	1.6±1.3	0.4±0.31	<0.0001
dR/dF	0.021±0.012	-0.01±0.001	<0.0001
X5 (kPa/l/s)	0.20±0.10	0.09±0.02	0.0007
X5ins (kPa/l/s)	-0.19±0.08	0.12±0.09	0.0013
X5exp (kPa/l/s)	-0.20±0.12	0.10±0.04	0.0007
ΔX5 (kPa/l/s)	0.07±0.12	0.03±0.02	0.0739

FVC: forced vital capacity; FEV_1: forced expiratory volume in the first second; PF: expiratory peak flow; MVV: maximal voluntary ventilation; MIP: maximal inspiratory pressure; MEP: maximal expiratory pressure. R0: resistance extrapolated for 0Hz; R5: resistance in 5Hz; R20: resistance in 20Hz; PR: peripheral resistance (R5-R20); Rm: mean resistance; TR: tissue resistance; f0: resonance frequency; AX: reactance integral between 5Hz and resonance frequency; dR/dF: dependence of respiratory system resistance on frequency; X5ins: inspiratory reactance in 5Hz; X5exp: expiratory reactance in 5Hz; ΔX5: difference between inspiratory and expiratory reactance. Values represented as mean ± standard deviation.

mechanics variable R20, and spirometry variables FVC (L), FEV1/FVC, PF (L) and MVV (% and L).

There were no associations between the hip circumference and the variables of respiratory mechanics, maximal static respiratory pressures and spirometry for morbid obese and non-obese groups.

There were correlations between WHR of morbid obese and the following respiratory variables: AX, f0, PF (%), MIP (%) and MEP (%). For non-obese individuals, WHR was correlated with R20, X5ins, delta X5, FVC (L), PF (L), MVV (L) and MEP (%), as shown in table 4.

The BMI was correlated with spirometric variables FVC (%), FEV_1 (%), PF (L/s) in the group of obese, and FEV_1/FVC, in addition to MIP (cmH_2O) and MEP (%) in the non-obese group (table 5).

DISCUSSION

Even though in this study the patients with morbid obesity did not show obstructive spirometric patterns, the values of total (R0 and R5), airways (Rm), peripheral (dR/dF and PR) and tissue resistance (TR) were higher than the values presented by the control group. In addition, the results related to respiratory system reactance (AX, X5, X5insp, and X5exp) were different from those of the control group, what can be interpreted as increased peripheral resistance or reduced respiratory system compliance. These results corroborated with those of other authors that observed increased respiratory system, airways[18] and peripheral resistances[7] in obese individuals using the forced oscillations technique. Yap et al.[19] also

Table 3. Correlation of the variables of respiratory mechanics, spirometry and static respiratory pressures with the waist circumference.

Variables	Morbid obese (n=50)		Non-obese (n=30)	
	r	P	r	P
R0 (kPa/l/s)	0.0959	0.5072	0.1961	0.2990
Rm (kPa/l/s)	0.1278	0.3763	0.2431	0.1956
TR (kPa/l/s)	0.0464	0.7487	0.2274	0.2268
R5 (kPa/l/s)	0.0526	0.7163	0.1976	0.2953
R20 (kPa/l/s)	0.2080	0.1472	0.3933	0.0316
X5 (kPa/l/s)	0.0364	0.8016	0.2273	0.2270
f0 (Hz)	-0.1918	0.1821	0.3093	0.0963
AX (kPa/l*Hz)	-0.0932	0.5196	0.0444	0.8156
X5 ins (kPa/l/s)	0.1523	0.2910	0.1521	0.4225
X5 exp (kPa/l/s)	0.0953	0.5101	0.1181	0.5342
Δ X5 (kPa/l/s)	-0.0777	0.5917	-0.0314	0.8689
dR/dF	0.0519	0.7204	0.0263	0.8900
FVC (L)	-0.1056	0.4656	-0.4564	0.0112
FVC (% pred)	-0.4257	0.0021	-0.1484	0.4339
FEV_1 (L)	-0.1164	0.4206	-0.3559	0.0536
FEV_1 (% pred)	-0.3671	0.0087	-0.0108	0.9545
FEV_1/FVC (L)	-0.0650	0.6536	-0.4240	0.0195
PF (L/s)	-0.3633	0.0095	-0.5788	0.0008
PF (% pred)	-0.2031	0.1573	-0.3334	0.0718
MVV (L)	-0.2788	0.0499	-0.4633	0.0099
MVV (% pred)	-0.0065	0.9637	-0.3712	0.0434
MIP (cmH_2O)	-0.2311	0.1063	-0.4446	0.0138
MIP (% pred)	-0.3758	0.0072	-0.1731	0.3603
MEP (cmH_2O)	-0.0545	0.7067	-0.2068	0.2730
MEP (% pred)	-0.3878	0.0054	-0.1667	0.3787

FVC: forced vital capacity; FEV_1: forced expiratory volume in the first second; PF: expiratory peak flow; MVV: maximal voluntary ventilation; MIP: maximal inspiratory pressure; MEP: maximal expiratory pressure. R0: resistance extrapolated for 0Hz; R5: resistance in 5Hz; R20: resistance in 20Hz; Rm: mean resistance; TR: tissue resistance; f0: resonance frequency; AX: reactance integral between 5Hz and resonance frequency; dR/dF: dependence of respiratory system resistance on frequency; X5ins: inspiratory reactance in 5Hz; X5exp: expiratory reactance in 5Hz; ΔX5: difference between inspiratory and expiratory reactance.

observed increased peripheral resistance in obese; however, in our sample, the values are 18.6% higher than the group of morbid obese in their study. Such fact can be explained by higher BMI values in our study (50.7±8.9 kg/m2 vs. 43.6±2.5 kg/m2). Several authors suggested that the increased airways resistance in obese individuals is related to the reduction of pulmonary volume; however, its pathophysiology remains unclear. One hypothesis is that the airway structure can be remodeled due to the exposure do proinflammatory adipokines or to the lipid deposition.[6] Mahadev[20] observed that, in addition to the FRC reduction, the airways resistance in morbid obese individuals can also be increased due to the remodeling, which is characterized by the fat deposit in its interior, bronchial mucosa injury related to the stress of opening and closure of small airways and by the chronic exposure to adipocytokines.

This hypothesis agrees with the increased peripheral resistance observed in our study. Zerah et al.[18] also observed that the difference between the respiratory system and airways resistance did not increase significantly with the level of obesity. Based on these results, the authors raised the hypothesis that the thoracic resistance does not increase proportionally to the level of obesity. Even though we did not compare different levels of obesity, the patients with morbid obesity presented higher tissue resistance than the control group, suggesting that the amount of fat tissue in the thoracoabdominal region is associated with a higher dissipation of energy with the respiratory system movement. This result somehow disagrees with Zerah et al.[18] hypothesis. One of the hypothesis for this discordance is the higher BMI of the subjects included in our study, since the sample also had individuals considered super obese. Santana et al.[21] demonstrated how the pulmonary function of super obese can be more affected when compared to morbid obese; however with smaller BMI.

One of the aims of this study was to evaluate the occurrence of expiratory flow limitation in the group of morbid obese patients. According to Lin & Lin[22] the

Table 4. Correlation of the variables of respiratory mechanics, spirometry and static respiratory pressures with the waist-to-hip ratio.

Variables	Morbid obese (n=50)		Non-obese (n=30)	
	r	P	r	P
R0 (kPa/l/s)	0.2162	0.1315	0.3472	0.0601
Rm (kPa/l/s)	0.1843	0.2002	0.3495	0.0584
TR (kPa/l/s)	0.2531	0.0761	0.06626	0.7279
R5 (kPa/l/s)	0.1109	0.4431	0.3367	0.0689
R20 (kPa/l/s)	0.1719	0.2325	0.3887	0.0338
X5 (kPa/l/s)	0.1613	0.2632	0.1907	0.3127
f0 (Hz)	-0.4358	0.0016	-0.06562	0.7304
AX (kPa/l*Hz)	-0.3176	0.0246	-0.1066	0.5749
X5ins (kPa/L/s)	0.2266	0.1135	0.4051	0.0264
X5exp (kPa/L/s)	0.2353	0.0999	0.1052	0.5801
Δ X5 (kPa/L/s)	-0.1408	0.3294	-0.4040	0.0268
dR/dF	0.2677	0.0602	0.2670	0.1538
FVC (L)	-0.1046	0.4695	-0.4276	0.0184
FVC (% pred)	-0.2612	0.0669	-0.1596	0.3995
FEV_1 (L)	-0.1525	0.2904	-0.4045	0.0266
FEV_1 (% pred)	-0.1902	0.1859	-0.08580	0.6521
FEV_1/FVC (L)	-0.1829	0.2036	-0.2069	0.2727
P (L/s)	-0.1386	0.3370	-0.3995	0.0287
PF (% pred)	-0.3715	0.0079	-0.01331	0.9443
MVV (L)	-0.3663	0.0089	-0.3824	0.0370
MVV (% pred)	-0.1856	0.1968	-0.1457	0.4424
MIP (cmH_2O)	-0.1979	0.1682	-0.1133	0.5511
MIP (% pred)	-0.3036	0.0321	-0.2380	0.2054
MEP (cmH_2O)	-0.1061	0.4633	-0.06478	0.7338
MEP (% pred)	-0.3764	0.0071	-0.3791	0.0388

FVC: forced vital capacity; FEV_1: forced expiratory volume in the first second; PF: expiratory peak flow; MVV: maximal voluntary ventilation; MIP: maximal inspiratory pressure; MEP: maximal expiratory pressure. R0: resistance extrapolated for 0Hz; R5: resistance in 5Hz; R20: resistance in 20Hz; Rm: mean resistance; TR: tissue resistance; f0: resonance frequency; AX: reactance integral between 5Hz and resonance frequency; dR/dF: dependence of respiratory system resistance on frequency; X5ins: inspiratory reactance in 5Hz; X5exp: expiratory reactance in 5Hz; ΔX5: difference between inspiratory and expiratory reactance.

reduced functional residual capacity and expiratory reserve volume of patients with morbid obesity increase the risk of dynamic compression and collapse of the airways, even during rest. Thus, it can occur the expiratory flow limitation (EFL) and air trapping, resulting in increased respiratory effort and dyspnea. The occurrence of EFL has been assessed in obese individuals using the expiratory negative pressure method.[23] In our study, the occurrence of EFL was measured via respiratory system reactance, as described by Dellaca and cols. in 2004 who validated the method using the technique of negative pressure as the golden standard.[24] Using the difference between inspiratory and expiratory reactance, Mahadev et al.[20] evaluated 18 patients with BMI = 41.3±6.8 kg/m and only 1 showed EFL. Similarly, no patient from our sample (mean BMI of 50.7±8.9 kg/m2) presented EFL. These results showed that, despite the reduced FRC and increased peripheral resistance observed in the patients with morbid obesity, the EFL is a common finding only when these individuals are in supine position, corroborating with the study by Pankow et al.[25] In supine position, the abdomen compressive effect reduce even more the FRC and, consequently, the diameter of the airway, resulting in dynamic compression and/or collapse.

The consensus among authors[18,22,23,25] is that even when isolated from other comorbidities, obesity is a preponderant factor for respiratory mechanics impairments, either by analysis of resistance variables or respiratory system compliance. Based on this assumption, the only possible solution for such problems is the weight reduction.

As expected, differently from the hip circumference, the abdominal circumference was associated with several respiratory variables (FVC, FEV_1, PF, MVV and respiratory pressures), probably due to the effect of restriction and increased intra-abdominal pressure that happens in morbid obese individuals, altering the elastic balance of the respiratory system and reducing the pulmonary volume.[9,26] The WHR was also associated with respiratory mechanics variables and maximal

Table 5. Correlation of the variables of respiratory mechanics, spirometry and static respiratory pressures with the body mass index.

Variables	Morbid obese (n=50)		Non-obese (n=30)	
	r	P	r	P
R0 (kPa/l/s)	0.00009	0.9995	0.07414	0.6970
Rm (kPa/l/s)	0.03030	0.8346	0.00081	0.9966
TR (kPa/l/s)	0.1091	0.4506	0.4199	0.1209
R5 (kPa/l/s)	0.03077	0.8320	0.05901	0.7567
R20 (kPa/l/s)	0.1275	0.3777	-0.1790	0.3438
X5 (kPa/l/s)	0.06057	0.6760	0.1759	0.3526
f0 (Hz)	-0.02165	0.8813	0.4168	0.2219
AX (kPa/l*Hz)	-0.01857	0.8982	0.2543	0.1751
X5ins (kPa/L/s)	0.01404	0.9229	-0.03390	0.8589
X5exp (kPa/L/s)	0.00568	0.9687	-0.1060	0.5773
Δ X5 (kPa/L/s)	-0.07194	0.6195	-0.1080	0.5702
dR/dF	0.04433	0.7599	0.2786	0.1360
FVC (L)	-0.04447	0.7591	-0.3361	0.0694
FVC (% pred)	-0.3847	0.0058	-0.2972	0.1107
FEV_1 (L)	-0.02432	0.8669	-0.2320	0.2174
FEV_1 (% pred)	-0.3517	0.0122	-0.06050	0.7508
FEV_1/FVC (L)	-0.05293	0.7151	-0.4029	0.0273
PF (L/s)	-0.2939	0.0383	-0.3230	0.0817
PF (% pred)	-0.1123	0.4374	-0.1225	0.5191
MVV (L)	-0.1098	0.4478	-0.3298	0.0752
MVV (% pred)	-0.06098	0.6740	-0.2338	0.2137
MIP (cmH_2O)	-0.1951	0.1746	-0.5408	0.0020
MIP (% pred)	-0.2941	0.0381	-0.5191	0.1067
MEP (cmH_2O)	-0.1746	0.6931	-0.2949	0.1136
MEP (% pred)	-0.2715	0.0565	-0.3627	0.0489

FVC: forced vital capacity; FEV_1: forced expiratory volume in the first second; PF: expiratory peak flow; MVV: maximal voluntary ventilation; MIP: maximal inspiratory pressure; MEP: maximal expiratory pressure. R0: resistance extrapolated for 0Hz; R5: resistance in 5Hz; R20: resistance in 20Hz; Rm: mean resistance; TR: tissue resistance; f0: resonance frequency; AX: reactance integral between 5Hz and resonance frequency; dR/dF: dependence of respiratory system resistance on frequency; X5ins: inspiratory reactance in 5Hz; X5exp: expiratory reactance in 5Hz; ΔX5: difference between inspiratory and expiratory reactance.

respiratory pressures, suggesting that not only BMI but also the pattern of body fat distribution affects the respiratory mechanics. This hypothesis corroborates with the findings of Chen et al.[27] that observed a negative correlation between the abdominal circumference ratio and the spirometric variables, regardless of the BMI. Canoy et al.[28] when analyzing 9,674 men and 11,876 women, observed that both FVC and FEV_1 were linear and inversely correlated with WHR.

As limitations of this study, there is the lack of static pulmonary volume measures, which would contribute to the understanding of the mechanisms involved in the respiratory mechanics alterations. However, our results showed that, even with spirometric values within normal, the patients with morbid obesity may present respiratory mechanics alterations that can be detected by impulse oscillometry. In addition, not only the BMI but also the pattern of body fat distribution can influence the behavior of the respiratory variables.

Thus, the respiratory mechanics assessment using the forced oscillations technique and measurement of anthropometric variables (circumference and WHR) significantly contribute to the follow-up of patients with morbid obesity, especially those with respiratory symptoms. Both methods are non-invasive and do not require special maneuvers. It is likely that the improvement of respiratory mechanics of these patients, especially the peripheral and tissue resistances (thoracic wall), may improve the exercise tolerance[29] with a positive impact on the functional independence and quality of life.

From the results of the present study, we conclude that patients with morbid obesity and no obstructive spirometric pattern have increased total, airways, peripheral, and tissue resistances of the respiratory system when compared to non-obese. These individuals, however, do not show expiratory flow limitation and reduced respiratory muscle strength.

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Reference values for the carbon monoxide diffusion (transfer factor) in a brazilian sample of white race

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Study carried out in six centers in Brazil, having as its coordinating center the Madre Teresa Hospital, Belo Horizonte, (MG) Brazil.

ABSTRACT

Objective: To derive reference values from white race adults, for DCO in a sample from different sites in Brazil, through the same equipment model (Sensormedics), and compare the results with the derivatives from Crapo, Miller, Neder equations and from the Global Lung Initiative (GLI) proposal. **Methods:** The tests were performed according to the norms suggested by ATS/ERS in 2005 in six Brazilian cities, with 120 adult volunteers of each gender, non-smokers, without referred anemia and without lung or cardio diseases. The expected values were derived from linear regressions and the differences between the values forecasted by some authors and the ones observed in the current study were calculated. **Results:** Among men, the age varied between 25 and 88 years old, and the height varied between 140 and 176 cm. DCO was correlated significantly and positively with the height and negatively with the age. The values forecasted by Crapo, Neder, and Miller equations were higher in comparison with the ones obtained by the current study ($p<0.01$) in both genders. Among men, the values did not differ when compared to the ones calculated by GLI ($p=0.29$); among women, the values derived by GLI were slightly higher: 0.99 ml/min/mmHg ($p<0.01$). **Conclusion:** new values forecasted for DCO were derived in a sample of white adults in Brazil. The forecasted values are similar to the ones complied by GLI equations and differ from the previously proposed equations.

Keywords: Transfer factor; Pulmonary diffusing capacity; Diffusion; Carbon monoxide; Reference values; Lung function tests.

INTRODUCTION

The measurement of the diffusion of carbon monoxide (DCO) or transfer factor for CO, by a single breath, is an essential test at the diagnostic assessment and at the functional follow up in several breathing conditions.[1] Reference values were derived and validated for the spirometry in Brazil.[2,3] The reference value selection for DCO is more difficult than the choice of the reference value for spirometry, due to the large variation among laboratories.[4] In 2005, the task force of ATS/ERS did not recommend the adoption of any specific equation for DCO. However, it suggested that the values forecasted for the alveolar volume (AV) for DCO and for the diffusion coefficient (kCO) should derive from the same source.[4]

In Brazil, Crapo proposed equations and the ones derived from Neder are used; however, the foreseen values are higher than other studies.[5-7] Yet, other equations, like the ones proposed by Miller, show lower forecast.[5,8]

In the last years, there was a great development in the lung function equipment, such as the advent of quick response gas analyzers, with excellent linearity and accuracy. This led to more precise results and most demanding proposals regarding the performance of single breath test for measuring DCO in comparison with the previously suggested guidelines.[9,10]

In 2017, the *Global Lung Initiative* (GLI) derived reference values for the DCO by compiling the obtained values in several studies made after the 2000, in more modern equipment. The foreseen values by this equation are lower in comparison with the ones previously published and must be validated.[11]

The objective of this study was to derive reference values from the white race to the DCO in a sample of different sites in Brazil by the same equipment model (Sensormedics) and to compare the results with the derived ones from Crapo, Miller, Neder equations and from GLI proposal.[6-8,11]

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METHODS

Data were obtained between 2015 and 2017 in six Brazilian cities by systems of the same brand (Sensormedics, Yorba Linda, California).

DCO was measured in all the sites according to the norms suggested by ATS/ERS in 2005, using the CO (0.30%) and CH4 (0.30%) as gases test.[9] FiO_2 was of 0.21. The lung volumes were simultaneously determined by plethysmography. The equipment measures the room temperature by electronic thermometer and the barometric pressure by internal gauge. It performs the conversion of the corrected exhaled gas volume for the corporal conditions of temperature and water vapor pressure into the barometric pressure (BTPS).

The equipment dead space and the valve volume, by *default,* are fixed, from 0.15 L and 0.08 L, respectively.

The individuals were selected by oral invitation, and they are more commonly family members or companions and, eventually, school staff, and of different socioeconomic levels. The volunteers that accepted and consented in participating initially answered a respiratory questionnaire translated from the American Thoracic Society/Division of Lung Diseases, validated in our country and signed the informed consent form.[12,13]

The devices were daily calibrated with a three-liter syringe and weekly submitted to biological controls by the lab employees. The exams were performed by technicians or doctors certified in lung function by the Brazilian Society of Pneumology and Tisiology (SBPT).

The study inclusion criteria were the same as the ones used in the study for the spirometry values derivation in 2007, added a question related to the presence of anemia, which should be absent.[2]

The weight and height were measured according to SBPT recommendations.[14] Obese people (BMI>30 kg/m^2) were excluded.

The DCO measures were performed after the spirometry measures.

They should meet the acceptance and reproducibility criteria suggested by SBPT.[14] The observed CVF values were compared to the ones forecasted for the Brazilian population derived in 2007.[2]

The volume inhaled in the maneuver should be ≥85% of the vital capacity and should be completed in less than 4s. At least two acceptable maneuvers with a difference of ±10% of the highest value and less than 3 ml/min/mmHg were obtained, with 4 min interval. The final registered value was derived from the average of the acceptable maneuver values.[9]

The inspiratory time, measured by Jones and Meade method, should be between 8-12s. As acceptance criteria, during the sustained respiration, there should not exist leaking, or excessive pressure variations in the mouth, exhibited in the monitor during the test performance, indicating Muller and Valsalva maneuver. The exhalation should last for less than 4s. The volume discarded at the exhalation before the alveolar gas sample collection was 0.75 L.[9]

The variables of numeric nature were analyzed by average and standard deviation and the amount of these variables were compared between the genders using the *t*-test of Student.

Linear regressions were used for reference values derivations, considering variables with p≤0.10 at the univariate analysis.

The differences between the values observed in the current study and the ones forecasted for CPT by Crapo, Miller, Neder equations and the ones suggested by GLI were calculated in the total sample and at representative ages and height of each gender. The average difference and its significance were calculated by the matched *t*-test.

All the tests were individually rechecked by one of the authors (CACP), and the ones that did not meet the acceptance and reproducibility criteria were excluded. The cases considered discrepant by distribution after graphs *blox plot* and the ones where the residues derived from the equations exceeded the acceptable values were also excluded.[15]

The statistical analysis was performed ofusing the statistics software SPSS-22. By the comparison multiplicity, the significant *p*-value was considered < 0.01.

With full documentation of all the involved sites, the project was approved by the Ethics and Research Committee of the Hospital Madre Teresa/Belo Horizonte, Minas Gerais, under register number 1617108.

RESULTS

Initially, 292 cases were evaluated; 45 were excluded for inadequate tests and 7 for discrepant values. In the end, 240 cases were included, 120 of each gender. In decreasing order, 153 (63.8%) were from São Paulo, 28 from Salvador, 25 from Criciúma, 25 from Belo Horizonte and 9 from other sites.

The distribution by age, height and BMI is separately shown by each gender in Table 1. Among men, the age varied from 25 to 88 years old, the average height was of 173cm, varying from 156 to 189cm. Among women, the age varied from 21 to 92 years old, the average height was 160cm, varying from 140 to 176cm.

The main functional parameters average, including values for DCO, kCO and alveolar volume (VA), are shown in Table 2. All the values were higher in the male gender, except for CVF in the percentage of the forecasted and kCO, that did not show a significant difference between the genders. CVF was 98.7% of the forecasted for both genders. The relation between the inspiratory vital ability of the diffusion maneuver and the slow vital ability, obtained separately, was 0.91 ± 0.04 in the total sample.

VA/CPT relation was in average 0.87 ± 0.07 among men and 0.86 ± 0.08 among women. In both genders the VA/CPT relation was directly correlated with the inspiratory vital ability (r = 0.44 among men and 0.43 among women, p<0.001) and inversely related

Table 1. Distribution of patients by gender, age, height, and body mass index.3

Variable	Female sex n = 120		Male sex n = 120	
	n	%	n	%
Age (years)				
20-24	4	3.3	----	----
25-34	30	25.0	24	20.0
35-44	18	15.0	20	16.7
45-54	18	15.0	26	21.7
55-64	24	20.0	17	14.2
65-74	13	10.8	25	20.8
≥75	13	10.8	8	6.7
Height (cm)				
140-154	28	23.3	---	----
155-164	62	51.7	13	10.8
165-174	29	24.2	62	51.7
175-184	1 (176 cm)	0.8	38	31.7
≥ 185	----	---	7	5.8
IMC (Kg/m^2)				
18-24	45	37.5	38	31.7
25-30	75	62.5	82	68.3

Table 2. Average of functional variables separated by gender.

Functional variable	Women (N = 120) X ± SD	Men (N = 120) X ± SD	P
CVF (L)	3.24 ± 0.62	4.59 ± 0.79	<0.01
CVF (% forecasted)	99.8 ± 12.3	97.5 ± 10.2	0.12
VEF1 (L)	2.63 ± 0.53	3.62 ± 0.63	<0.01
VEF1/CVF%	0.81 ± 0.05	0.79 ± 0.05	<0.01
CV (L)	3.30 ± 0.60	4.71 ± 0.82	<0.01
VR (L)	1.58 ± 0.46	2.00 ± 0.51	<0.01
CPT (L)	4.88 ± 0.63	6.71 ± 0.84	<0.01
DCO (ml/min/mmHg)	19.29 ± 3.86	27.90 ± 5.19	<0.01
kCO ($ml.\ min^{-1}.\ mmHg^{-1}.\ L^{-1}$)	3.97 ± 0.58	4.09 ± 0.61	0.12
VA (L)	4.18 ± 0.64	5.92 ± 0.85	<0.01

to age (r = -0.31 among men, and -0.33 among women, p<0.001).

The correlation between DCO and age and height in both genders and the lower limits determined by the 5th percentile of residues are shown in the Figure 1.

The linear equations derived for the DCO, kCO, and VA are shown in Table 3. DCO significantly correlated with age and height in both genders, VA with height in both genders, kCO only with age in the male gender, and in a poor way only with height in the female gender. By considering the obtained average values, the lower limits, determined by the 5th residue percentile, they were less distant from the average among men (82%), in comparison with the women (78%). The same was observed with kCO: 80% among men and 74% among women.

The differences were calculated for men and women, between the forecasted values for individuals of the same age and height, by the selected authors, and the ones observed for DCO in this study. In the male gender, the differences were Neder = 7.7 (IC95% = 7.1-8.3); Crapo = 6.5 (IC95% = 5.8-7.2); Miller = 1.7 (IC95% = 1.0-2.3), all of them with p<0.01. The values did not significantly differ when compared to the derived by GLI: -0.32 (IC95% = -0.93 to 0.28).

In the female gender, the differences were also positive. For Crapo = 6.2 (IC95% = 5.7-6.7); Neder = 6.0 (IC95% = 5.5-6.4); Miller = 3.0 (IC95% = 2.5-3.5), all of them with p<0.01. The lower difference was observed with the valued derived by GLI, although in a significant way: 0.99 (IC95% = 0.52 -1.46), p<0.01.

Table 4 shows the comparisons among the average values and the lower limits calculated by the regression equations by the several authors and the values observed in this study, in individuals with representative age and height. The average values and limits closer

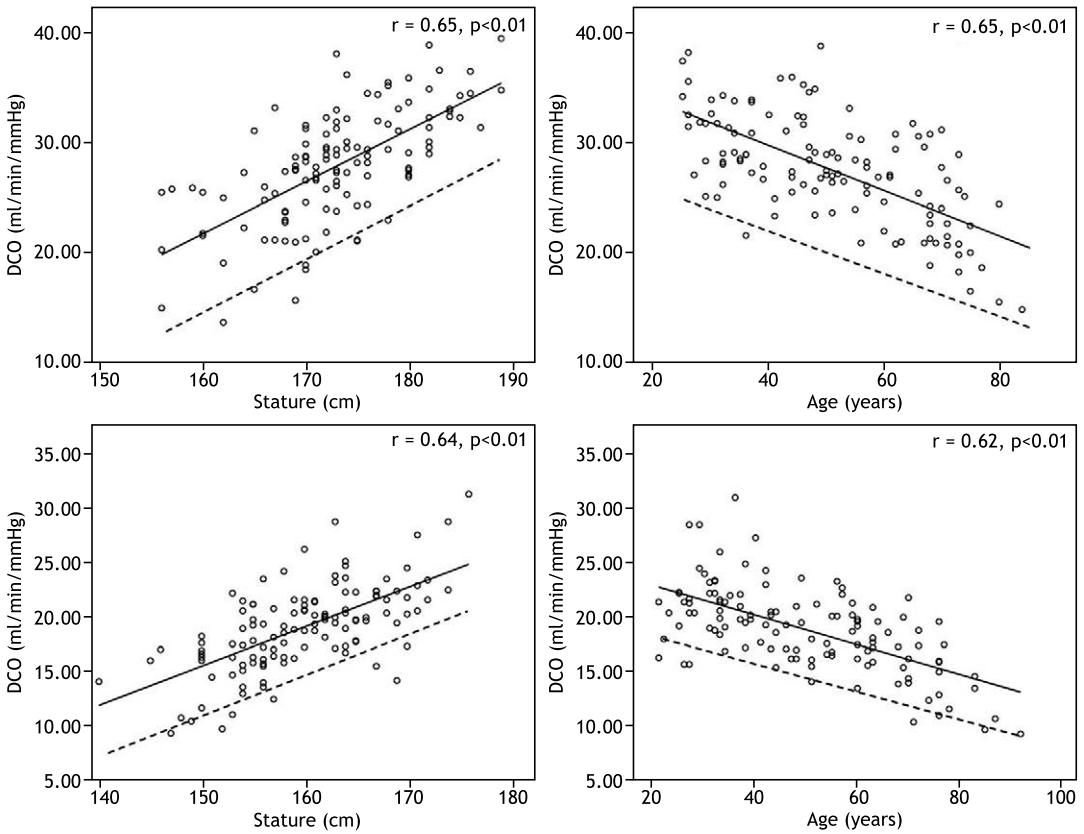

Figure 1. Dispersion of the values for the CO Diffusion with height and age of the reference population in the genders male (above) and female (below).

Table 3. Regression equations, explanation coefficient (r^2) and lower limits for CO diffusion, CO diffusion constant and alveolar volume in the reference population of the female and male genders.

Female, 21-92 years, 140-176 cm height, white race (n = 120)						
	Height coefficient	Age coefficient	Constant	r^2 adjusted	5th residue percentile	Lower limit
DCO (ml/min/mmHg)	0.244	- 0.087	- 15.32	0.53	4.18	P-4.18
VA (L)	0.058	---------	- 5.06	0.40	0.83	P-0.83
KCO (ml. min^{-1}. $mmHg^{-1}$. L^{-1})	0.019	---------	+ 0.98	0.05	1.05	P-1.05
Male, 25-88 years, 156-189 cm height, white race (n = 120)						
	Height coefficient	Age coefficient	Constant	r^2 adjusted	5th residue percentile	Lower limit
DCO (ml/min/mmHg)	0.335	- 0.148	- 22.48	0.60	5.00	P-5.00
VA (L)	0.091	---------	- 9.76	0.56	1.00	P-1.00
KCO (ml. min^{-1}. $mmHg^{-1}$. L^{-1})	-------	- 0.019	5.03	0.25	0.82	P-0.82

Table 4. Average values and lower limits calculated by the current equation compared to values calculated by the equations of other authors in individuals with representative age and height.

Male		Author, average forecasted value and lower limit				
Age	Height	Current	Crapo	Neder	Miller	GLI
26	177	32.97/27.97	41.60/33.4	40.19/30.31	35.99/28.05	32.73/25.84
50	173	28.08/23.08	34.68/26.48	35.79/25.91	29.83/21.89	27.71/21.17
75	168	22.70/17.70	27.12/18.92	30.94/21.06	23.29/15.35	22.26/16.26
Female		**Author, average forecasted value and lower limit**				
Age	Height	Current	Crapo	Neder	Miller	GLI
25	167	23.25/19.07	30.85/24.25	28.38/24.40	26.18/19.68	23.73/18.47
52	161	19.44/15.26	25.43/18.83	25.28/21.30	22.2/15.73	20.46/15.72
76	156	16.13/11.95	20.69/14.09	22.58/18.60	18.76/12.26	17.43/13.05

to the forecasted values and lower limits with the current equations were the ones proposed by GLI. The differences from Neder proposed equations are due to the higher values observed by this author for VA: in the male gender 7.50 L vs 5.92 L in this study ($p<0.001$) and in the female gender 4.88 L vs 4.18 L ($p<0.001$). By linear equations, the explanation coefficient (r^2) at Neder equation was of 0.24 in the male gender and 0.36 in the female gender, in comparison with the values of 0.60 and 0.53 among men and women, respectively, in this sample.

DISCUSSION

New forecasted values for the DCO measure by a single breath were derived in a multi-centric sample of the Brazilian population of the white race.

In this study, DCO values were expressed in traditional units (ml/min/mmHg). For the conversion into mmol/min/kPa, the values should be divided by 2.987.[11]

The forecasted values for DCO were influenced by gender, age, and height. Despite the weight does not affect the DCO average in obese individuals, VA can be lower and kCO higher, that is why the exclusion of obese individuals in the present study.[16]

At the linear equations, the lower limits should be calculated by the subtraction of the 5th residue percentile, a fixed value, of forecasted values.[2] Similar to other studies, the women had higher dispersion of the reference values; that is why the lower limits had been more distant from the median values.[11]

Among adults, DCO along with aging follows a decreasing curve, with relatively stable values in younger individuals and more markedly decline along with aging. This is due to a faster loss of the gas exchange surface, and worsening of the ventilation distribution with aging.[7,17]

The upper limit for DCO was not shown in this study. The meeting value of DCO above the upper limit is small.[11] kCO and VA values were also derived. DCO is the product of kCO x VA; however, the report of DCO/VA relation should be abandoned.[11] There is a great deal of controversy, within the literature, regarding the kCO value at DCO interpretation.[18,19] If a normal individual performs a submaximal inhalation, during the maneuver for measuring DCO, kCO will be high, and so the kCO can only be valued when the VA falls in the forecasted range.[11] In these cases, when kCO is reduced, in general, DCO will be equally reduced.

DCO is measured during a maneuver sustained in plenary inspiration. The inhalation of tracer gas, non-absorbable, allows estimating the lung volume ("a single maneuver CPT") and the dilution occurred to CO. VA calculation represents an estimate of the lung gas volume in which CO is distributed through the alveolar-capillary membrane. Therefore, it is essential to measuring DCO. In normal individuals, the adding of VA and the dead space gets close to the CPT measured by plethysmography.[9]

In the present study, the relation between VA/CPT observed, on average 0.87 ± 0.08, was lower than the reported of 0.94 ± 0.07.[18] Also, different from what has been reported, there was an inverse correlation of this relation with age, suggesting that even in normal individuals, the ventilation distribution, which worsens at aging, can influence VA measure VA.[18]

In this study, it was not done DCO correction for altitude. The barometric pressure (Pb) decreases with attitude, resulting in lower O_2 (PiO_2) inhaled pressure, lower O_2 (PaO_2) alveolar pressure and increase of DCO, for lower "competition" of O_2 with CO at the connection with hemoglobin (Hb). It has been suggested, that the reference values for DCO be adjusted to Pb at sea level (760 mmHg). In a study performed in 4 cities in Latin America, the altitude has influenced DCO measures, with higher values observed in the cities of Mexico (2240m) and Bogota (2640 m) in comparison with the ones observed in Santiago (650m) and Caracas (900m).[20] In this study, the altitude of the evaluated sites varied from 8 m (Salvador) to 852 m (Belo-Horizonte). When the several altitudes were included in the analyses for DCO prediction in this study, they did not havesignificant influence. The relation between DCO and Pb was not confirmed with the new systems that use fast action analyzers.[10] The DCO correction to Pb in altitudes below 1500m is based in scarce data and should be better evaluated.[10]

Ideally, DCO measures should be corrected for the individual level of Hb, but rare laboratories routinely do this correction. In the present study, patients who referred anemia through the questionnaire were excluded. Most of the studies published for the derivation of the reference value did not use correction for Hb level.[11]

The dead space must be considered at VA calculation. In 1995, ATS suggested that fixed value of 0.15 L was used. However, in 2005 the estimated value by the equation weight × 2.2 in ml was suggested in non-obese individuals.[9,21] By this equation, in the present sample, the average ± SD of the dead space would be among men 0.17 ± 0.02 L and among women 0.14 ± 0.02 L, values very close to the fixed amount used by default, of 0.15 L.

In this study, the tests were obtained in Sensormedics equipment.

Several equipment were used in GLI study and 29.5% of Sensormedics brand and the average values obtained did not differ among the different equipment.

The derived values in this study were lower thanthe suggested values by Miller, Neder, and Crapo.[6-8] Crapo evaluated 122 individuals of the female gender and 123 of the male gender in Salt Lake City (altitude 1400m).[6] The sample selection method was not described. DCO was corrected to Hb. The authors used FiO_2 of 0.25, to simulate FIO_2 observed at sea level.

Miller and cols derived values for DCO in a randomized and stratified sample of the state of Michigan.[8] Values

for non-smokers were derived in 74 men and in 130 women. The values were corrected to Hb.

Neder and cols derived reference values in 50 individuals of each gender, from 20-80 years old, selected at random among the staff od a large hospital in São Paulo.[7] Racial profiling was variable. Hb was not measured. Linear equations were used; however, the explanation coefficient was low, indicating large variability of the forecasted values.

At the system used by Neder (MedGraphics), the exhaled gases are analyzed by chromatography, what results in a hyper estimate of the lung volumes, as demonstrated by the VA values compared with the ones observed in the present study.[22,23]

GLI project has recently published reference values for DCO in white children and adults, by data compilation derived from 18 sites, obtained after 2000.[11] The amounts were derived by LMS (lambda, mu, sigma) methods. The most outstanding result was the meeting of lower values than the suggested by elder equations; however, similar to the ones observed in this study.

Limitations should be recognized in the current study. The most obvious limitation is the uncertainty of data extension to the black race, prevailing in Brazil. Volunteers were invited to attend. Reference value derivation for the lung function should only include non-smoking individuals, without symptoms or cardiorespiratory diseases. For this purpose, a validated breathing epidemiologic questionnaire must be applied. After meeting the above-mentioned conditions, the use of volunteers for establishing the reference value is considered valid.[24,25]

Diabetic patients were not excluded from the sample. Diabetic white people have lower values for DCO. In a study, when diabetic white people were paired with non-diabetic controls, the DCO was 1.44 ml/min/mmHg lower in the diabetic ones.[26]

In coclusion, new forecasted values for DCO were derived in a significant sample of white adults in Brazil. The forecasted values are similar to the ones obtained from more modern systems, compiled by GLI, and differ from previously proposed equations.

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Prescribing trends in and perceptions of the treatment of asthma: a survey among pulmonologists in Brazil

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TO THE EDITOR:

Asthma management in Brazil remains unsatisfactory, as shown by the low rates of disease control.[1] Therefore, gaining knowledge of the prescribing habits of pulmonologists in the treatment of asthma in Brazil can assist in the development of strategies and public policies for improving asthma control and reducing future disease-related risks. The objective of the present study was to evaluate prescribing trends of pulmonologists in the treatment of asthma.

This was a cross-sectional study in which telephone interviews were conducted with 300 pulmonologists selected probabilistically after stratification by Brazilian region. To that end, we used data extracted from the database of a market survey investigating prescribing trends of pulmonologists in the treatment of asthma in Brazil. Participants completed a standardized questionnaire consisting of 22 open-ended or closed-ended questions about the major factors affecting prescribing decisions about asthma medications, including preference for a particular medication and/or inhaler device, reliability, access, cost, adherence, safety, and personal experience. All respondents and interviewers were unaware of the study sponsor's identity. The sample size was calculated assuming an error of 5% and a confidence interval of 95%. The process of sampling and contacting participants was carried out by an independent survey institute. Pulmonologists who treated patients with asthma on a regular basis were included. The questionnaire was validated by two pulmonologists who did not participate in the study and by pre-testing in a pilot study. The interviews, conducted by 20 professionals who specialized in telephone surveys, had a mean duration of 12 min and were audio-recorded to ensure accuracy of data. Continuous variables are expressed as mean and standard deviation. Categorical variables are presented as absolute and relative frequencies.

The mean work experience as a pulmonologist among the respondents was 22.1 years. Most of them (76%) worked primarily in private practice, although 49% of the respondents also worked in the public health care system. The proportion of physicians working predominantly in the private sector was found to be highest in southern Brazil (81%) and lowest in central-western Brazil (27%). The respondents estimated that one third of their outpatient cases involved patients with asthma. Of all respondents, 62% reported that their patients paid for their medications, whereas 38% reported that their patients received their medications through the Brazilian *Sistema Único de Saúde* (SUS, Unified Health Care System). The proportion of patients who paid for their medications was highest in southern Brazil (76%) and lowest in northeastern Brazil (54%).

The asthma medications most commonly prescribed by the responding pulmonologists were budesonide/formoterol (Aerocaps®; 36%), fluticasone furoate/vilanterol (Ellipta®; 15%) and budesonide/formoterol (Turbuhaler®; 14%; Figure 1A). In the respondents' opinion, the most relevant medication-related characteristics that explained their prescribing preference were a comfortable dosing schedule, an affordable price, personal experience with the product, medication availability within the SUS, and ease of use of the inhaler device (Figure 1B). From the respondents' perception, the major factors for improving treatment adherence were medication access via the SUS (44%), medication price (33%), inhaler device type (14%), and a comfortable dosing schedule (6%). When analyzing these criteria by stratifying them on the basis of the profile of pulmonologists, that is, on the basis of whether they worked predominantly in the public or private sector, we found that medication access via the SUS (59%) and medication price (26%) were the major factors considered relevant for improving treatment adherence.

The results of the present study show that the most relevant factors for the choice of medications by the responding pulmonologists were medication availability within the SUS, an affordable price, and ease of use of the inhaler device. These were also the factors considered important for improving asthma treatment adherence. Among the various therapeutic options available on the market in Brazil, the budesonide/formoterol combination (Aerocaps®) was reported to be the most commonly prescribed therapy, followed by fluticasone furoate/vilanterol (Ellipta®) and budesonide/formoterol (Turbuhaler®). These data are important because they represent real-life information on asthma management by specialists working in Brazil.

Our results indicate great concern among pulmonologists in Brazil regarding patient access to the pharmacological treatment of asthma, even among those physicians who reported predominantly treating private patients.

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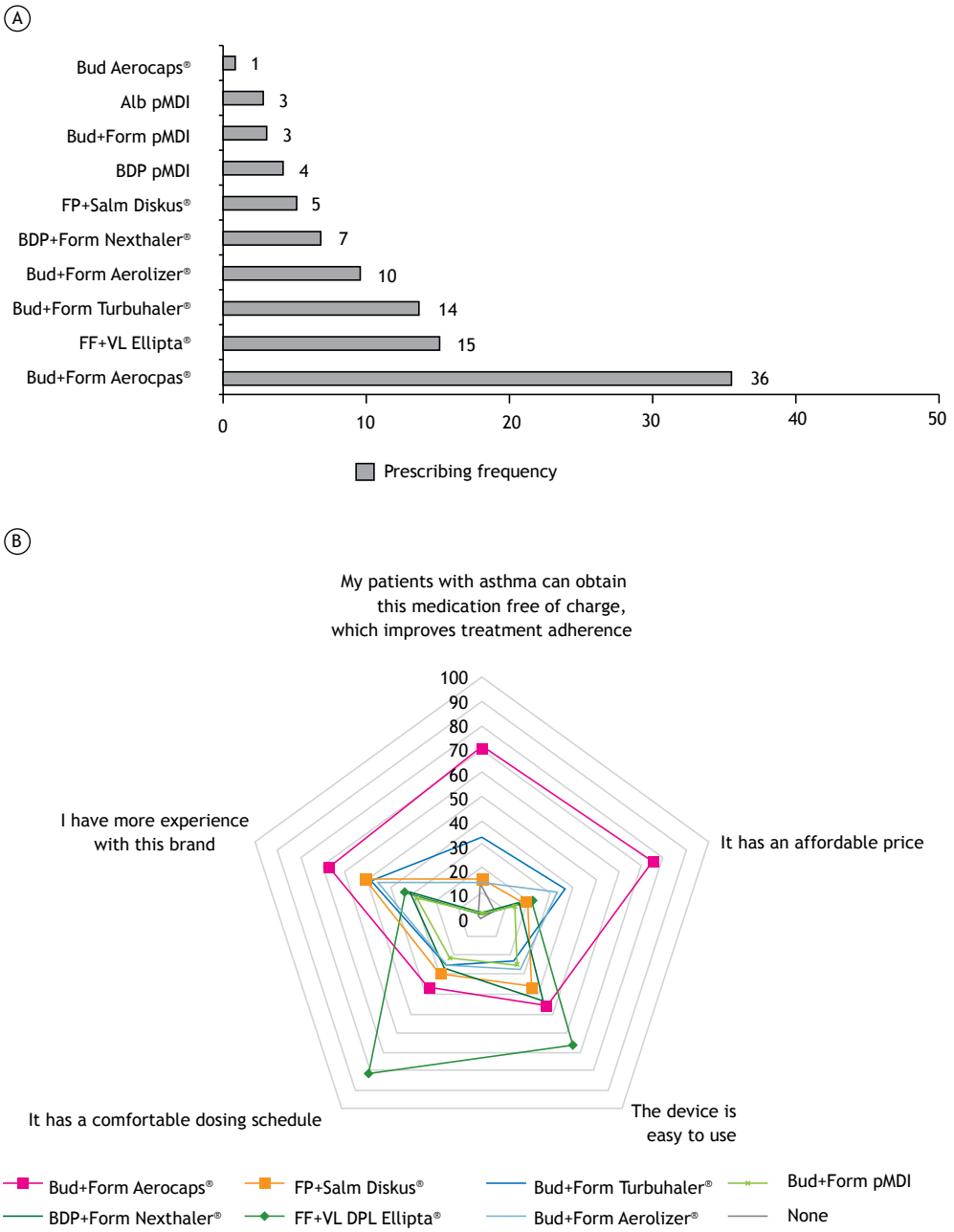

Figure 1. In A, distribution of the most commonly prescribed treatments (treatments available in Brazil during the study period). In B, phrases associated by pulmonologists with each of the main asthma treatments available in Brazil. Bud: budesonide; Alb: albuterol; pMDI: pressurized metered dose inhaler; Form: formoterol; BDP: beclomethasone; FP: fluticasone propionate; Salm: salmeterol; FF: fluticasone furoate; VI: vilanterol; and DPI: dry powder inhaler.

Financial difficulty gaining access to medications is one of the causes of unintentional poor adherence to asthma treatment.[2-4] In addition, socioeconomic status is directly related to worse asthma outcomes, which results in unnecessary additional costs for the patient and the health system.[4] Our results are in contrast with those of previous studies that showed that ease of use of the inhaler device is a predictor of treatment adherence and better outcomes.[5,6] In the present study, ease of use of the inhaler device was not one of the aspects most commonly reported as important for treatment adherence. The reasons for these discrepancies may be variations in the methodologies used and need to be better explored in future studies.

To understand the reasons why budesonide/formoterol (dry powder inhaler: Aerocaps®) was reported to be the most commonly prescribed therapy, we need to analyze the various criteria related to the respondents' prescribing trends. If the choice of this combination therapy had been predominantly motivated by its availability within the public health system, it would be

expected that pulmonologists working in the public sector would differ from those working in the private sector in their choices of treatment, which did not occur. This is supported by the respondents' answers showing that the choice of the most commonly prescribed therapy was based on the fact that this therapy was perceived as having the best combination of price, availability via the SUS, and ease of use of the inhaler device.

In summary, factors related to medication access such as availability within the SUS and price were the characteristics most commonly reported by the respondents, both in terms of their decision about choosing a treatment and in terms of the importance of treatment choice for treatment adherence. These results are relevant for understanding the complexity of the existing scenario in the treatment of asthma in Brazil, characterized by a wide choice of drugs and inhaler devices and, despite that, a low rate of asthma control.

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Diffuse pulmonary lymphangiomatosis

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TO THE EDITOR:

A 14-year-old male with a history of pericardial effusion and pulmonary infiltrate presented to a routine medical visit with complaints of dyspnea. Physical examination revealed signs of pleural effusion (absence of breath sounds and dullness to percussion) in the lower part of the right hemithorax. No other abnormalities were observed. Chest x-ray and ultrasonography confirmed the presence of pleural effusion, and diagnostic thoracocentesis was performed. The analysis of the pleural fluid showed high levels of triglycerides (136 mg/dL), and chylothorax was diagnosed. A previously performed chest CT examination showed interlobular septal and peribronchovascular thickening, as well as pleural and mediastinal soft tissue infiltration (Figures 1A-C). The patient was hospitalized for further investigation, and pleural biopsy was performed. Microscopically, the lesion was characterized by the proliferation and dilatation of lymphatic channels, and showed immunopositivity for CD31 (Figure 1D), CD34, factor VIII-related antigen, actin, desmin, and vimentin. On the basis of the findings, the diagnosis of diffuse pulmonary lymphangiomatosis (DPL) was confirmed.

DPL is an extremely rare benign disease characterized by abnormal proliferation, dilatation, and thickening of lymphatic channels in the lungs, pleura, and mediastinal soft tissue. The disease can affect people of all ages, but it occurs predominantly in children and young adults, regardless of gender. Although the pathogenesis remains controversial, the disease seems to result from abnormal lymphatic development. The proliferative lymphatic aspect suggests a neoplastic etiology, and the structural disorganization indicates a hamartomatous origin. Most symptoms are mild; patients present with cough, shortness of breath, and hemoptysis (with or without chylous effusion), pleuropericardial effusion, and pneumothorax.[1-4]

The proliferation of lymphatic channels explains the most common thoracic imaging findings of DPL. On chest CT scans, the findings include thickening of the interlobular septa and bronchovascular bundles, patchy ground-glass opacities, diffuse infiltration of mediastinal and hilar soft tissue, and pleural effusion.[1,2,4] In our case, the imaging findings were thickening of the interlobular septa and bronchovascular bundles, mediastinal and pleural infiltration, and associated pleural effusion, all of which are compatible with DPL. The major differential diagnosis is pulmonary lymphangiectasia, a rare condition characterized by diffuse dilatation of the

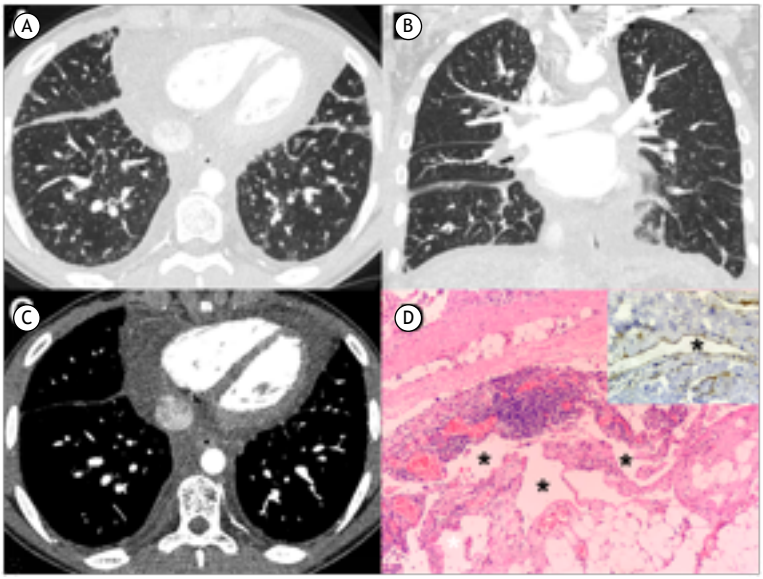

Figure 1. Contrast-enhanced reformatted axial (in A) and coronal (in B) chest CT images, as well as an axial image with mediastinal window settings (in C) showing peribronchovascular and interlobular septal thickening, associated with extensive pleural and mediastinal soft-tissue infiltration. In D, a photomicrograph showing diffuse proliferation of lymphatic channels (asterisks) along the pleura and immunopositivity of the endothelial cells in the lymphatic channels for CD31 (H&E and immunohistochemical staining; magnification, ×100).

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pulmonary lymphatics. It is classified as congenital, presenting shortly after birth and being associated with high neonatal morbidity and mortality, or secondary, when there is evidence of pulmonary hypertension or venous obstruction. Although the chest CT findings of DPL and pulmonary lymphangiectasia are virtually identical, histopathologically, lymphangiomatosis is characterized by an increased number of variably sized lymphatic vessels. In contrast, microscopic examination reveals nonproliferative dilated lymphatic channels in cases of pulmonary lymphangiectasia.[5]

Biopsy with histological and immunohistochemical studies guarantees a definite diagnosis of DPL. Pathological examination shows the proliferation of complex, anastomotic, endothelium-lined spaces, with asymmetrically spaced bundles of spindle-shaped cells and collagen surrounding the endothelium-lined channels. On immunohistochemical staining, the endothelial cells in lymphangiomatosis cases are usually positive for D2-40, CD31, and factor VIII-related antigen.[3] Our patient showed positivity for CD31 and factor VIII-related antigen, among others, leading to the diagnosis of DPL.

No specific treatment for DPL is universally accepted. Current therapies are supportive and essentially palliative, aiming to relieve clinical symptoms. The disease is progressive and prognosis is generally poor. The evolution is often slow, with recurrent chylous effusion and mediastinal compression. Respiratory failure secondary to infection and accumulation of chylous fluid are the major causes of death among patients with DPL.[2,4]

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Biodegradable stent in a patient with recurrent stenosis after lung transplantation

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TO THE EDITOR,

Airway complications occur after lung transplantation in 2-18% of cases, bronchial stenosis being particularly prevalent. The initial management of bronchial stenosis is via bronchoscopic dilatation, with or without stent placement.[1] Among the most popular types of stents used for this purpose are the silicone and metal models, which can be rigid or self-expanding. However, post-placement complications, including fistulas and inflammatory reactions, can occur. In this context, biodegradable stents appear as an alternative, offering benefits such as long-term maintenance of airway patency, as well as minimizing the complications related to fistulous formations and inflammatory reactions, which are more common when non-biodegradable stents are employed.

Although biodegradable stents have been used in the treatment of various gastrointestinal and vascular conditions, its use in the treatment of airway stenosis is recent and has been the object of research.[2] The case described here illustrates the successful use of biodegradable stent placement in the clinical management of central airway stenosis. This is the first report of such use of a biodegradable stent in Brazil.

A 23-year-old male patient with a history of bronchiolitis obliterans underwent bilateral lung transplantation. One month after the procedure, balloon dilatation was performed because there was stenosis in the anastomosis of the left main bronchus (Figure 1A). The patient eventually required five additional endoscopic dilatation procedures for the same reason. In one of those procedures, a small laceration was accidentally made in the posterior bronchial wall. An attempt was then made to install a silicone stent, which was unsuccessful because of the proximity of the stenosis to the secondary carina, which prevented the stent from remaining in the correct position. Consequently, a custom-made biodegradable stent (ELLA-CS, Hradec Králové, Czech Republic) was successfully implanted (Figure 1B). However, endoscopic dilatation was again required two months later. At 14 months after the last procedure (i.e., after 16 months of follow-up), the stenosis remained controlled (Figure 1C), with no recurrence. At this writing, the patient was clinically stable.

The incidence of central airway stenosis after lung transplantation has decreased. However, such stenosis continues to pose a challenge, with the potential to impair the quality of life, as well as to reduce the survival, of patients who undergo lung transplantation. There have been no randomized trials examining the management of this complication.[1] Various therapeutic methods are available, including endoscopic dilatation, surgical treatment, ablation techniques, and the use of various types of stents. There is no consensus, however, regarding the best method or timing of the treatment.[3] In this context, non-biodegradable stents play a crucial role in the management of benign tracheobronchial stenosis. However, they have been associated with several complications such as the formation of hyperplastic granulation tissue, erosion, and bleeding. For this reason, bioabsorbable stents—specifically biodegradable stents—have emerged as an important alternative. This modality has its widespread use for esophageal, intestinal, biliary, or vascular stenoses. Biodegradable stents are made of polydioxanone (PDO), a material that has shown an acceptable level of tolerance by the tracheal mucosa, preventing rejection due to immune-mediated reactions. However, the size and shape of PDO stents must be adapted to the anatomical characteristics of each patient.[4]

In the case described above, several unsuccessful attempts were made to manage the stenosis by endoscopic dilatation, one of which resulted in laceration of the bronchial wall. The attempt to put a silicone stent in place was unsuccessfully because the stent was incompatible with the bronchial anatomy of the patient. The placement of a biodegradable PDO stent, customized to the anatomical characteristics and needs of the patient, was successful, and the patient showed no complications during 16 months of follow-up. Our report suggests that biodegradable stents are a viable alternative for the management of tracheobronchial stenosis, with a safety profile that is more favorable than that of traditional stents.[5] Further studies are needed in order to clarify the precise recommendations for the use of biodegradable stents in cases of benign stenosis of the airways, especially in patients who have undergone lung transplantation.

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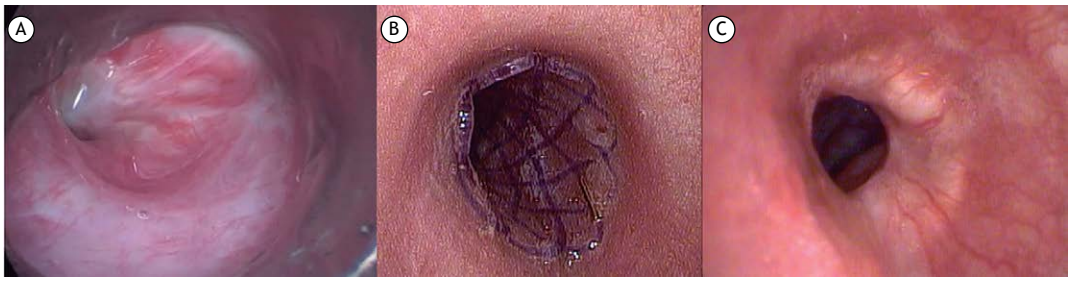

Figure 1. In A, stenosis of the left main bronchus. In B, the biodegradable stent after placement. In C, the site of bronchial stenosis after 16 months of follow-up.

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Clinical, functional, and cytological evaluation of sputum in postinfectious bronchiolitis obliterans: a possible overlap with asthma?

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DEAR EDITOR:

Postinfectious bronchiolitis obliterans (PIBO) is a chronic obstructive pulmonary disease associated with inflammation of the lower airways. The inflammatory process is secondary to infectious bronchiolitis, which can be caused by viruses, atypical germs (especially *Mycoplasma pneumoniae*), and other bacteria.[1,2] Although the clinical manifestations of PIBO can vary widely, its main characteristic is that patients with the condition present with signs and symptoms of a severe and persistent lower airway obstruction.[2]

The objective of the present study was to evaluate the clinical presentation, pulmonary function, CT findings, and sputum cellularity in patients with PIBO, as well as to correlate sputum cell pattern with spirometry and other imaging findings, clinical manifestations, and atopy.

This is a cross-sectional analytical study with patients diagnosed with PIBO and under follow-up at the Pediatric Pulmonology Center of the Clinical Hospital Complex of the Federal University of Paraná, Curitiba, state of Paraná, Brazil. The study included patients under 21 years of age with a diagnosis of PIBO related to a history of severe viral bronchiolitis before the onset of the respiratory symptoms and imaging studies with radiological findings showing involvement of the small airways and/or spirometry characterizing an obstructive defect. Exclusion criteria were the presence of other lung diseases, such as cystic fibrosis, primary or secondary immunodeficiencies, and other chronic pulmonary diseases.

After selection, patients underwent an initial clinical evaluation followed by complete spirometry—satisfying the acceptability and repeatability criteria established by international guidelines[3]—and post-bronchodilator (salbutamol, 400 µg) evaluation. The classification of the obstructive ventilatory defect into mild or moderate followed the recommendations of the *American Thoracic Society*.[4] The bronchodilator test was considered positive when the difference in FEV_1 was greater than 12% of the predicted value, as recommended by the Global Initiative for Asthma.[5] Sputum was induced via inhalation of a hypertonic saline solution, using a 2 L/min oxygen cylinder, and with the assistance of a physical therapist. The process used a hypertonic saline solution with concentrations gradually increasing from 3% to 5% and 7%, when necessary, and lasted a minimum of 20 min per patient. After the minimum time, patients were stimulated to cough and expectorate into a sterile vial. The processes of sputum induction and sample processing followed a laboratory technique described by Pizzichini et al.[6] Only samples with cell viability above 50% were considered for the analysis.[7] The patterns found were divided into eosinophilic (eosinophils > 2.5% and neutrophils ≤ 54%), neutrophilic (eosinophils ≤ 2.5%, neutrophils > 54%), and mixed (eosinophilic/neutrophilic; eosinophils > 2.5% and neutrophils > 54%).[8] The study was approved by the research ethics committee of the institution (Protocol No. 2.062.062). All parents/guardians gave written informed consent.

Our sample was initially composed of 23 patients with a clinical and radiological diagnosis of PIBO, who also met all other inclusion criteria. Of these, 1 patient refused to participate, and we were unable to get hold of another 9 patients. Therefore, 13 patients were enrolled in the study (8 of them male), with a median age of 12.1 years (range: 7-20 years). All 13 patients (100%) had been hospitalized in their first year of life due to a disease whose manifestations were compatible with acute viral bronchiolitis. In addition, 8 (61.5%) had a positive skin prick test for at least one aeroallergen, 7 (53.8%) had rhinitis and/or atopic dermatitis, and 9 (69.2%) were making use of inhaled corticosteroids.

All study participants had undergone at least one chest CT scan. The most prevalent CT finding was a mosaic pattern, found in 11 patients (84%); followed by bronchial wall thickening, in 10 (76%); bronchiectasis, in 4 (30%); and atelectasis, in 4 (30%).

Of the 12 participants who underwent complete spirometry, 11 (91.6%) had obstructive ventilatory defect. Of these, 7 (63.6%) were classified as mild ($60\% < FEV_1 < 90\%$) and 4 (36.4%) as moderate ($40\% < FEV_1 < 60\%$). Four patients had a positive bronchodilator test (33.3%).

As for sputum cytology, the samples of 3 patients were considered inadequate for cytology studies for not having sufficient cell viability. Of the 10 samples

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Table 1. Clinical, functional, and CT variables in relation to sputum cell pattern (N = 10).

Variables	Cell pattern		
	Neutrophilic (n = 4)	Eosinophilic/neutrophilic (n = 4)	Eosinophilic (n = 2)
Positive skin prick test	3	3	2
Daily symptoms	2	1	1
Symptoms when exercising	1	2	2
Bronchiectasis	0	2	0
Ground-glass opacities	1	2	0
Positive bronchodilator test	1	2	1

considered viable, 4 (40%) had a neutrophilic pattern; 4 (40%) had a neutrophilic/eosinophilic pattern (mixed); and 2 (20%) had an eosinophilic pattern. One of the samples was considered neutrophilic in spite of having a neutrophil rate below 54% because of its high cell viability and absence of eosinophils.

Sputum cytological patterns were compared with the CT findings, skin prick test results, presence or absence of daily symptoms and/or symptoms when exercising (especially dry cough and dyspnea), and bronchodilator test results (Table 1).

PIBO is a rare chronic lung disease resulting from severe lung injury following acute infectious bronchiolitis that causes varying degrees of inflammation with narrowing or total obliteration of the small airways in susceptible individuals.[9]

Supposedly, sputum cytology findings should be similar to those of previous bronchoalveolar lavages,[10] with a marked increase in the number of neutrophils. However, only 4 patients presented an exclusively neutrophilic pattern, and, in 2, the pattern was predominantly eosinophilic, contrary to the initial assumption. Such disagreement was seen in atopic patients with a positive skin prick test and a diagnosis of concomitant rhinitis, indicating a probable coexistence of allergic asthma with previously diagnosed PIBO, an overlap suggested in a previous study.[11]

The bronchodilator test turned out positive in all cytological patterns, including the exclusively neutrophilic one, corroborating studies with long-term follow-up of patients with PIBO.[12,13] Those studies have shown severe and permanent impairment of lung function, though air trapping slowly decreased with patient growth.[1,12,13]

There were no significant correlations between sputum cellularity and the clinical, functional, and CT variables studied. The lack of statistical correlation between the variables in the present study was probably due to the small sample size; the low prevalence of the disease represents an analytical challenge.

The lack of predominance of a specific cytological pattern could suggest a potential overlap of PIBO and asthma, which can indicate a need for new diagnostic and therapeutic approaches aimed at controlling both diseases. A deeper understanding of PIBO will favor an individualized approach of these cases. Similar multicenter studies may help deepen our understanding by providing us with the possibility of evaluating larger samples of such a rare disease.

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An unusual cause of pleural effusion in a patient with heart failure

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A 56-year-old female patient with a previous diagnosis of idiopathic dilated cardiomyopathy presented with worsening dyspnea over four days. Her medical history included a diagnosis of xanthogranulomatous pyelonephritis, which had required a left nephrostomy eight months prior to her presentation. On admission, a chest X-ray showed left pleural effusion and cardiomegaly. A sepsis protocol was initiated owing to hypotension and a concern for parapneumonic pleural effusion or empyema. A chest HRCT revealed an atrophic left kidney with multiple hypoattenuating areas with gas bubbles (collections) associated with calculi in the renal pelvis. One of the collections had clear contiguity with the perirenal space next to the diaphragmatic pillar. A diagnostic thoracentesis showed a yellow exudate with low pH and glucose levels and high lactate dehydrogenase and creatinine levels. The patient was diagnosed with urinothorax and renal abscess, received antibiotic therapy, and underwent total nephrectomy. Urinothorax is a rare cause of pleural effusion, most frequently resulting from obstructive uropathy or iatrogenic/traumatic genitourinary injury.[1-3] Pleural fluid from urinothorax generally reveals a transudate that resolves after removing the urinary tract obstruction. Associated infection leads to pleural fluid with low pH and glucose levels.

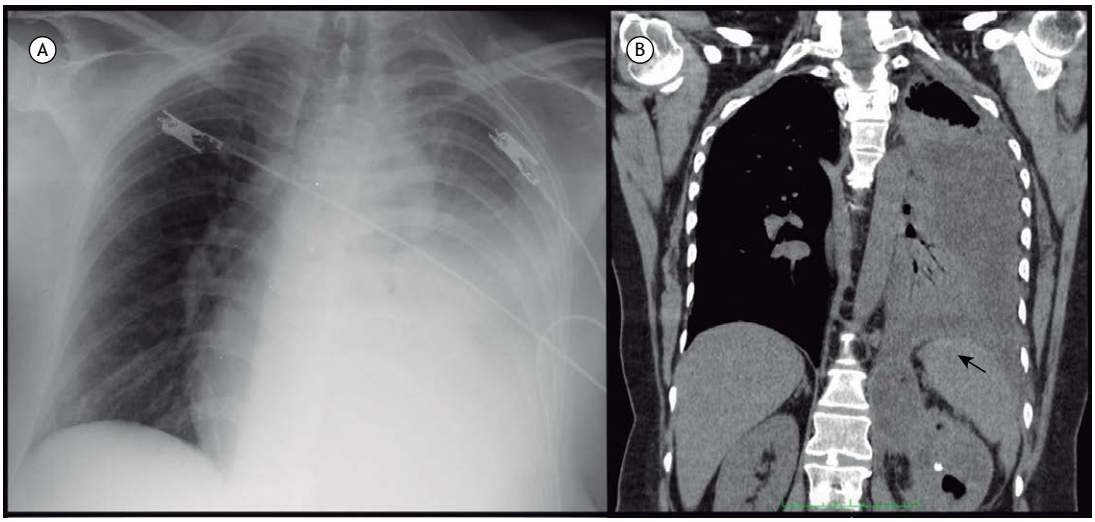

Figure 1. In A, an X-ray of the chest showing extensive left pleural effusion. In B, coronal reconstruction from a CT showing the left kidney with a calcified calculus and hypoattenuated areas, one of which draining to the perirenal space and causing left pleural effusion (black arrow).

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