ISSN 1806-3713

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

Volume 44, Number 4
July | August
2018

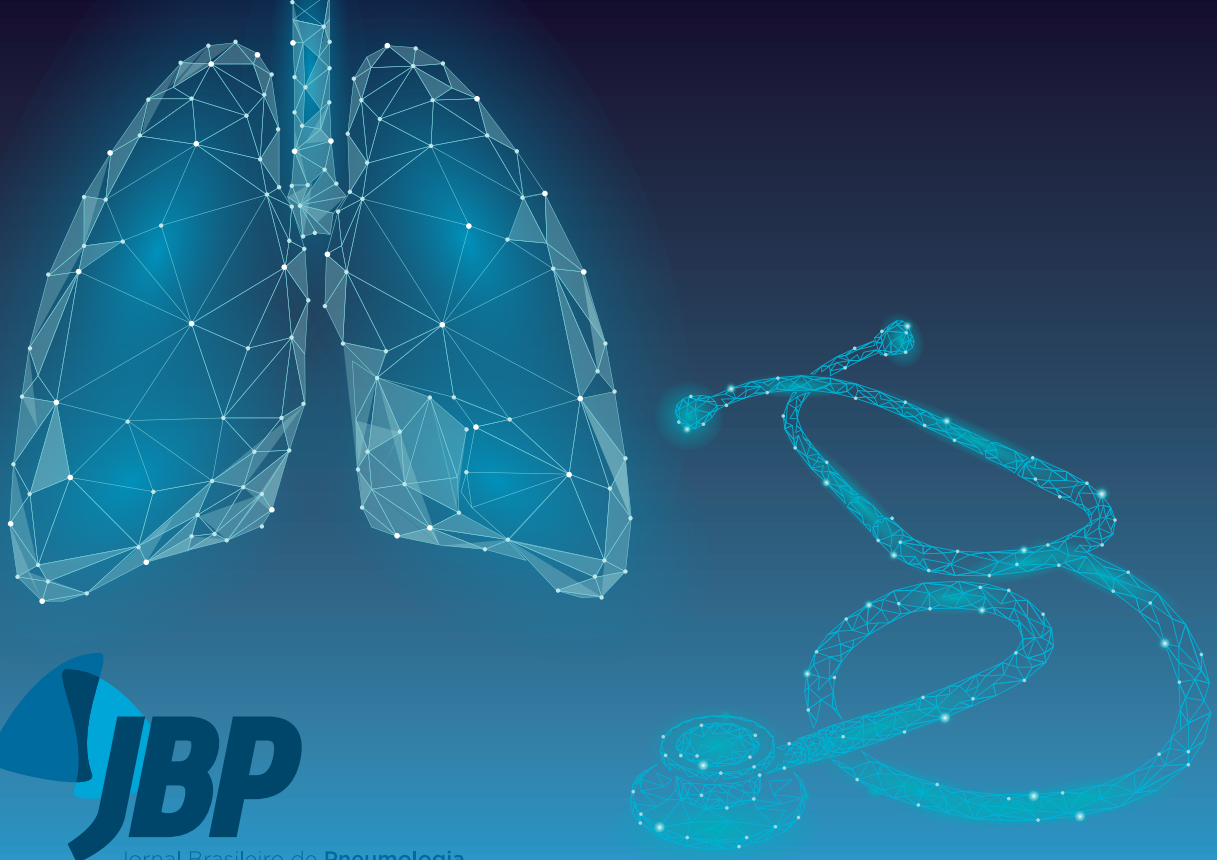
Volume 44, Number 4 July | August 2018

HIGHLIGHT

Community-acquired pneumonia

Patient-ventilator asynchrony

Six-minute walk test and idiopathic pulmonary fibrosis



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1937

ISSN 1806-3713

JBP
Jornal Brasileiro de Pneumologia

Published once every two months J Bras Pneumol. v.44, number 4, p. 253-340 July/August 2018

ISSN 1806-3713

JBP
Jornal Brasileiro de Pneumologia

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ADMINISTRATIVE SECRETARIAT OF THE BRAZILIAN JOURNAL OF PULMONOLOGY
Address: SCS Quadra 01, Bloco K, Asa Sul, salas 203/204. Edifício Denasa, CEP 70398-900, Brasília, DF, Brazil. Tel. +55 61 3245-1030/+55 0800 616218.
Assistant Managing Editor: Luana Maria Bernardes Campos.
E-mail: jbp@jbp.org.br | jbp@sbpt.org.br
Circulation: 4.000 copies
Distribution: Free to members of the BTS and libraries
Printed on acid-free paper

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ISSN 1806-3713

JBP
Jornal Brasileiro de Pneumologia

Published once every two months J Bras Pneumol. v.44, number 4, p. 253-340 July/August 2018

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ISSN 1806-3713

Jornal Brasileiro de Pneumologia

Published once every two months J Bras Pneumol. v.44, number 4, p. 253-340 July/August 2018

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J Bras Pneumol. 2018;44(4):253-253
http://dx.doi.org/10.1590/S1806-37562018000040003

A teacher to remember and to emulate

Ana Luisa Godoy Fernandes[1,a], Sonia Maria Faresin[1,b]

Professor Manuel Lopes dos Santos was always an uncommon teacher. In addition to being a natural leader, he knew how to encourage and recognize the quality of each member of his team, as well as how to bring new members into the group. It was thus that he formed and directed the Discipline of Pulmonology of the *Escola Paulista de Medicina* (EPM, Paulista School of Medicine), in the city of São Paulo, Brazil, which is recognized as a center of excellence in pulmonology training, at the national and international level. He was the first preceptor of the residency program at the Hospital São Paulo (HSP), operated by the EPM, demonstrating the relevance of in-service training, which is the gold standard for professional training. He was a manager of the center of excellence, head of the discipline, director of the HSP, and director of the EPM, which he transformed into the Federal University of São Paulo, becoming its first rector. He founded the Paulista Society of Pulmonology and Phthisiology, after which he launched the Journal of Pulmonology (which would later become the JBP) and was its first editor.

It was common to hear Professor Santos say, "São Paulo owes a debt to the country. We must train pulmonologists as a group of critical thinkers who will disseminate knowledge throughout the country." In addition to receiving students from other countries in Latin America, he taught students from every state in Brazil, making the EPM Discipline of Pulmonology the leading producer of pulmonology specialists in the country. He also actively collaborated in the development of the first graduate program in pulmonology in Brazil. His ability to impart knowledge was without par, due to the empathy he had for all who wanted to learn and work, as well as the unconditional love he had for the mission of teaching.

Although Professor Santos could have been treated at any other hospital, including one of those with virtually infinite resources, he always chose the HSP, where, despite a lack of material resources, he could be surrounded by the throng of critically thinking, humane professionals that he had helped educate. In addition, he always had the good sense to use the facility in which he believed and at which he had treated all of his own patients.

The loss of Professor Santos will felt for years to come. During this moment of reflection and mourning, we ponder how great Brazil would be if there were more individuals of his ilk in the country.

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J Bras Pneumol. 2018;44(4):254-256
http://dx.doi.org/10.1590/S1806-37562018000040002

EDITORIAL

Community-acquired pneumonia: challenges of the situation in Brazil

Mauro Gomes[1,2,a]

Community-acquired pneumonia (CAP) is the leading cause of morbidity, hospitalization, and mortality worldwide and represents a diagnostic and treatment challenge.[1] In Brazil, CAP constitutes the leading cause of hospitalization (excluding causes related to pregnancy, childbirth, and puerperium) via the Brazilian Unified Health Care System. In 2017, there were 598,668 CAP-related hospitalizations and 52,776 CAP-related deaths in our country.[2] Although CAP is one of the most common infections, there have been few clinical or epidemiological studies of CAP in Brazil.

In the current issue of the JBP, Bahlis et al.[3] publish a single-center cohort study of CAP conducted in the interior of Brazil and involving all patients hospitalized for CAP over a one-year period. Despite some limitations, the study has the great virtue of reinforcing some of our conceptions about CAP and alerting to the need for implementing measures to improve the management of CAP in our country. Chief among these conceptions are initial misdiagnosis of pneumonia, difficulty in identifying the pathogen, the advantages of using severity scores in the initial assessment of patients, and the importance of implementing measures to improve in-hospital management of cases.

We see in daily clinical practice that there is a lot of misdiagnosis when it comes to CAP. Clinical and laboratory signs that are characteristic of severe infection, such as tachycardia, fever, and altered leukocyte counts, are nonspecific and are frequently present in other acute conditions. Biomarkers, such as C-reactive protein and procalcitonin, are also nonspecific and have more value in ruling out a diagnosis of infection than in establishing a definitive diagnosis. It has long been known that errors in radiological interpretation made by non-pulmonary specialists working at emergency rooms occur relatively frequently.[4] As a result of these difficulties in the initial clinical assessment, an accurate diagnosis of CAP can often be a challenge. It is of note in the study by Bahlis et al.[3] that practically one third of the patients hospitalized for respiratory infection did not meet the diagnostic criteria for CAP and were excluded from the analysis. This may raise a debate as to whether the data for a large number of hospitalizations for CAP in Brazil are correct. Would our statistics for CAP be inflated by inclusion of other respiratory infections misdiagnosed as CAP?

After diagnosis, major guidelines recommend that CAP severity should be assessed against criteria to determine the place of treatment and antibiotic therapy. The implementation of guidelines into care protocols has always been a major challenge, because, in daily practice, severity scores are not used by all emergency department attending physicians. However, despite assessment errors that are attributable to these scores, their implementation reduces mortality.[5] Silveira et al.[6] reported that admission and treatment criteria were guideline-concordant in most of a sample of Brazilian patients (in 73.2% and 58.9%, respectively), and that guideline-concordant treatment was associated with lower 30-day mortality. In addition, Bahlis et al.[3] found that major severity scores showed good ability to predict in-hospital mortality, with no statistical differences between the **C**onfusion, **U**rea, **R**espiratory rate, **B**lood pressure, and age > **65** years (CURB-65) score and the Pneumonia Severity Index (PSI). Therefore, especially with regard to using severity scores in the initial assessment of patients, we might apply the old saying "bad with them, worse without them."

Difficulty in identifying the pathogen causing the infection increases the challenge in CAP management. Certain microorganisms are particularly difficult to cultivate, requiring specific culture media or a particular environment. Although it is well established that *Streptococcus pneumoniae* is the pathogen most commonly associated with CAP, the fact is that studies of the etiology of CAP fail to identify the pathogen in most patients.[7] The currently published study[3] is not different in this respect and identified the pathogen in only 17% of the cases, with the most commonly isolated agent being *Streptococcus pneumoniae* (in 36%).

Knowing the potential etiologic agents in CAP, which ones are increasing in incidence, their degree of resistance, and their lethality rate is critical to an effective therapy. Bahlis et al.[3] observed a high rate of change in antibiotic regimen during hospitalization (63%). In most cases, the initial treatment regimen consisted of amoxicillin + clavulanate, and the most common change was the addition of azithromycin to the regimen, on the basis of clinical assessment by the attending physician. The mean length of hospital

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ISSN 1806-3713

stay was 7.2 days (median, 5 days), and, over the patients' course, 29% required ICU treatment and 15.5% died in hospital.

If early identification of the etiologic agent were possible, a likely consequence would be a more rational use of antibiotics, with a reduction in complications and mortality from CAP. However, the current standard for diagnosis is blood culture, which usually takes at least 48-72 h to obtain a result, and cultures often remain negative even when bacterial or fungal infections are strongly suspected. This results in patients being initially treated empirically and often with broader spectrum antibiotics to increase the likelihood that a pathogenic organism will be adequately covered. This approach, despite being currently valid, has negative aspects, which include the potential for toxicity from use of multiple antibiotics, the high associated costs, and the development of resistance to antimicrobials.

Results after the recent development of rapid and highly sensitive molecular assays have produced surprising information about the causes of CAP. For the first time, multiple agents that had not been observed in older studies were detected. These methods increasingly identify respiratory viruses, including rhinovirus and influenza virus, in patients with CAP.[8] Pathogens were identified in the bloodstream of infected patients within 6 h, with high sensitivity and with a three times higher likelihood of identification than that of standard culture. These findings could potentially have resulted in a change in antibiotic treatment in up to 57% of the patients studied.[9]

Knowledge about CAP has undergone phases in which the presence of the so-called atypical pathogens was highly valued, and today we are going through a phase in which viruses are being strongly considered. The true importance of finding viruses in the respiratory secretions of patients with CAP has yet to be established, as it remains unknown whether viruses are effective pathogens or copathogens in pneumonias. We also need to develop skills to handle molecular tests; they bring the prospect of rapidly defining the cause of CAP and changing the initial approach. This may allow targeted antibiotic therapy rather than empirical antibiotic therapy, which is what we currently use.

Another important challenge when it comes to treatment of CAP is the time from diagnosis to initiation of antibiotic therapy. Studies have established that a delay in initiation of antibiotic therapy of more than 4 h increases the potential risk of complications and death.[10] Current guidelines on sepsis recommend that antibiotic therapy ideally be initiated within the first hour, given that any delay in therapy can result in decreased survival.[11] The study published in the current issue of the JBP[3] also raises this issue when it reports the long elapsed time to initiation of antibiotic therapy (mean, 10 h), with few patients receiving antibiotics within the first 4 h: only 19%. Because the vast majority of patients received the first dose of antibiotics after quite a long time, the authors could not correlate this delay with the high in-hospital mortality rate and the great need for ICU admission in the study population. These data alert to the need for hospitals to implement measures to expedite administration of the first dose of antibiotics in cases of CAP in the emergency room, with the suggestion that this be done even for those as outpatients.

CAP constitutes a serious public health problem in Brazil. At a time when we are reviewing and updating the Brazilian guidelines for the management of CAP, studies that lay bare the situation in the country and alert to the need for measures to improve the diagnosis and therapeutic management of CAP are essential. Promoting the adoption of care protocols in health facilities, with measures tailored to the situation in our country, can reduce excessive hospitalizations and the rate of mortality from pneumonia in Brazil.

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J Bras Pneumol. 2018;44(4):257-258
http://dx.doi.org/10.1590/S1806-37562018000040001

Six-minute walk test in patients with idiopathic pulmonary fibrosis

José Antônio Baddini-Martinez[1,a]

The six-minute walk test (6MWT) is a simple method for investigating exercise capacity in patients with advanced lung disease.[1,2] Unlike patients undergoing traditional cardiopulmonary exercise testing, those undergoing the 6MWT do not, as a rule, reach maximal respiratory and heart rates, the 6MWT therefore being a submaximal test. The 6MWT is advantageous because walking is a task that patients are familiar with and because the 6MWT is inexpensive, requiring only a trained health professional, a flat corridor of approximately 30 m in length, a sphygmomanometer, and a pulse oximeter.

Although the 6MWT does not allow identification of the mechanisms involved in exercise limitation, the six-minute walk distance (6MWD) is an overall measure of integration among systems (i.e., the respiratory, cardiovascular, and locomotor systems). There is increasing evidence that a low 6MWD is strongly associated with an increased risk of hospitalization and mortality in patients with advanced lung disease.[1,2]

Although the 6MWT has good test-retest reliability, there is a learning effect with repeated testing. Therefore, at least two tests should be performed on the same day, at least 30 min apart (in order to allow for rest between tests), the longest 6MWD being selected for analysis.[2,3]

Although the primary physiological measure of interest is the 6MWD, other parameters of interest include the SaO_2 nadir, heart rate recovery at 1 min after exercise, and the product of the 6MWD by the lowest measured SpO_2.[4]

Although the 6MWT is easily performed, it should not be performed in patients with disabling dyspnea, in those with significant orthopedic abnormalities, or in those with cardiovascular conditions such as recent myocardial infarction, severe aortic stenosis, and decompensated heart failure.[2,3] Patients showing an SpO_2 of < 88% on room air should receive supplemental oxygen during the test, which should be interrupted if the SpO_2 on room air falls below 80% for 6 s or more; the test can be resumed when SpO_2 is ≥ 85% on room air.[2,3]

In recent years, there has been increasing interest in using the 6MWT in patients with idiopathic pulmonary fibrosis (IPF) not only in routine clinical practice but also in controlled clinical trials.[4,5] An initial test, performed at the first consultation, can provide information on exercise capacity and the need for supplemental oxygen during physical activity, as well as prognostic data. It is well recognized that an SpO_2 of ≤ 88% is a reliable indicator of poor survival in IPF patients undergoing a 6MWT without supplemental oxygen.[6]

Although there have been quite a few studies involving patients with IPF and the 6MWT, the most reliable data were provided by two large clinical trials of new drugs for the treatment of IPF, a substantial number of patients having been included in those trials.[7-9] The studies showed that the 6MWD correlated significantly with quality of life and dyspnea, as well as with lung function variables.

An analysis of 748 volunteers included in one of the aforementioned studies[7] showed that a 6MWD of < 250 m on the initial test was associated with double the risk of mortality after approximately one year of follow-up. In addition, decreases of more than 50 m in the 6MWD on tests performed 24 weeks after the first resulted in a three-fold increased risk of death in the following 24 weeks. Minimal clinically important differences were calculated from data from the aforementioned studies[8,9] and were found to be 24-45 m and 21.7-37.0 m. The results of the two aforementioned clinical trials[7-9] clearly show that the 6MWT is a valid and useful tool for the management of patients with IPF.

In the current issue of the JBP, Mancuso et al.[10] report the 6MWD in 70 IPF patients retrospectively selected from among those treated at either of two referral centers for interstitial lung disease in Brazil. The major finding of the study is that a 6MWD of < 330 m or < 70% of the predicted value is associated with a substantially decreased survival rate and should be considered an indicator of poor prognosis in patients with IPF in Brazil.

The first question is why the indicator of poor prognosis found in a study conducted in Brazil[10] is significantly different from those found in studies conducted elsewhere.[7,11-13] According to Mancuso et al.,[10] this might be due to differences in reference values for the 6MWT across countries.[14] There is evidence that the 6MWD is longer in individuals living in Latin America than in those living in Europe or the USA.[14] This appears to be due to the fact that physical demands are higher in individuals living in developing countries, with lower socioeconomic status. It appears that such an association also applies to respiratory diseases such as COPD and IPF. However, the difference between the values found by Mancuso et al.[10] and those found by other authors might be due to the study design and the analyses performed in the study. Because it is impossible to compare the study conducted by Mancuso et al.[10] with all previous studies, I will compare it with the study involving the highest number of patients and based on data from the study by du Bois et al.[7]

In the study by Mancuso et al.,[10] patients presenting with an SpO_2 of < 89% were excluded, whereas, in the

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study by du Bois et al.,[7] 11.5% of the participants were receiving oxygen therapy. The difference in findings between the two studies might be explained, at least in part, by the fact that the latter study included patients who were more severely ill, including patients with severe pulmonary hypertension. Although this is a reasonable explanation, it should be noted that the mean 6MWD is very similar between the two studies. In fact, the mean 6MWD was higher in the study by du Bois et al. than in the study by Mancuso et al. (397 ± 107 m vs. 380 ± 115 m).[7,10]

The difference in findings between the two studies might also be due to different follow-up periods. In the study by du Bois et al.,[7] patients were followed for 48 weeks, whereas, in the study by Mancuso et al.,[10] the median follow-up period was 37.6 months (range, 5-129 months). Therefore, it is possible that the results were affected by the fact that follow-up was limited to the duration of the trial and therefore prevented a more detailed characterization of patients in whom the disease behaved in a more benign manner.

Differences between the two studies regarding the statistical methods used and how the results were reported should also be taken into account. According to du Bois et al.,[7] a 6MWD of < 250 m is associated with double the risk of mortality after 48 weeks of follow-up. According to Mancuso et al.,[10] a 6MWD of < 330 m is associated with a survival of 24 months, whereas a longer 6MWD is associated with a median survival of 59 months.

The study by Mancuso et al.[10] reinforces the prognostic importance of the 6MWT in patients with IPF. However, the 6MWD should be evaluated in conjunction with other clinical and physiological data, such as dyspnea intensity, FVC, and DLCO.

Pulmonologists in Brazil should be alert to the possibility of encountering IPF patients with absolute 6MWD values indicating a poor prognosis, these values being higher than those recommended in the international literature. If we analyze the 6MWD in isolation and use as an indicator of poor prognosis any of the absolute 6MWD values recommended in the international literature, we run the risk of underestimating the severity of lung disease.

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J Bras Pneumol. 2018;44(4):259-259
http://dx.doi.org/10.1590/S1806-37562018000000155

Nodular fissure

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

A 37-year-old male civil engineer arrived at the outpatient clinic with complaints of dry cough for three months, followed by dyspnea upon exertion. Physical examination was normal. HRCT scanning showed small disseminated nodules and nodular fissures (Figure 1).

The patient presented with small interstitial nodules on HRCT. The pattern of small nodules or pulmonary micronodules corresponds to the presence of multiple rounded opacities, with soft-tissue density and diameter <1 cm, distributed in the lung parenchyma.[1] They can be classified according to the distribution in the secondary pulmonary lobe (SPL) as random, centrilobular, or perilymphatic.

The random pattern is characterized by the presence of small nodules distributed randomly in relation to the SPL and uniformly dispersed by the lungs. This pattern is observed in diseases with blood-borne dissemination, such as metastases and miliary granulomatous diseases, especially tuberculosis and histoplasmosis. The centrilobular distribution is characterized by the presence of nodules in the central region of the SPL, a few millimeters from the pleural surface and the fissures; however, without touching them. Hypersensitivity pneumonitis and infectious bronchiolitis are examples of diseases that occur with this pattern. The perilymphatic pattern is characterized by the presence of small nodules that distribute preferentially along the SPL compartments that contain lymphatic structures (peribronchovascular interstitium, interlobular septa, and subpleural regions). The diseases that most commonly present with this distribution pattern are sarcoidosis, silicosis, and carcinomatous lymphangitis.

Sarcoidosis and silicosis tend to spare interlobular septa, whereas lymphangitis frequently affects that region.[2] Silicosis also tends to preserve the peribronchovascular interstitium, whereas lymphangitis and sarcoidosis often affect it: lymphangitis has a more smooth appearance, whereas sarcoidosis has a more nodular appearance. Subpleural nodules are more easily seen in the fissures, giving rise to what is called the nodular fissure pattern. These three diseases affect the pleural surface, but silicosis rarely presents with nodular fissures. A nodular fissure pattern corresponds, in most cases, to carcinomatous lymphangitis or sarcoidosis. Eventually, peri-fissural nodules are also seen in miliary infectious diseases (tuberculosis or histoplasmosis); however, the nodules are generally smaller and less profuse than in the case reported here.

Clinically, the patient had no history of exposure to silica. The health status of the patient was very good, there was no evidence of disease elsewhere, and dyspnea was mild, data that rule out the diagnosis of carcinomatous lymphangitis. Transbronchial biopsy showed sarcoid granulomas, with no caseous necrosis. The final diagnosis was sarcoidosis.

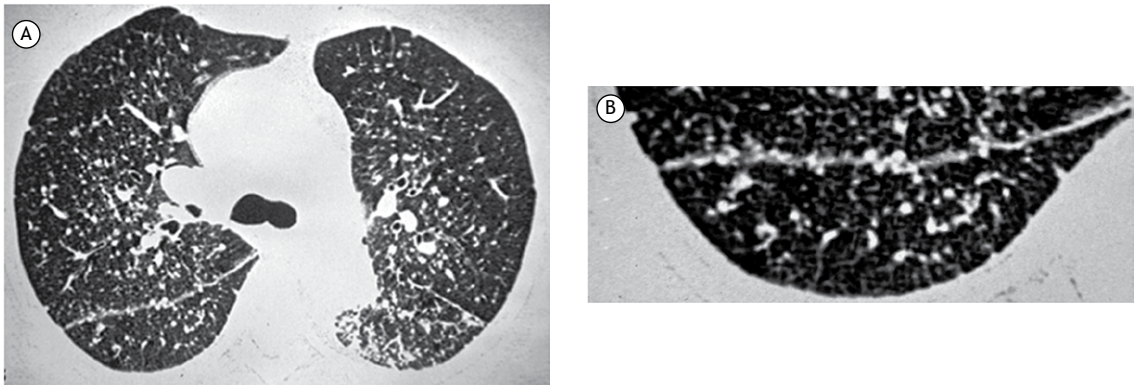

Figure 1. HRCT scans with lung window settings at the level of the bronchial bifurcation evidence small interstitial nodules distributed in the lungs. Note that there is an accumulation of nodules along the fissures (detail in B), characterizing the pattern of nodular fissure.

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Twelve tips to write an abstract for a conference: advice for young and experienced investigators

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As we have returned from the successful XXXIX Brazilian Thoracic Society Conference in Goiânia, Brazil—where more than 600 abstracts have been presented—and prepare for the American Thoracic Society International Conference deadline for submitting abstracts by November this year, we would like to emphasize the importance of presenting high-quality scientific abstracts at such conferences.

Presenting clinical research results in the form of abstracts in national and international meetings is common and expected among clinical researchers in academic and nonacademic settings, giving researchers the opportunity to present their work in person, network with researchers working in the same field, receive feedback from peers, and publish their results as abstracts in conference proceedings.

Writing abstracts that are clear and informative, following both the conference and internationally endorsed reporting guidelines, is very important for various reasons: abstracts are used by conference program committees to select the best suited ones for oral presentations; abstracts are usually available online prior to the conference and attendees can select which presentations they will attend; abstracts are usually published and, therefore, may be cited by other authors on their peer-reviewed publications; and finally, health care professionals may base medical decisions on results of studies that have been published only as a conference abstract. Therefore, in order to guide investigators how to write high quality conference abstracts, we have developed 12 tips for young and experienced investigators:

1. **Identify and carefully follow specific guidelines** suggested by the conference. Usually an abstract contains the following: title, background/introduction, objectives, methods, results, and conclusion; however, this format varies across conferences. Pay close attention to information such as word limit and how the abstract should be structured.
2. **Follow internationally endorsed reporting guidelines** specifically developed for conference abstracts. The **E**nhancing the **QUA**lity and **T**ransparency **O**f health **R**esearch (EQUATOR) Network is an international initiative that seeks to improve the quality of published health research globally by developing reporting guidelines for several types of study designs.[1] Many reporting guidelines have extensions focusing specifically on abstracts.[2] Read them before starting to write your abstract.
3. **Think carefully about the title** because this is what readers look at first. Compose a clear, objective title and, whenever possible, include the study design. You can make it attractive, but avoid trying to be too clever (especially for beginners).
4. **Do not waste words on the introduction**. Be brief and straight to the point. Save space here, so you can provide more details in the methods and results sections, which are novel and particular to your study.
5. **Clearly state the objectives of the study**. The objective derives from your research question and should clearly align with results and conclusion.
6. **Make sure that the methods section is detailed enough**—but not too technical—and include the study design, setting, study participants, and eligibility criteria. You should also include a description of the important variables of the study, such as the exposure, intervention, predictors, and outcome, as well as the analytic approach used to answer the research question.
7. **Be precise and specific when writing the results**. Report the number of participants that were included the analysis, and, most importantly, always report the results that actually answer your research question (e.g., the difference between groups with a measure of precision such as an SD or 95% CI) and never just a p value.
8. **Be realistic in the conclusion**. Mention the impact of your study, but avoid speculating beyond what your results show; you can also mention future directions in the area of study, but avoid the overused "more studies are needed..."
9. **Perform a careful spell and language check**, especially if you are not writing in your native language.
10. **Avoid or minimize abbreviations**. Readers can feel frustrated when they have to go back to remember what an abbreviation stands for (e.g., EQUATOR in this paper).
11. **Get feedback** from your coauthors, mentor, and colleagues outside your team. The goal is to use their help to identify unclear sentences and missing or inaccurate information, as well as to make sure that the writing is high quality. They can also help you to make sure that the title, objectives, methods, results, and conclusion are all aligned with the research question.
12. **Do NOT wait until the last minute** to write and proofread the content. Writing and reviewing the abstract for quality always takes more time than you initially thought it would. Moreover, glitches in the submission process are always possible, so you want to give yourself time to contact the conference staff for help, if necessary.

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ISSN 1806-3713

J Bras Pneumol. 2018;44(4):261-266
http://dx.doi.org/10.1590/S1806-37562017000000434

ORIGINAL ARTICLE

Clinical, epidemiological, and etiological profile of inpatients with community-acquired pneumonia in a public hospital in the interior of Brazil

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Submitted: 15 December 2017.
Accepted: 18 April 2018.

Study carried out under the auspices of the Programa de Pós-Graduação em Epidemiologia, Universidade Federal do Rio Grande do Sul – UFRGS – Porto Alegre (RS) and at the Hospital Montenegro, Montenegro (RS) Brasil.

ABSTRACT

Objective: To describe the patient profile, mortality rates, the accuracy of prognostic scores, and mortality-associated factors in patients with community-acquired pneumonia (CAP) in a general hospital in Brazil. **Methods:** This was a cohort study involving patients with a clinical and laboratory diagnosis of CAP and requiring admission to a public hospital in the interior of Brazil between March 2014 and April 2015. We performed multivariate analysis using a Poisson regression model with robust variance to identify factors associated with in-hospital mortality. **Results:** We included 304 patients. Approximately 70% of the patients were classified as severely ill on the basis of the severity criteria used. The mortality rate was 15.5%, and the ICU admission rate was 29.3%. After multivariate analysis, the factors associated with in-hospital mortality were need for mechanical ventilation (**OR:** 3.60; 95% **CI:** 1.85-7.47); a Charlson Comorbidity Index score > 3 (**OR:** 1.30; 95% **CI:** 1.18-1.43); and a mental Confusion, Urea, Respiratory rate, Blood pressure, and age > 65 years (CURB-65) score > 2 (**OR:** 1.46; 95% **CI:** 1.09-1.98). The mean time from patient arrival at the emergency room to initiation of antibiotic therapy was 10 h. **Conclusions:** The in-hospital mortality rate of 15.5% and the need for ICU admission in almost one third of the patients reflect the major impact of CAP on patients and the health care system. Individuals with a high burden of comorbidities, a high CURB-65 score, and a need for mechanical ventilation had a worse prognosis. Measures to reduce the time to initiation of antibiotic therapy may result in better outcomes in this group of patients.

Keywords: Community-acquired infections; Pneumonia; Hospital mortality; Risk factors.

INTRODUCTION

Community-acquired pneumonia (CAP) is one of the leading causes of death from infectious diseases worldwide.[1] It is a public health problem and is a cause of morbidity and mortality in all age groups.[2] Mortality rates vary according to the population and context studied, ranging from 1%, in outpatients, to 50%, in inpatients.[3,4] High mortality rates are more common in developing countries, such as Brazil, Argentina, and India.[5,6] CAP is responsible for high costs in public and private health care facilities, whether in outpatient clinics, emergency rooms, or hospital wards.[7,8] In Brazil, data from the Brazilian Unified Health Care System show that pneumonia was the second leading cause of hospitalization in 2017, accounting for approximately 14% of all hospitalizations.[9]

Although CAP is a high-incidence disease, with multiple studies having been conducted on risk factors and available therapies, several issues regarding CAP remain controversial.[10] Using guidelines for the treatment of pneumonia has been shown to reduce hospital stays, mortality rates, and complications rates.[11-13] However, a recent study conducted in Brazil showed that slightly more than half of the patients admitted to a university hospital were treated in accordance with current guidelines.[14] With regard to assessment of disease severity, studies have shown that using clinical judgment alone can either underestimate or overestimate the severity of the clinical presentation. This strategy can lead to unnecessary hospitalizations, as well as to interventions that are less aggressive than those required in more severe cases, culminating in negative outcomes.[15-17] Nevertheless, a study published in 2015 showed that most physicians in Brazil use clinical judgment alone to assess disease severity in patients with CAP.[14]

It is possible to suspect that the aforementioned discrepancies are partly due to the fact that the major guidelines and severity scores are based on large international studies, and, despite the high reported incidence of CAP in Brazil, little is known about local microbiological patterns and disease severity at the regional level.[18] Therefore, we conducted a cohort study involving patients with CAP admitted to a hospital in the interior of Brazil over a one-year period, in order to describe the patient profile, mortality rates, the accuracy

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Financial support: None.

of prognostic scores, and factors associated with in-hospital mortality in these patients.

METHODS

Study population

The present study was conducted in a secondary-care general hospital, with 130 beds, located in the city of Montenegro, Brazil. The hospital provides care via the Brazilian Unified Health Care System to approximately 160,000 people, many of whom reside in one of 19 surrounding municipalities. In 2015, respiratory infections represented the leading cause of admission to the hospital, and the rate of in-hospital mortality was 10.2%.[19]

Study design

We screened for patients who were 14 years of age or older, had respiratory symptoms, and were referred for hospital admission between May 2014 and April 2015. Patient inclusion in the cohort at baseline was based on a clinical and radiographic diagnosis of CAP and a referral by the attending physician for hospitalization. We excluded patients with nosocomial pneumonia—characterized by hospitalization for 2 or more days in the past three months—residents of nursing or retirement homes; those who received intravenous antibiotics, chemotherapy, or scar treatment in the past 30 days; and those undergoing renal replacement therapy. Patients were assessed using the following severity scores: Charlson Comorbidity Index (CCI); mental Confusion, Urea, Respiratory rate, Blood pressure, and age > 65 years (CURB-65) score; and Pneumonia Severity Index (PSI), on the basis of data documented in the cohort's medical records collected at baseline. We assessed the clinical course of patients during in-hospital follow-up and determined clinical outcomes at the time of hospital discharge.

Cases of pneumonia were defined in accordance with the criteria established by the Centers for Disease Control and Prevention,[20] on the basis of chest X-rays with at least one of the following findings: new or progressive and persistent infiltrate, consolidation, and/or cavitation; and at least one of the following signs or symptoms: fever (> 38 °C) with no other cause detected; leukopenia (< 4,000 leukocytes/mm^3) or leukocytosis (≥ 12,000 leukocytes /mm^3); and, for adults aged 70 years or older, a change in mental state with no other cause identified. In addition, there should be at least two of the following findings: new onset of purulent sputum or change in character of sputum; increased respiratory secretions; increased frequency of aspiration; onset or worsening of cough, dyspnea, or tachypnea; bronchial breath sounds; worsening of gas exchange (e.g., oxygen desaturation, with a PaO_2/FiO_2 ratio ≤ 240); increased need for oxygen; or need for mechanical ventilation.

The study was approved by the Porto Alegre *Hospital de Clínicas* Research Ethics Committee (Protocol GPPG no. 150168), which is accredited by the Office of Human Research Protections as an institutional review board, and researchers signed a data use agreement protecting the confidentiality of medical records.

Study variables

Clinical, laboratory, and radiological data for the first 24 h following the emergency room visit were obtained from a review of medical records, and included the following variables: age; gender; place of residence; RR; arterial blood pressure; axillary temperature; HR; presence of mental confusion; SpO_2; comorbidities (as documented by the attending physician); history of hospitalization; chest X-ray findings (as assessed by a radiologist); and laboratory tests ordered in the emergency room. Laboratory tests included arterial blood gas analysis, urea, serum creatinine, blood glucose, sodium, and blood count. We recorded the antibiotics administered during hospitalization, as well as total length of hospital stay, length of ICU stay, and need for mechanical ventilation. The primary outcome was all-cause in-hospital mortality, as documented in the medical records and confirmed by review of hospital discharge summaries or death certificates, as appropriate. All patients had medical records, and their discharge summaries were completed by the attending physician within 48 h of discharge.

It is important to emphasize that patient management, treatment choice, and outcomes suffered no interference from this study, because it was an observational study and we had no contact with either the patients or the attending physicians, who were responsible for all clinical decisions. In the hospital, there is a care protocol for the treatment of pneumonia, and inpatients are treated by a physician team, which was composed of five members at the time of the study.

Data analysis

Data were entered into an Excel® database by two different individuals and subsequently compared to identify possible typographical errors. Continuous variables are expressed as mean and standard deviation; categorical variables are expressed as frequency and proportion. The bivariate analysis between clinical characteristics and mortality was performed by using the Student's t-test (for means and standard deviations) or Pearson's chi-square test (for proportions). ROC curve analysis was performed to evaluate the prognostic indices. A Poisson regression model with robust variance was used to assess the relationship between the variables and the primary outcome (in-hospital mortality). Analyses with a two-tailed p value < 0.05 were considered statistically significant.

All analyses were performed with the Statistical Package for the Social Sciences, version 17.0 (SPSS Inc., Chicago, IL, USA) and the R software, version 4.0-1 (The R Foundation for Statistical Computing, Vienna, Austria).[21-24]

RESULTS

Between March 2014 and April 2015, we assessed 459 patients with respiratory infection, 155 of whom did

not meet the diagnostic criteria for CAP, and, therefore, 304 patients were included in the final analysis (Figure 1). Of those, 171 (56%) were male, and the mean age was 67.1 ± 17.2 years. Most participants (69%) resided in the city of Montenegro. Of the patients in the final sample, 150 (49%) had asthma or COPD (previous lung disease), and 155 (51%) were smokers. The mean CCI score was 4.9 ± 3.1. The characteristics of the patients are presented in Table 1.

The mean CURB-65 score was 2.2 ± 1.1, and 71% of the patients were considered to have severe CAP (CURB-65 scores ≥ 2). The mean PSI score was 3.8 ± 1.3, and 74% of the patients were considered to have severe CAP (PSI scores > 3). The two indices showed good ability to predict in-hospital mortality, with areas under the ROC curve being 0.73 for the CURB-65 score (95% CI: 0.66-0.80; p < 0.001) and 0.75 for the PSI (95% CI: 0.68-0.82; p < 0.001); there was no statistically significant difference between the indices (p = 0.65), as shown in Figure 2.

The mean time from patient arrival at the emergency room to initiation of antibiotic therapy was 10.4 ± 7.7 h. Blood or sputum samples were collected for culture from 101 patients (33%), and the infectious agent was isolated in 53 patients (17%). The most commonly isolated agent was *Streptococcus pneumoniae* (in 36% of positive cultures). The most commonly used antibiotic regimen was amoxicillin plus clavulanate, in 219 patients (72%), followed by azithromycin, in 200 (66%).

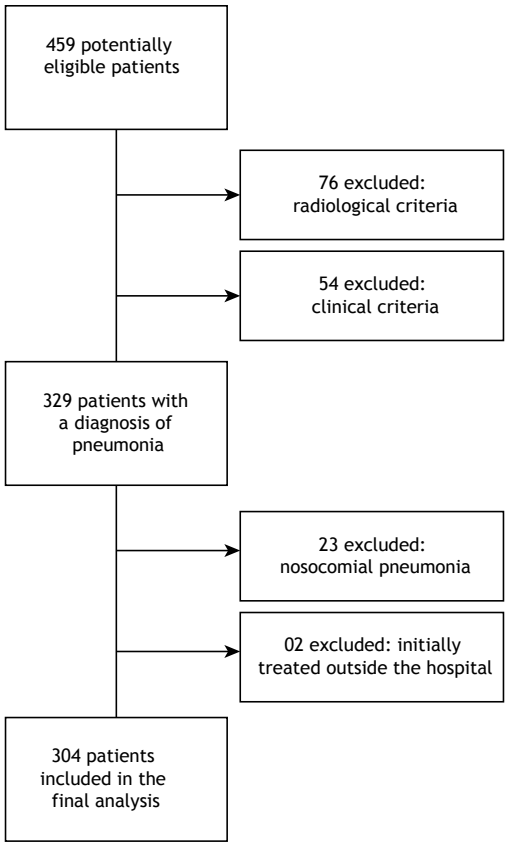

Figure 1. Flow chart of patient inclusion in the study.

We found that 191 (63%) of the patients required a change in the antibiotic regimen during hospitalization. The most common change was the addition of azithromycin to the antimicrobial regimen, on the basis of clinical assessment by the attending physician. During the in-hospital follow-up period, 47 (15.5%) of the patients died, 89 (29.3%) required ICU treatment, and 98 (32.2%) underwent mechanical ventilation. The mean length of hospital stay was 7.2 ± 7.3 days (median, 5 days).

Univariate analysis showed that the factors associated with increased risk for in-hospital mortality were: a CCI score > 3 (OR: 7.18; 95% CI: 2.28-22.58; p < 0.001); a CURB-65 score > 2 (OR: 4.45; 95% CI: 1.64-12.02; p = 0.001); a PSI score > 3 (OR: 9.05; 95% CI: 1.27-64.14; p = 0.004); need for a change in the antibiotic regimen (OR: 2.15; 95% CI: 1.05-4.42; p = 0.02); need for mechanical ventilation (OR: 6.13; 95% CI: 3.33-11.28; p < 0.001); age > 62 years (OR: 6.73; 95% CI: 2.35-19.34; p < 0.001); and being institutionalized (OR: 2.82; 95% CI: 1.08-7.35; p = 0.03).

After multivariate analysis, the factors that remained associated with in-hospital mortality were need for mechanical ventilation (OR: 3.58; 95% CI: 1.92-6.67; p < 0.001); a CCI score > 3 (OR: 1.30; 95% CI: 1.22-1.39; p < 0.001); and a CURB-65 score > 2 (OR: 1.45; 95% CI: 1.05-2.00; p = 0.04; Table 2).

DISCUSSION

CAP continues to be one of the leading causes of death from infectious disease worldwide. Despite the large number of international studies on this subject, there are few studies describing the impact of CAP on patients and the characteristics of the disease in Brazil, especially in inpatient units. In our study, we assessed inpatients with CAP in a secondary-care hospital in Brazil over a one-year period. The observed in-hospital mortality rate of 15.5% reflects the major impact of this disease, being similar to that found in other national and international studies.[25,26] In addition, ICU admission was required in almost one third of the cases (29.3%), which increases the impact of CAP on patients and the health care system.

In our study, we found no relationship between the time of initiation of antibiotic therapy and mortality, possibly because of the long elapsed time to initiation of antibiotic therapy (a mean of 10 h) and the low proportion of patients (19%) who received antibiotic therapy within the first 4 hours. Difficulty in prompt initiation of antibiotic therapy had been reported in another study conducted in Brazil.[27] In the present study, we found that, even after the implementation of a protocol for the treatment of pneumonia, there was no success in the attempt to reduce the time to initiation of antibiotic therapy. This is probably due to a tendency to administer antibiotics at scheduled

Table 1. Characteristics of the total study sample and subgroups.[a]

Variable	Total	In-hospital mortality		p
		Yes	No	
	(N = 304)	(n = 47)	(n = 257)	
Gender				
Male	171 (56.2)	28 (16.4)	143 (83.6)	0.6
Female	133 (43.8)	19 (14.3)	114 (85.7)	
Age, years	67 ± 17.3	77.5 ± 12.7	65.2 ± 17.3	0.6
Race				0.7
White	290 (95.4)	46 (15.9)	244 (84.1)	
Non-White	14 (4.6)	1 (7.1)	13 (92.9)	
CCI score	4.9 ± 3.1	8.11± 2.8	4.3 ± 2.8	< 0.001
CURB-65 score	2.2 ± 1.1	3.0 ± 1.0	2.0 ± 1.1	< 0.001
PSI score	107.2 ± 50.6	147.3 ± 32.5	99.9 ± 50.0	< 0.001
Smoking	155 (51.0)	23 (14.8)	132 (85.2)	0.9
Dementia	65 (21.4)	23 (35.4)	42 (64.6)	< 0.001
Diabetes	46 (15.5)	8 (17.4)	132 (85.2)	0.7
Heart failure	71 (23.4)	15 (21.1)	56 (78.9)	0.14
Neoplasia	39 (12.8)	15 (38.5)	24 (61.5)	< 0.001
Renal disease	34 (11.2)	13 (38.2)	21 (61.8)	< 0.001
Chronic lung disease	150 (49.3)	23 (15.3)	127 (84.7)	1.0
Institutionalized	22 (7.2)	7 (31.8)	15 (68.2)	0.03

CCI: Charlson Comorbidity Index; CURB-65: mental Confusion, Urea, Respiratory rate, Blood pressure, and age > 65 years; and PSI: Pneumonia Severity Index. [a]Values expressed as n (%) or as mean ± SD.

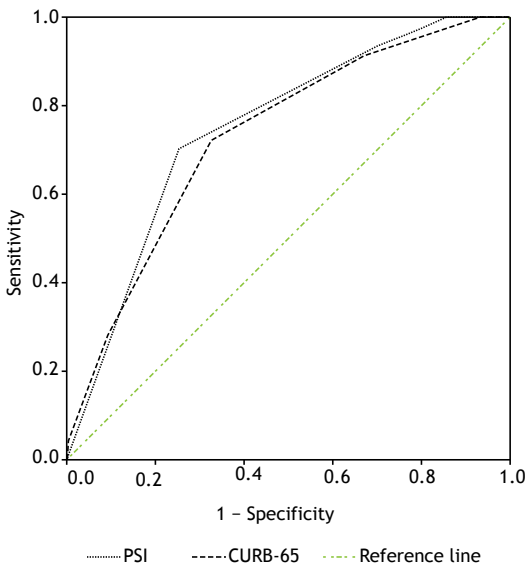

Figure 2. ROC curve of severity indices for prediction of in-hospital mortality. PSI: Pneumonia Severity Index; and CURB-65: mental Confusion, Urea, Respiratory rate, Blood pressure, and age > 65 years.

times that are pre-determined by routine hospital protocols. Given that early initiation of medication is associated with better outcomes, with a study reporting a reduction of up to 30% in mortality when antibiotics are administered within the first hours of admission,[28] efforts to reduce the time to treatment initiation are needed.

In a recent study, Rabello et al.[14] reported that only 40% of the physicians used a validated prognostic score to assess patients with CAP, with clinical assessment alone remaining the most commonly used way to assess disease severity. In our study, the severity scores performed well in predicting in-hospital mortality, with areas under the ROC curve being 0.73 for the CURB-65 score and 0.75 for the PSI, similarly to previous and recent international studies.[12,29] These findings reinforce that these scores are useful for use in the Brazilian population as well and justify the efforts to promote their routine use in health care facilities.

The risk factors that remained associated with mortality after logistic regression were need for mechanical ventilation, a high CCI score, and a high CURB-65 score. The CCI is considered a good predictor of mortality in several settings, being an important marker of the patient's underlying health status, since it evaluates comorbidities in relation to acute infection. Although the CCI has been validated in several settings, including in patients with COPD,[30] it has not commonly been reported as a risk factor for negative outcomes in other studies of CAP. The CURB-65 score, in addition to showing good prognostic ability, was independently associated with in-hospital mortality (OR, 1.45). It is of note that the PSI did not show significance in the logistic regression model, probably because of the overlapping of variables assessed by the CURB-65 score and the CCI. Given that the CURB-65 score is much simpler (only five variables assessed) than the PSI (twenty variables assessed) and both are similar in terms of efficacy, the routine use of the CURB-65 score is justified. Lastly, need for mechanical ventilation is widely associated with worse outcomes, probably because it is an important marker of severity.

Table 2. Factors associated with in-hospital mortality after multivariate analysis.

Factor	OR (95% CI)	p
Need for mechanical ventilation	3.60 (1.85-7.47)	< 0.001
CCI score	1.30 (1.18-1.43)	< 0.001
CURB-65 score	1.46 (1.09-1.98)	0.006

CCI: Charlson Comorbidity Index; and CURB-65: mental Confusion, Urea, Respiratory rate, Blood pressure, and age > 65 years.

Our study has some limitations. The major limitation is that this was a single-center study involving a relatively small number of patients. However, our study is unique, since it is one of the few involving data from the interior of Brazil and involving all patients who were hospitalized for CAP over a one-year period, which is important in this disease with a seasonal variation. No patients were lost during the in-hospital follow-up period, and the severity profile of the patients was monitored in terms of underlying diseases, by using the CCI, and in terms of acute disease, by using the PSI and the CURB-65 score.

In conclusion, the findings of our study, such as the high in-hospital mortality rate and the need for ICU admission in almost on third of the patients, emphasize the impact that CAP has on individuals and the health care system. Individuals with a high burden of comorbidities, a high CURB-65 score, and a need for mechanical ventilation had a worse prognosis. Lastly, we observed delayed initiation of antibiotic therapy, even in a hospital setting. Measures to reduce the time to initiation of antibiotic therapy may result in better outcomes in this group of patients.

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J Bras Pneumol. 2018;44(4):267-272
http://dx.doi.org/10.1590/S1806-37562018000000049

ORIGINAL ARTICLE

Six-minute walk distance and survival time in patients with idiopathic pulmonary fibrosis in Brazil

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Submitted: 19 February 2018.
Accepted: 8 June 2018.

Study carried out at the Hospital do Servidor Público Estadual de São Paulo, São Paulo (SP) Brasil, and at the Hospital das Clínicas, Faculdade de Medicina, Universidade Federal de Minas Gerais, Belo Horizonte (MG) Brasil.

ABSTRACT

Objective: To determine the cut-off point for the six-minute walk distance (6MWD) that indicates lower survival time in patients with idiopathic pulmonary fibrosis (IPF) in Brazil. **Methods:** This was retrospective study carried out in two referral centers for IPF. The 6MWT was performed twice, considering the highest value of the 6MWD. Various cut-off points were estimated, in absolute values and in percentage of predicted values, using ROC curves, the Kaplan-Meier method, and data from other studies. **Results:** The sample comprised 70 patients with IPF. The mean age was 71.9 ± 6.4 years, and 50 patients (71.4%) were male. The mean FVC was 76.6 ± 18.2% of predicted value. The mean SpO_2 at rest before and after 6MWT were 93.8 ± 2.5% and 85.3 ± 6.5%, respectively. The median survival time was 44 months (95% CI: 37-51 months). The mean 6MWD was 381 ± 115 m (79.2 ± 24.0% of predicted). After the analyses, the best cut-off points for estimating survival were 6MWD < 330 m and < 70% of predicted. The median survival time of patients with a 6MWD < 330 m was 24 months (95% CI: 3-45 months), whereas that of those with a 6MWD ≥ 330 m was 59 months (95% CI: 41-77 months; p = 0.009). Similarly, the median survival times of those with a 6MWD < 70% and ≥ 70% of predicted, respectively, were 24 months (95% CI: 13-35 months) and 59 months (95% CI: 38-80 months; p = 0.013). Cox multivariate regression models including age, sex, smoking status, SpO_2 at the end of the 6MWT, and FVC% showed that 6MWD remained significantly associated with survival (p = 0.003). **Conclusions:** Values of 6MWD < 330 m and < 70% of predicted value were associated with lower survival time in IPF patients in Brazil.

Keywords: Lung diseases, interstitial; Pulmonary fibrosis; Exercise tolerance.

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is an interstitial lung disease (ILD) of unknown etiology, which is accompanied by functional loss, progressive dyspnea, and impaired quality of life.[1] The median survival, prior to the therapeutic era, was between 2 and 4 years.[2] The clinical course of IPF is highly variable. This great variability in the evolution of IPF makes its staging and prognosis a challenge. Some individual predictors of survival have already been established, such as increased dyspnea on initial presentation, digital clubbing, pulmonary hypertension, increased extent of fibrosis on HRCT scans, and increased number of hospital admissions, mainly due to respiratory failure.[3,4] Lung function plays a key role in prognostic evaluation.[3,5] Baseline values of FVC < 70%, DLCO < 40%, and SpO_2 < 89% during physical exertion indicate worse survival.[6-9]

Another way of assessing prognosis during the initial evaluation includes the use of predictive composite statistical models or scoring systems that combine functional variables, clinical data, and other prognostic tests. These models are more effective in predicting survival than are individual variables. Various studies have appeared in the past years with this proposal, some even emphasizing the six-minute walk distance (6MWD) as having prognostic value.[10-15]

The six-minute walk test (6MWT) is, by definition, an endurance test, i.e., a submaximal test. For most patients with mild-to-moderate cardiopulmonary disease, the metabolic demand is lower than is the maximum demand obtained from an incremental test, and, therefore, maximum limits are seldom reached. However, for a group of patients with more severe disease, such as in patients with interstitial lung disease, the 6MWT can be considered a "near-maximal" test, because the metabolic/energy expenditure during the test approaches the maximum limit, due to the symptoms of these patients.[16]

An evaluation of a global integrated response of all the systems involved in performing the exercise (pulmonary system, cardiovascular system, systemic/peripheral circulation, blood, neuromuscular unit, and muscle metabolism) is provided by the 6MWT.[17-20] The 6MWT is extremely useful in clinical practice for the evaluation of patients with various advanced cardiopulmonary

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Financial support: None.

conditions, and it has been included in clinical trials on IPF treatment for the determination of outcomes.[19,21]

Three studies have evaluated baseline 6MWD as an independent variable associated with mortality in patients with IPF, suggesting cut-off values of 181 m, 207 m, and 212 m.[15,22,23] One study reported lower baseline 6MWD results in patients with ILDs and pulmonary hypertension, who, consequently, had a worse prognosis.[24] A post-hoc analysis of a clinical trial[25] showed that baseline 6MWD and a decrease in 6MWD at week 24 were significantly associated with 1-year mortality, despite the poor correlation between 6MWD results and other pulmonary function test measurements. A subsequent analysis using the same database showed that baseline 6MWD < 250 m was associated with a 1-year mortality rate twice as high (hazard ratio = 2.12).[26]

IPF usually affects older patients, who may present with various comorbidities. The prevalence of cardiovascular disease in patients with IPF can reach up to 26% and contribute to 10% of the mortality rate.[27]

In a recent review, the authors have made relevant considerations on the relationship between 6MWD and mortality, emphasizing the importance of 6MWD in the evaluation of comorbidities and quality of life in patients with IPF.[28] In Brazil, healthy individuals older than 40 years of age walk greater distances in the 6MWT when compared with individuals in other countries.[29]

The objective of the present study was to determine the cut-off point for 6MWD that indicates lower survival in patients with IPF in a cohort of patients in Brazil.

METHODS

This was a retrospective study involving patients from two referral centers for the treatment of ILDs in Brazil, namely, *Ambulatório de Doenças Pulmonares Intersticiais* (Interstitial Lung Disease Outpatient Clinic), *Hospital das Clínicas*, *Faculdade de Medicina*, *Universidade Federal de Minas Gerais*, located in the city of Belo Horizonte, Brazil, and *Ambulatório de Doenças Pulmonares Intersticiais*, *Faculdade de Medicina*, *Universidade Federal de São Paulo*, located in the city of São Paulo, Brazil, between June 4, 1993 and September 30, 2017. The date of diagnosis was used as the initial date for the analysis of survival.

The study was approved by the research ethics committee of the coordinating center (CAAE protocol no. 44843215.50000.5149).

The diagnosis of IPF was performed based on recommendations from an international guideline.[2] All of the cases were reviewed by two pulmonologists and one radiologist, and biopsies were reviewed by a pathologist with extended experience in lung biopsies. The three professionals are specialists in ILDs.

We excluded patients with an SpO_2 < 89% at rest on room air; patients with degenerative locomotor or neuromuscular diseases or with functional limitations that prevented test performance; patients with a history of acute myocardial infarction within the last month; and patients with decompensated heart failure, unstable angina, syncope, or cardiac arrhythmia.

The date of diagnosis, sex, age, duration of symptoms, history of smoking, and perception of dyspnea (determined by the modified scale of the Medical Research Council)[30] were collected from the medical records and inserted into a specific form for the systematic evaluation of patients with ILD.[29]

The 6MWT was performed in a 30-m corridor, using a portable oximeter (Nonin Medical, Inc., Plymouth, MN, USA), following international recommendations.[17,19,20] All patients performed two tests, with a minimum time interval of 30 min; verbal encouragement was given every minute. The following parameters were recorded at the beginning and at the end of the tests: HR, RR, perception of dyspnea by the Borg scale score (data not shown), SpO_2 measured by pulse oximetry, and 6MWD, the latter being expressed in absolute values and in percentage of predicted values, which were calculated by means of the reference equation proposed by Soares et al. for the Brazilian population.[31]

Although this was a retrospective and multicenter study, the same type of equipment was used in both centers: Collins CPL system (Ferraris Respiratory, Louisville, CO, USA). Acceptability and reproducibility criteria for pulmonary function tests followed the recommendations by the American Thoracic Society.[32] The results were described as absolute values and as percentage of predicted values for the Brazilian population.[33] The studied variables were FVC, FEV_1, and FEV_1/FVC ratio. DLCO measurements were performed using the single-breath method. The predicted values suggested by Crapo et al. were used.[34]

Continuous variables were presented as means and standard deviations or medians and minimum and maximum values, when indicated; categorical variables were described as proportions. Various cut-off points, including those suggested in the literature, were tested by the Kaplan-Meier method and ROC curves to identify the cut-off point with the highest discriminatory value, both for absolute values and percentage of predicted values for 6MWD. Using the ROC curves, sensitivity vs. 1 – specificity points closer to 10% were selected, because many false-positive results can be obtained from points with the highest sum of sensitivity and specificity. These cut-off points were similar to those observed by testing various cut-off points using the Kaplan-Meier curves, the highest value being determined for the log-rank test.

Survival curves were constructed using the Kaplan-Meier method. Cox multivariate regression models were analyzed in order to measure the associations between mortality and 6MWD, taking into account the following variables: age, sex, smoking status, and FVC in % of predicted value. A p-value < 0.05 was considered statistically significant for all tests. All the analyses were performed using the statistical package

IBM SPSS Statistics, version 21.0 (IBM Corporation, Armonk, NY, USA).

RESULTS

A total of 70 patients were included in the study. The mean age was 71.9 ± 6.5 years. Most of the patients were male (71.4%) and smokers or former smokers (71.4%). The diagnosis of IPF was reached by clinical data, in 87.1% of the sample, and by surgical lung biopsy, in 22.9%. The mean 6MWD was 380 ± 115 m. The median follow-up time was 37.6 months. Clinical and functional characteristics are summarized in Tables 1 and 2.

The median survival was 44 months (95% CI: 37-51 months). After various analyses, the best cut-off points for estimating survival based on 6MWD results were 330 m and 70% of predicted values. Both ROC curves were significant. The area under the curve for 6MWD in absolute values and in percentage of predicted value were, respectively, 0.70 (p = 0.008) and 0.65 (p = 0.047). Sensitivity for the selected absolute cut-off point (330 m) was 39%, and 1 – specificity (false positive) was 13%, with a likelihood ratio of 3.00. For the cut-off point of 70% of the predicted value, sensitivity was 38%, and false-positive value was 13%, with a likelihood ratio of 2.92, i.e., they are almost identical.

Of the 70 patients in the sample, 21 (30%) had a 6MWD < 70% of predicted and 22 (31.4%) had a 6MWD < 330 m. The median survival time of the patients with a 6MWD < 330 m was 24 months (95% CI: 3-45 months), whereas the median survival time of those with a 6MWD ≥ 330 m was 59 months (95% CI: 38-80 months; log rank: 6.78; p = 0.009; Figure 1). Similarly, the median survival time of patients with a 6MWD < 70% of predicted value was 24 months (95% CI: 13-35 months),and that of those with a 6MWD ≥ 70% of predicted value was 59 months (95% CI: 38-80 months; log-rank: 6.17; p = 0.013; Figure 2).

The analysis of Cox multivariate regression models, considering age, sex, smoking status, SpO_2 at the end of the 6MWT, and FVC% showed that 6MWD remained significantly associated with survival (p = 0.003).

DISCUSSION

The present study demonstrated that a 6MWD < 330 m or < 70% of the predicted value was associated with a median survival time of only 24 months in patients with IPF in Brazil.

The 6MWT has been used as a valid, simple, and reliable instrument for the evaluation of exercise capacity in patients with chronic respiratory diseases, including IPF.[15,22,23,35] In addition, the 6MWT is a better predictor of exercise capacity when compared with functional tests (spirometry) and quality of life tests.[18]

The 6MWT is well standardized and easily reproduced, has low costs, and is safe.[18] However, it can be influenced by the size of the corridor, as well as by baseline hypoxemia, reduced muscle strength, sedentary lifestyle, and associated heart and muscle disease of the patient. These factors should be taken into consideration in the interpretation of 6MWT results.[18] In order to reduce the learning effect, two tests were performed in our study, the highest value obtained being selected and compared with the predicted result derived from one of the reference equations proposed for the Brazilian population.[17,18,31]

The 6MWT has an advantage over static measures of lung function, because it provides a functional measure of the general cardiopulmonary reserve of the patient and can incorporate other important prognostic parameters for evaluation.

Andersen et al.[24] studied 212 patients with IPD and found that a 6MWD < 345 m was independently associated with the presence of pulmonary hypertension. In our results, 6MWD < 330 m (p = 0.009) or < 70% of predicted (p = 0.013) was associated with a three-fold

Table 1. Clinical characteristics of patients with interstitial pulmonary fibrosis included in the study (N = 70).[a]

Variable	Result
Center	
HSPE/SP	39 (57)
HC-UFMG	31 (43)
Age, years	71.9 ± 6.5
Males	50 (71.4)
Smoking status	
Never smoker	20 (28.6)
Smoker or former smoker	50(71.4)
Diagnosis	
Clinical	61 (87.1)
Biopsy	9 (12.9)
Survival time, months	44 [37-51]
Follow-up period. months	36.5 [5-129]

HSPE/SP: *Hospital do Servidor Público Estadual de São Paulo*; HC-UFMG: *Hospital das Clínicas da Universidade Federal de Minas Gerais*. [a]Values expressed in n (%), mean ± SD or median [minimum-maximum].

Table 2. Functional characteristics of patients with interstitial pulmonary fibrosis included in the study (N = 70).[a]

Variable	Result
Spirometry	
FVC, L	2.54 ± 0.84
FVC, % predicted	76.61 ± 18.23
FEV_1, L	2.11 ± 0.57
FEV_1, % predicted	75.74 ± 21.35
FEV_1/FVC, %	83.09 ± 7.83
DLCO, L	12.6 ± 4.09
DLCO, % predicted	52.7 ± 13.9
6MWT	
6MWD, m	380 ± 115
6MWD, % predicted	79.2 ± 24.0
Pre-6MWT SpO_2	93.81 ± 2.47
Post-6MWT SpO_2	85.29 ± 6.53

6MWT: six-minute walk test; 6MWD: six-minute walk distance. [a]Values expressed in mean ± SD.

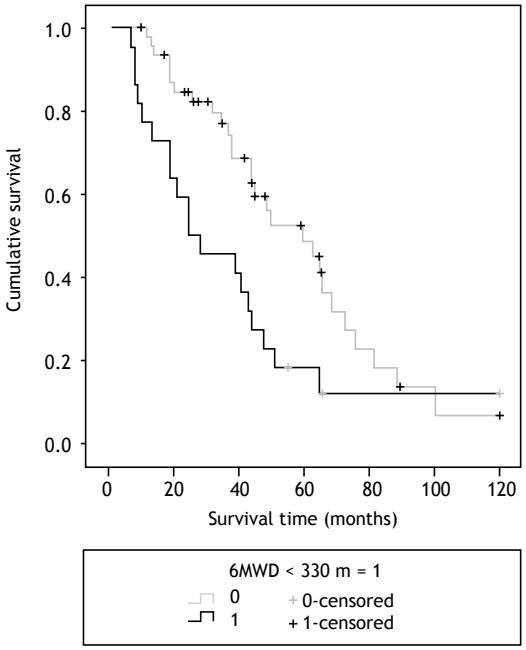

Figure 1. Survival time in patients with interstitial lung fibrosis according to the six-minute walk test distance (6MWD) < 330 m or ≥ 330 m (log-rank test: 6.78; p = 0.009).

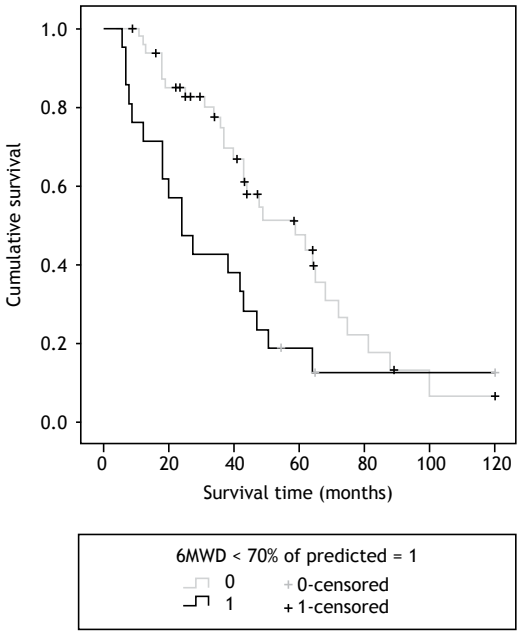

Figure 2. Survival time in patients with interstitial lung fibrosis according to the six-minute walk distance (6MWD) < 70% or ≥ 70% of predicted values (log-rank test: 6.17; p = 0.013).

increased risk of mortality and decreased survival; however, the presence of pulmonary hypertension was not evaluated. Lettieri et al.,[15] in a study involving 81 patients (48 survivors and 33 nonsurvivors on a waiting list for lung transplantation), found that the 6MWD was significantly higher in the survivors than in the nonsurvivors (407 m vs. 181 m; p < 0.005). In that study, 38% of patients were on oxygen therapy, and the 1-year mortality rate was 41%, compared with 14% in the present sample; this difference might be explained by the inclusion of more severe patients on the waiting list for transplantation in that study.[15] Another study involving 454 patients with IPF who were also on the waiting list for lung transplantation demonstrated that patients with a 6MWD < 207 m were associated with a four-fold mortality risk at six months when compared with those with a 6MWD ≥ 207 m, regardless of gender, age, and baseline FVC.[23] In that study,[23] the patients were younger (55 ± 9 years) and presented with more severe disease (FVC = 47 ± 14%) when compared with the patients in the present study, who had a higher mean age (71.9 ± 6.5 years) and higher mean FVC% (76.61 ± 18.23%).

Caminati et al.[22] showed that a 6MWD < 212 m was associated with shorter survival time (log-rank test; p < 0.036) in a group of 44 patients with IPF. The median 6MWD was 375 m in survivors, compared with 200 m in nonsurvivors. The median length of follow-up was 19.8 months (3.2-46.4 months).[22] Unlike our results, which showed a frequency of 71% of male patients, in the study by Caminati et al.,[22] that frequency was 52%; however, FVC% was comparable in both studies (76% vs. 74%). It is postulated that male gender is a factor associated with higher 6MWD.[29]

The Latin-American Thoracic Association demonstrated that Latin-American samples (including a Brazilian one in the city of São Paulo) presented with higher values of 6MWD when compared with those found in countries in the northern hemisphere (Spain and the USA),[29] a finding that might be related to the characteristics of COPD patients with similar degrees of functional loss: such patients in Brazil tend to walk longer and more often than do patients in the USA. Therefore, there is still no definitive answer regarding 6MWD values that undoubtedly characterize and qualify the functional incapacity of patients with chronic lung diseases, except in extreme cases. In this context, we decided to evaluate the 6MWD in a cohort of patients with IPF in Brazil to determine whether this could be as high as in patients with COPD[29]; our hypothesis was confirmed. The geographic variations found here can not be explained by anthropometric factors. It is speculated that other factors, such as walking speed or cultural aspects related to lifestyle, mood, attitudes, and motivation of these individuals, might have influenced the 6MWD results. However, further studies exploring the physiological variables and their responses to exercise are necessary.[29]

IPF is a progressive disease with a very poor prognosis. A practical application of the results in our study would be the immediate referral of patients with a 6MWD < 330 m or < 70% of predicted to be specifically assessed for lung transplantation. The median survival time in patients with a 6MWD < 330 m was 24 months in the present study. The mean time on the waiting list for

lung transplantation in the state of São Paulo, Brazil, is 18 months.[35]

Some limitations of the present study should be considered. The first one is related to the sample, which was relatively small, but equivalent to those in other studies in the literature.[16,22,36] However, our median follow-up period was 38 months, which greatly strengthens the present study, when compared with a follow-up period of 13 months in studies with larger samples.[26,35] Another limitation is related to the exclusion of patients with SpO_2 < 89% at rest and of all users of supplemental oxygen, which determines a worse prognosis in such patients. In addition, ours was a retrospective study; however, the variables were collected by experienced and trained teams, by means of a standardized and structured protocol that made it possible to review the diagnosis of IPF carefully. Because the study was performed in only two centers, it was also possible to compare and ensure that the methodology used to perform the 6MWT in these centers was identical.

In conclusion, a 6MWD < 330 m or < 70% of the predicted value is significantly associated with a shorter survival time in patients with IPF in Brazil.

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J Bras Pneumol. 2018;44(4):273-278
http://dx.doi.org/10.1590/S1806-37562017000000216

ORIGINAL ARTICLE

Asthma control, lung function, nutritional status, and health-related quality of life: differences between adult males and females with asthma

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Submitted: 19 June 2017.
Accepted: 30 October 2017.

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ABSTRACT

Objective: To evaluate health-related quality of life in asthma patients treated at a referral center in southern Brazil, identifying differences between male and female patients, as well as to evaluate differences between the males and females in terms of asthma control, lung function, and nutritional status. **Methods:** This was a cross-sectional study involving patients ≥ 18 years of age treated at an asthma outpatient clinic. We evaluated clinical parameters, lung function, nutritional status, and quality of life. **Results:** A total of 198 patients completed the study. The mean age was 56.2 ± 14.8 years, and 81.8% were female. The proportion of patients with uncontrolled asthma was higher among females than among males (63.0% vs. 44.4%; p = 0.041). The body mass index (BMI) and percentage of body fat were higher in females than in males (30.2 ± 5.8 kg/m^2 vs. 26.9 ± 4.5 kg/m^2 and 37.4 ± 6.4% vs. 26.5 ± 7.4%; p = 0.002 and p < 0.001, respectively). Quality of life was lower in females than in males in the following domains: symptoms (3.8 ± 1.5 vs. 4.6 ± 1.7; p = 0.006); activity limitation (3.6 ± 1.3 vs. 4.4 ± 1.5; p = 0.001); emotional function (3.6 ± 1.9 vs. 4.5 ± 1.7; p = 0.014); and environmental stimuli (3.2 ± 1.6 vs. 4.3 ± 1.9; p = 0.001). **Conclusions:** Male asthma patients appear to fare better than do female asthma patients in terms of health-related quality of life, asthma control, BMI, percentage of body fat, and comorbidities.

Keywords: Asthma; Nutritional status; Quality of life; Adult.

INTRODUCTION

Asthma is a chronic inflammatory disease of the airways characterized by respiratory symptoms such as wheeze, shortness of breath, chest tightness, and cough that vary over time and in intensity, as well as by variable expiratory airflow limitation and airway hyperresponsiveness to direct or indirect stimuli. It is a prevalent disease that impairs quality of life, being a major public health problem. Asthma affects approximately 10% of adults worldwide.[1] The prevalence of asthma follows a characteristic age- and gender-related pattern, being highest during childhood and predominantly affecting males.[2] After puberty, the prevalence of asthma is higher in females than in males.[2,3]

Many mechanisms are involved in the clinical expression of asthma, including sex hormones, airway caliber, obesity, type of exposure, and age at onset.[4,5] Although males and females with asthma share the common clinical features of the disease, the natural course of asthma differs between the genders. Takeda et al.[6] suggested that sex hormones and gender differences are involved in cellular functions in airway remodeling. Several studies have reported that asthma is more prevalent and more severe in adult females. In a cross-sectional study, asthma severity was found to have increased with the body mass index (BMI), although only in females; however, the reason for this has yet to be explained.[7-9] Zillmer et al.[10] noted that poorly controlled asthma and respiratory symptoms were more common in females than in males. In addition, self-reported quality of life is often worse in females than in males, probably due to dyspnea that is more severe and increased drug use.[11] As a result of this clinical heterogeneity, treatment approaches need to be individualized and modified in order to maintain adequate symptom and disease control over time.[12]

Although several studies have examined gender differences in asthma patients, few have investigated the impact of asthma on health-related quality of life and nutritional status.[11,13] In addition, there are differences and regional disparities in disease control and clinical expression among asthma patients.[14] Therefore, it is important to evaluate gender differences in different populations of adults with asthma.

The primary objective of the present study was to evaluate differences in health-related quality of life between adult males and females with asthma treated at a referral center in southern Brazil. A secondary objective was to

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Financial support: This study received financial support from the *Fundo de Incentivo à Pesquisa do Hospital de Clínicas de Porto Alegre* (FIPE-HCPA, Research Incentive Fund of the Porto Alegre *Hospital de Clínicas*), the *Coordenação de Aperfeiçoamento de Pessoal de Nível Superior* (CAPES, Office for the Advancement of Higher Education), and the Brazilian *Conselho Nacional de Desenvolvimento Científico e Tecnológico* (CNPq, National Council for Scientific and Technological Development). Gabriele Carra Forte and Maria Luiza Hennemann are recipients of grants from CAPES/CNPq.

evaluate differences in asthma control, lung function, and nutritional status between those two groups.

METHODS

In a cross-sectional study of prospectively collected data, we assessed consecutive adult patients with asthma recruited from among those treated at a referral center for asthma in southern Brazil. The study protocol was approved by the Research Ethics Committee of the *Hospital de Clínicas de Porto Alegre* (HCPA), located in the city of Porto Alegre, Brazil (Protocol no. 12.0103), and written informed consent was obtained from all patients.

Patients were recruited from among those treated at the HCPA asthma outpatient clinic, located in the city of Porto Alegre, Brazil. The study included patients who were 18 years of age or older and who had physician-diagnosed asthma. The diagnosis of asthma was confirmed by a member of the research team on the basis of the following criteria: symptoms of asthma, accompanied by reversible airflow obstruction (an increase of at least 12% and 200 mL in FEV_1 after administration of a short-acting β_2 agonist) or bronchial hyperresponsiveness to a bronchoconstricting agent (methacholine).[1]

The exclusion criteria were as follows: chronic lung diseases other than asthma (such as COPD and bronchiectasis); lobectomy; abnormal chest X-ray findings; pregnancy; and current or past smoking (a smoking history of more than 10 pack-years).

During an outpatient visit, participants underwent a comprehensive clinical evaluation and completed questionnaires regarding the following: medical history; socioeconomic status; demographic characteristics; smoking history; chronic comorbidities; medication use; menopause (no menstruation in the last 12 months); nutritional status; asthma severity; level of asthma control; and health-related quality of life.

Nutritional status was assessed by the body mass index (BMI), which was calculated by the formula weight/height^2 (kg/m^2). On the basis of their BMI, participants were stratified into the following categories[15]: underweight (< 18.5 kg/m^2); normal weight (18.5-24.9 kg/m^2); overweight (25-29.9 kg/m^2); and obese (≥ 30 kg/m^2). Bioelectrical impedance analysis was used in order to assess body composition (i.e., the proportions of muscle, fat, and water).[16]

Asthma severity was determined in accordance with the Global Initiative for Asthma (GINA) guidelines,[1] patients being classified as having mild intermittent asthma, mild persistent asthma, moderate persistent asthma, or severe persistent asthma on the basis of daily medication use. The level of asthma control was also determined in accordance with the GINA guidelines,[1] patients being classified as having well-controlled, partly controlled, or uncontrolled asthma on the basis of the following: frequency of daytime and nighttime symptoms; rescue medication use; limitation of daily physical activity; and number of exacerbations in the last 4 weeks.

Spirometry was performed with a v4.31a spirometer (Jaeger, Würzburg, Germany). FVC, FEV_1, and the FEV_1/FVC ratio were measured three times, the best of the three measurements being recorded. All pulmonary function test results were expressed as a percentage of the predicted values for age, height, and gender.[17]

Quality of life was assessed by the Asthma Quality of Life Questionnaire (AQLQ),[18] which had previously been translated to Portuguese and validated for use in Brazil.[19] The AQLQ is divided into four domains: symptoms; activity limitation; emotional function; and environmental stimuli. Each domain is scored from 1 to 7, a score of 1 indicating maximum impairment and a score of 7 indicating no impairment.

Sample size calculation was based on a study by Dalcin et al.[14] For a proportion of 60% of female patients with uncontrolled asthma, a proportion of 45% of male patients with uncontrolled asthma, a total width of 0.15, a type I error of 0.05 (two-sided), and a type II error of 0.20 (or a study power of 0.80), the required sample size was calculated to be 186.

Statistical analysis of the data was performed with the IBM SPSS Statistics software package, version 20.0 (IBM Corporation, Armonk, NY, USA). Quantitative data were expressed as mean ± standard deviation or median (interquartile range), and qualitative data were expressed as n (%). Categorical variables were compared by the chi-square test with adjusted standardized residuals, Yates' correction or Fisher's exact test being used as appropriate. For continuous variables, the Student's t-test or the Mann-Whitney U test was used for between-group comparisons. All statistical tests were two-tailed, and the level of significance was set at $p < 0.05$.

RESULTS

Between March and December of 2013, we evaluated 344 patients with asthma. Of those, 75 declined to participate, 53 were excluded because they had chronic lung diseases other than asthma, 8 were excluded because they were smokers or former smokers (with a smoking history of more than 10 pack-years), and 10 were excluded because they failed to have all of the required assessments performed. Therefore, the final sample consisted of 198 patients.

The general characteristics of the participating patients are presented in Table 1. Of the 198 participants, 162 (81.8%) were female. The mean age was 56.2 ± 14.8 years. With regard to the severity of asthma, 144 patients (72.2%) had severe persistent asthma, 31 (15.7%) had moderate persistent asthma, and 23 (11.6%) had mild persistent asthma. With regard to the level of asthma control, 118 patients (59.6%) had uncontrolled asthma, 28 (14.1%) had partly controlled asthma, and 52 (26.3%) had well-controlled asthma. The mean BMI was 29.6 ± 5.7 kg/m^2, 83 patients (41.9%) being classified as obese, 72 (36.4%) being

Table 1. General characteristics of the patients with asthma in the present study.[a]

Variable	N = 198
Gender	
Female	162 (81.8)
Male	36 (18.2)
Age, years[b]	56.2 ± 14.8
Menopause	115 (71)
Race	
White	150 (75.3)
Non-White	48 (24.2)
Age at diagnosis, years[c]	20.5 (44)
Smoking status	
Never smoker	138 (69.7)
Former smoker	60 (30.3)
GINA asthma severity classification	
Mild	23 (11.6)
Moderate	31 (15.7)
Severe	144 (72.7)
GINA asthma control	
Well-controlled	52 (26.3)
Partly controlled	28 (14.1)
Uncontrolled	118 (59.6)
BMI, kg/m^2[b]	29.6 ± 5.7
Nutritional status	
Normal weight	43 (21.7)
Overweight	72 (36.4)
Obesity	83 (41.9)
Pre-bronchodilator lung function[b]	
FVC, L	2.5 ± 0.9
FVC, % predicted	81.2 ± 21.3
FEV_1, L	1.7 ± 0.7
FEV_1, % predicted	68.2 ± 22.2
FEV_1/FVC, % predicted	82.1 ± 13.0

GINA: Global Initiative for Asthma; and BMI: body mass index. [a]Data expressed as n (%), except where otherwise indicated. [b]Data expressed as mean ± SD. [c]Data expressed as median (interquartile range).

classified as overweight, and 43 (21.7%) being classified as normal weight.

Table 2 shows a comparison between the genders in terms of clinical characteristics, health-related quality of life, level of asthma control, lung function, and nutritional status. The prevalence of White patients was higher among males than among females (91.7% vs. 72.0%; p = 0.024). Quality of life was lower in females than in males in all four AQLQ domains: symptoms (3.8 ± 1.5 vs. 4.6 ± 1.7; p = 0.006); activity limitation (3.6 ± 1.3 vs. 4.4 ± 1.5; p = 0.001); emotional function (3.6 ± 1.9 vs. 4.5 ± 1.7; p = 0.014); and environmental stimuli (3.2 ± 1.6 vs. 4.3 ± 1.9; p = 0.001). The proportion of patients with uncontrolled asthma was higher among females than among males (63.0% vs. 44.4%; p = 0.041). In addition, the BMI and percentage of body fat were higher in females than in males (30.2 ± 5.8 kg/m^2 and 37.4 ± 6.4% vs. 26.9 ± 4.5 kg/m^2 and 26.5 ± 7.4%; p = 0.002 and p < 0.001, respectively). Chronic comorbidities were more commonly reported by females than by males (68.5% vs. 38.9%; p = 0.001), as were cardiovascular comorbidities (58.0% vs. 36.1%; p = 0.028). There were no significant differences between the genders regarding age (p = 0.805), asthma severity (p = 0.401), percent predicted FVC (p = 0.078), or percent predicted FEV_1 (p = 0.085). In addition, there was no association between menopause and the study outcomes.

DISCUSSION

In the present study, females predominated among adult patients with asthma treated at a referral outpatient clinic in southern Brazil. Health-related quality of life was found to be lower in females than in males in all four AQLQ domains. In addition, the proportion of patients with uncontrolled asthma was higher among females than among males, as were the BMI and percentage of body fat. Furthermore, comorbidities were more commonly reported by females than by males.

The high prevalence of asthma in adult females in the present study is consistent with the literature.[20-22] Zillmer et al.[10] interviewed 400 asthma patients in four Brazilian cities and reported that 272 (68%) were female. Dursun et al.[23] studied 242 adult patients with asthma in Turkey and reported that 77.3% were female. Schatz & Camargo[24] used computerized data from Kaiser-Permanente Southern California in order to identify patients with asthma. Among the 60,694 asthma patients, the female-male prevalence ratio was approximately 65:35 in the 23- to 64-year age bracket. Previous studies conducted at our institution in different settings and involving different samples of adults have shown a high (68.6-75%) prevalence of females seeking hospital treatment for asthma.[7,25,26] There is compelling evidence that sex hormones are major determinants of at least these biological differences in asthma prevalence.[20] It has been reported that estrogen receptor 1 polymorphisms are associated with bronchial hyperresponsiveness and lung function decline, especially in females with asthma.[4]

The overall health-related quality of life in our sample was moderate, AQLQ scores being significantly lower among females than among males. Other studies have shown that health-related quality of life is worse in female asthma patients than in male asthma patients.[11,27,28] In a cross-sectional study, Lisspers et al.[29] investigated 1,226 patients in a primary care setting and 499 patients in a secondary care setting. They concluded that quality of life and the level of asthma control were lower in young females than in young males, although no such differences were found between older females and older males. Female sex hormones could be an important factor affecting these outcomes. Correia de Sousa et al.[30] found that females were 3.8 times more likely to have poorer quality of life than were males. This finding was associated with

Table 2. Comparison between the genders in terms of clinical characteristics, level of asthma control, lung function, nutritional status, and health-related quality of life.[a]

Variable	Females (n = 162)	Males (n = 36)	p*
Age, years[b]	56.3 ± 14.2	55.7 ± 17.8	0.805
Race			
White	116 (72)	33 (91.7)	0.024
Non-White	45 (28)	3 (8.3)	
Age at diagnosis, years[c]	18 (43)	29 (44)	0.021
Smoking status			
Never smoker	116 (71.6)	22 (61.1)	0.150
Former smoker	46 (28.4)	14 (38.9)	
GINA asthma severity classification			
Mild	21 (13)	2 (5.6)	
Moderate	24 (14.8)	7 (19.4)	0.401
Severe	117 (72.2)	27 (75)	
GINA asthma control			
Well-controlled/partly controlled	60 (37.0)	20 (55.6)	0.041
Uncontrolled	102 (63.0)	16 (44.4)	
Nutritional markers[b]			
BMI, kg/m^2	30.2 ± 5.8	26.9 ± 4.5	0.002
Body fat, %	37.4 ± 6.4	26.5 ± 7.4	< 0.001
Comorbidities	111 (68.5)	14 (38.9)	0.001
Cardiovascular comorbidities	94 (58.0)	13 (36.1)	0.028
Pre-bronchodilator lung function[b]			
FVC, L	2.3 ± 0.7	3.3 ± 1.0	< 0.001
FVC, % predicted	83.2 ± 20.9	76.3 ± 22.0	0.078
FEV_1, L	1.6 ± 0.6	2.2 ± 0.9	< 0.001
FEV_1, % predicted	69.5 ± 21.7	62.4 ± 23.9	0.085
FEV_1/FVC, % predicted	82.4 ± 12.3	80.8 ± 15.9	0.492
Quality of life[b]			
Symptoms	3.8 ± 1.5	4.6 ± 1.7	0.006
Activity limitation	3.6 ± 1.3	4.4 ± 1.5	0.001
Emotional function	3.6 ± 1.9	4.5 ± 1.7	0.014
Environmental stimuli	3.2 ± 1.6	4.3 ± 1.9	0.001

GINA: Global Initiative for Asthma; and BMI: body mass index. *Values of $p < 0.05$ were considered significant. [a]Data expressed as n (%), except where otherwise indicated. [b]Data expressed as mean ± SD. [c]Data expressed as median (interquartile range).

higher rates of anxiety and depression in the female population.[13] A possible explanation for this finding is that being overweight and having uncontrolled asthma is more common in females than in males. These findings are consistent with those of Xu et al.,[31] who investigated the association between obesity and asthma outcomes in older adults.

In the present study, asthma severity was assessed by the GINA classification system on the basis of daily medication use,[1] meaning that although effective therapy was able to control the disease, it did not interfere with the classification of disease severity. The proportion of patients with severe persistent asthma was high in the present study (i.e., 72.7%). However, asthma severity and lung function (as assessed by percent predicted FVC and FEV_1) did not differ between males and females. In contrast, Carvalho-Pinto et al.[22] reported that the female predominance in their group of patients suggested that severe asthma was a gender-related disease.

Asthma control, which is defined as the extent to which the various manifestations of asthma are reduced or removed by treatment, is increasingly receiving attention not only in clinical trials but also in clinical practice.[21] In the present study, the proportion of patients with uncontrolled asthma was higher among females than among males. Previous studies have shown a lower level of asthma control in females than in males, despite a higher use of inhaled corticosteroids and more frequent visits to an asthma treatment center among the former.[22,32] It has also been reported that females are 3.2 times more likely to have uncontrolled asthma than are males.[30] Poor asthma control in females might also be related to being overweight. Although mechanisms linking both conditions are still poorly understood, there is evidence that obesity impairs clinical control.[33] Although clinical observations indicate that

menopause is generally associated with weight gain, exacerbation of asthma, and, consequently, worsening of asthma control,[34] we found no association between menopause and the study outcomes.

Obesity is defined as an increase in body weight resulting from excess body fat. Previous studies have shown a high prevalence of obesity among asthma patients treated at an asthma outpatient clinic,[7,35,36] a finding that is consistent with those of the present study, in which the BMI and percentage of body fat were found to be higher in females than in males. Of the patients in our sample, 155 (78.3%) were overweight (i.e., had a BMI ≥ 25 kg/m^2), and 133 (82%) were female. A high BMI has been associated with poor asthma control and quality of life.[22,33] Another finding that might have been influenced by excess weight and body fat is lung function. Dunn et al.[37] found that FEV_1 values were significantly higher in females than in males (84.5% vs. 81.1%; $p < 0.001$). However, in the present study, no significant differences were found between the genders regarding lung function parameters (i.e., percent predicted FVC, FEV_1, and FEV_1/FVC).

Asthma is often associated with various comorbidities, the most common being rhinitis, sinusitis, gastroesophageal reflux disease, obstructive sleep apnea, hormonal disorders, and psychopathologies.[38] These conditions might share a common pathophysiological mechanism with asthma, influence asthma control, or be more prevalent in asthma patients, having, however, no obvious influence on asthma.[38] Peters et al.[39] reported that comorbidities were significantly associated with uncontrolled asthma. In the present study, chronic and cardiovascular comorbidities were more commonly reported by females than by males. Cazzola et al.[40] reported that being female slightly increased the association of all cardiovascular diseases with asthma. They also reported that the association of asthma with diabetes mellitus, dyslipidemia, osteoporosis, depression, and psychiatric disorders was stronger in females than in males.

The present study has potential limitations. Given that it was a cross-sectional study, it was impossible to establish a temporal sequence between gender and the factors studied. In addition, this was a single-center study, and the sample size was small. Furthermore, the study population was selected from among patients treated at a referral center and was probably biased toward those with disease that is more severe.

In summary, health-related quality of life is lower in adult females with asthma than in adult males with asthma, as evidenced by lower scores in all four AQLQ domains. In addition, the proportion of patients with uncontrolled asthma is higher among females than among males, as are the BMI, percentage of body fat, and reported rates of comorbidities.

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J Bras Pneumol. 2018;44(4):279-284
http://dx.doi.org/10.1590/S1806-37562017000000031

ORIGINAL ARTICLE

Correlation of lung function and respiratory muscle strength with functional exercise capacity in obese individuals with obstructive sleep apnea syndrome

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Submitted: 7 February 2017.
Accepted: 7 December 2017.

Study carried out in the Ambulatório de Pneumologia, Hospital Otávio de Freitas – HGOF – Recife (PE) Brasil.

ABSTRACT

Objective: To evaluate lung function and inspiratory muscle strength, correlating them with exercise tolerance, in obese individuals with obstructive sleep apnea syndrome (OSAS). **Methods:** The sample comprised 31 adult subjects with moderate-to-severe OSAS diagnosed by polysomnography. We used spirometry to measure FVC, FEV_1, and FVC/FEV_1 ratio, using pressure manometry to measure MIP and MEP. The incremental shuttle walk test (ISWT) and the six-minute walk test (6MWT) were used in order to determine functional exercise capacity. **Results:** In this sample, the mean values for FVC (% of predicted), FEV_1 (% of predicted): MIP, and MEP were 76.4 ± 12.3%, 80.1 ± 6.3%, 60.0 ± 21.9 cmH_2O, and 81.3 ± 22.2 cmH_2O, respectively. The mean distances covered on the ISWT and 6MWT were 221 ± 97 m and 480.8 ± 67.3 m, respectively. The ISWT distance showed moderate positive correlations with FVC ($r = 0.658$; $p = 0.001$) and FEV_1 ($r = 0.522$; $p = 0.003$). **Conclusions:** In this sample of obese subjects with untreated OSAS, lung function, inspiratory muscle strength, and exercise tolerance were all below normal. In addition, we found that a decline in lung function, but not in respiratory muscle strength, was associated with exercise tolerance in these patients.

Keywords: Sleep apnea syndromes; Exercise tolerance; Respiratory function tests; Respiratory muscles.

INTRODUCTION

Obstructive sleep apnea syndrome (OSAS) is characterized by partial or total obstruction of the upper airways during sleep.[1-3] Obstructive events are associated with oxyhemoglobin desaturation, sleep fragmentation or deprivation, hypoxemia, hypercapnia, dyspnea, as well as diurnal symptoms such as excessive daytime sleepiness.[3,4] The etiology of OSAS is multifactorial, including craniofacial anatomical changes and obesity. Obese individuals present a higher risk of pharyngeal occlusion and altered respiratory mechanics.[5]

An increase in the volume of adipose tissue in the thoracic and abdominal regions impairs diaphragmatic function and reduces chest cavity compliance and lung volumes, leading to an increase in inspiratory muscle work.[6,7] Episodes of recurrent hypoxia in OSAS are usually accompanied by microarousals to reestablish normal ventilation after occlusion of the upper airways.[8] In addition, recurrent episodes of hypoxia and reoxygenation related to upper airway obstruction in OSAS are associated with abnormal partial pressure of oxygen and of carbon dioxide, reducing respiratory muscle activity and lung volumes. These factors generate new episodes of apnea-hypopnea throughout the night, limiting the ability to perform activities of daily living.[9-11]

Obesity and OSAS are factors that potentially alter aerobic capacity and exercise tolerance in different ways. The initial impairment of lung function and respiratory muscle function seen in obese individuals is related to reductions in functional exercise capacity and quality of life.[12,13] There is also evidence that the lower-than-normal exercise tolerance in OSAS patients is due to OSAS-related episodes of dyspnea, intermittent hypoxemia, respiratory muscle dysfunction, and pulmonary hypertension.[14,15] In obese patients with OSAS, cardiovascular diseases such as arterial hypertension, cardiac arrhythmia, and systolic dysfunction can also limit exercise tolerance, as can increased work of breathing, hypoventilation, and a sedentary lifestyle.[16,17]

The present study aimed to evaluate lung function and inspiratory muscle strength, correlating them with exercise tolerance, in obese individuals with OSAS.

METHODS

This was a cross-sectional, descriptive, observational study with quantitative analysis. We recruited individuals of either gender with a diagnosis of OSAS, confirmed through polysomnography, who were evaluated and treated at the Pulmonology Outpatient Clinic of the

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Financial support: This study received financial support from *Coordenação de Aperfeiçoamento de Pessoal de Nível Superior* (CAPES, Office for the Advancement of Higher Education).

Hospital Otávio de Freitas, located in the city of Recife (PE), Brazil. We applied the following inclusion criteria: having been diagnosed with moderate or severe OSAS; being between 50 and 70 years of age; being able to perform stress tests for functional capacity assessment; and having a body mass index (BMI) between 18 kg/m^2 and 40 kg/m^2. Patients with mild apnea—defined as a apnea-hypopnea index (AHI) between 5-15 events/h—were excluded, as were those with cardiopulmonary, neuromuscular, or orthopedic diseases that could influence or limit their ability to perform the tests, those with a BMI > 40 kg/m^2, and those being treated with continuous positive airway pressure. We initially evaluated 150 patients for eligibility, and 81 of those patients did not meet the inclusion criteria. Therefore, 69 patients were selected to perform the tests. However, 38 were excluded during the evaluation. Consequently, the final sample comprised 31 patients (Figure 1).

The sample size calculation was performed with MedCalc software, version 17.9.5 (MedCalc Software, Mariakerke, Belgium), considering as parameters a probabilistic error of 0.05 (5% alpha) and a statistical power of 80%. Thus, the minimum number of subjects required was calculated to be 24.

The research was approved by the human research ethics committee of the institution. All participants gave written informed consent.

All of the patients completed the Pittsburgh Sleep Quality Index questionnaire, which evaluates sleep quality in the last month.[18] The Epworth Sleepiness Scale was used for the evaluation of excessive daytime sleepiness.[19] The heart rate was measured with a heart monitor (model FT1; Polar, Kempele, Finland). Blood pressure was measured with an aneroid sphygmomanometer with an arm cuff (Premium model; Missouri Mikatos, Embu, Brazil) and a Rappaport premium stethoscope (Accumed, Rio de Janeiro, Brazil). The heart rate was measured at rest and immediately after the test. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured at rest, 1 min after the test, 3 min after the test, 5 min after the test, and 10 min after the test. The measurement of MIP and MEP followed the methodological recommendations of the American Thoracic Society/European Respiratory Society[20] and the Brazilian Thoracic Association,[21] with the use of a manometer (model MVD300; Globalmed, Porto Alegre, Brazil). We selected three (not necessarily sequential) tests that were considered acceptable (i.e., that met the reproducibility criteria). We used the measurement with the highest value, as long as it did not vary more than 10% in relation to the other values.

Through spirometry, also following the methodological recommendations of the Brazilian Thoracic Association,[21] the following variables were obtained: FVC, FEV_1, and the FEV_1/FVC ratio.

We applied the incremental shuttle walk test (ISWT), in which the patient has to walk a 20-m path (10 m forward and 10 m back), according to the protocol

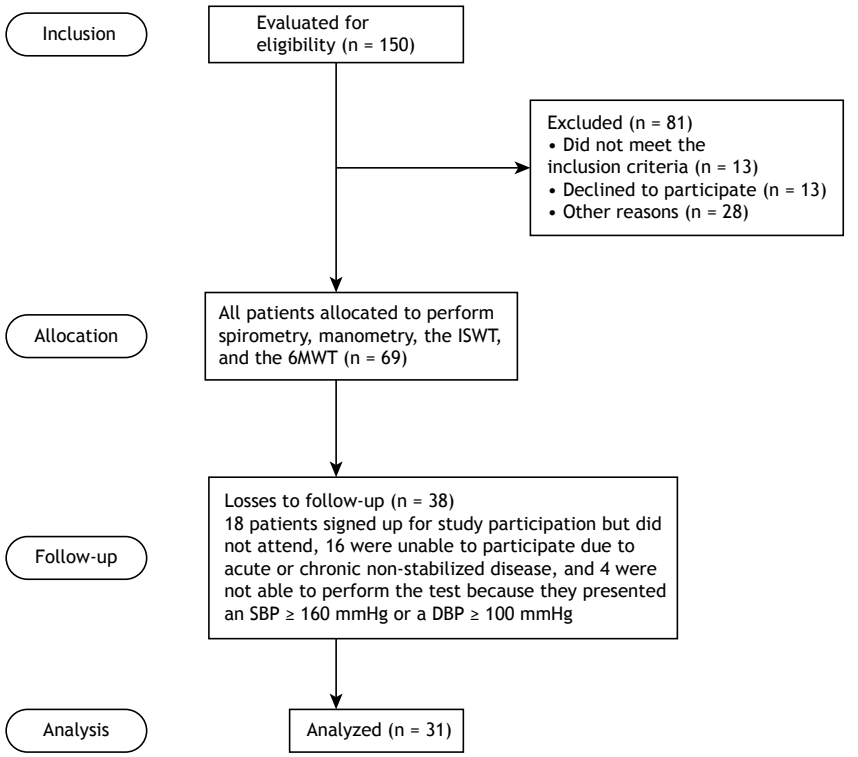

Figure 1. Flowchart of the study selection, allocation, follow-up, and analysis. ISWT: incremental shuttle walk test; 6MWT: six-minute walk test; SBP: systolic blood pressure; and DBP: diastolic blood pressure

developed by Singh et al.[22] The path was delineated with two traffic cones. We also applied the six-minute walk test (6MWT), which was performed in accordance with the American Thoracic Society specifications.[23]

Descriptive analyses were presented as a mean ± standard deviation or as median and interquartile range, as appropriate, according to the results of the Kolmogorov-Smirnov test. The correlations between variables were analyzed by Spearman's test, and the differences between the means were evaluated with the Student's t-test for independent samples. Values of $p < 0.05$ were considered significant. The data were processed with the Statistical Package for the Social Sciences, version 16.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Table 1 presents demographic and polysomnographic characteristics of the population studied. We evaluated 31 patients, of whom 10 (32.2%) were male and 21 (67.8%) were female. The mean age was 58.8 ± 5.4 years, and the mean BMI was 31.2 ± 5.0 kg/m^2. The mean AHI was 35.0 ± 12.8 events/h. Of the 31 patients evaluated, 14 (45.2%) had moderate OSAS and 17 (54.8%) had severe OSAS. Although all of the patients had poor sleep quality according to the Pittsburgh Sleep Quality Index, none showed excessive daytime sleepiness according to the Epworth Sleepiness Scale.

Table 2 presents data on lung function and respiratory muscle strength.

Table 3 presents comparisons of heart rates and blood pressure levels during the ISWT and the 6MWT. The following variables were significantly higher during the ISWT than during the 6MWT: SBP 1 min after the test ($p = 0.004$), SBP 3 min after the test ($p = 0.01$), SBP 5 min after the test ($p = 0.03$), DBP 3 min after the test ($p = 0.07$), and DBP 5 min after the test ($p = 0.001$). The other variables did not present significant differences in the comparison between the two tests.

Table 4 shows Spearman's correlation coefficients for the anthropometric, spirometric, and inspiratory muscle strength variables related to the distances covered on the ISWT and the 6MWT. There was a strong, positive correlation between FVC and the distance covered on the ISWT ($r = 0.658$, $p = 0.001$), as well as a moderate positive correlation between the FEV_1 and the distance covered on the ISWT ($r = 0.522$; $p = 0.003$). However, we found no correlations in relation to any of the other parameters evaluated.

Table 1. Characteristics of the sample (N = 31).[a]

Variables	Results
Female	21 (67.7)
Age, years	58.8 ± 5.4
Weight, kg	82.2 ± 16.7
Height, m	1.63 ± 0.06
BMI, kg/m	2 31.2 ± 5.0
Abdominal circumference, cm	99.4 ± 16.7
Neck circumference, cm	35.7 ± 2.8
AHI, events/h	35.0 ± 12.8
15-30 events/h	14 (45.2)
> 30 events/h	17 (54,8)
ESE	9.19 ± 4.4
PSQI	6.48 ± 1.61
Comorbidities[b]	
Hypertension	29 (91.0)
Diabetes	22 (61.5)

BMI: body mass index; AHI: apnea-hypopnea index; ESS: Epworth Sleepiness Scale; and PSQI: Pittsburgh Sleep Quality Index.[a]Values expressed in n (%) or mean ± SD.[b]Patients with these comorbidities were receiving antihypertensive or hypoglycemic medications.

DISCUSSION

The main findings of the present study show that, in our obese patients with OSAS, lung function and inspiratory muscle strength were impaired. In addition, the functional exercise capacity was reduced and there was a significant positive correlation between the distance covered on the ISWT and the variables related to pulmonary function.

In the present study, the values obtained for spirometric parameters and respiratory muscle strength were lower than the reference values for the healthy Brazilian population.[24] In the study conducted by Tassinari et al.,[25] no impairment of lung function or the respiratory musculature was observed in patients with OSAS. However, the OSAS patients evaluated in that study were of normal weight, unlike those in our sample, all of whom were obese. Likewise, Gontijo et al.,[26] studying obese individuals who did not present OSAS, obtained spirometric values within the limits of normality. The authors concluded that obesity would not be a factor associated with impairment of lung function. Studies indicate that obese individuals, due to the deposition of fat in the chest wall and abdomen, present a reduction in thoracic compliance, thus increasing the total work of breathing.[3,27,28] The upper airway collapse and the apnea-hypopnea events resulting from OSAS have respiratory consequences, such as hypoxemia, alveolar hypoventilation, and hypercapnia. Hypoxia-reoxygenation events lead to the activation of peripheral chemoreceptors leading to increased ventilation to correct alterations in blood gases.[10] Changes in O_2 and CO_2 concentrations result in a decrease in respiratory muscle activity and a reduction in lung volumes.[8,9]

Table 2. Data on pulmonary function and respiratory muscle strength.[a]

Variable	Result
FVC, L	2.4 ± 0.6
FVC, % predicted	76.4 ± 12.3
FEV_1,% predicted	80.1 ± 6.32
FEV_1, L	2.0 ± 0.4
FEV_1/FVC ratio	79.6 ± 5.8
MIP, cmH_2O	60.0 ± 21.9
MEP, cmH_2O	81.3 ± 22.2

[a]Values expressed as mean ± SD.

Table 3. Variables collected during the incremental shuttle walk test and the six-minute walk test.[a]

Variable	ISWT	6MWT	Δintergroup (95% CI)	p*
$HR_{rest,}$ bpm	72.9 ± 7.9	73.2 ± 8.3	−2.5 (−4.3 to 3.6)	0.901
$HR_{max,}$ bpm	121.9 ± 14.7	109.7 ± 18.6	12.1 (3.6-20.7)	0.006
SBP_{rest}, mmHg	117.1 ± 5.8	115.8 ± 6.7	1.2 (−1.9 to 4.4)	0.424
$SBP_{recovery\ 1'}$, mmHg	152.2 ± 13.0	138.3 ± 10.0*	13.8 (7.9-19.7)	0.001
$SBP_{recovery\ 3'}$, mmHg	137.1 ± 9.4	128.0 ± 7.9*	9.0 (4.6-13.4)	0.01
$SBP_{recovery\ 5'}$, mmHg	127.4 ± 6.3	119.3 ± 6.9*	8.0 (4.7-11.3)	0.001
$SBP_{recovery\ 10'}$, mmHg	119.3 ± 4.4	117.1 ± 5.8	2.2 (−3.8 to 4.9)	0.093
DBP_{rest}, mmHg	82.5 ± 7.2	82.2 ± 7.1	3.3 (−3.3 to 3.8)	0.861
$DBP_{recovery\ 1'}$, mmHg	118.0 ± 10.4	108.0± 11.3*	10.0 (4.4-15.5)	0.001
$DBP_{recovery\ 3'}$, mmHg	112.9 ± 9.3	103.5 ± 13.5*	9.3 (3.4-15.2)	0.002
$DBP_{recovery\ 5'}$, mmHg	101.9 ± 12.2	88.0 ± 11.3*	13.8 (7.8-19.8)	0.001
$DBP_{recovery\ 10'}$, mmHg	88.0 ± 11.3	82.9 ± 7.8*	5.1 (0.19-10.1)	0.042
Walk distance, m	221.0 ± 97.0	480.8 ± 67.3		

ISWT: incremental shuttle walk test; 6MWT: six-minute walk test; SBP: systolic blood pressure; and DBP: diastolic blood pressure. [a]Values expressed as mean ± SD. *t-test for independent samples.

Table 4. Correlation between the selected variables and the distances covered on the incremental shuttle walk test and six-minute walk test.

Variables	ISWT		6MWT	
	r	p	r	p
BMI	−0.320	0.07	−0.062	0.741
FEV_1	0.522	0.003	0.117	0.532
FVC	0.658	0.001	0.189	0.308
MIP	0.075	0.069	−0.105	0.575
Abdominal circumference	0.056	0.996	−0.110	0.858
Neck circumference	−0.032	0.862	−0.121	0.574
AHI	0.070	0.710	−0.111	0.551

ISWT: incremental shuttle walk test; 6MWT: six-minute walk test; BMI: body mass index; and AHI: index of apnea and hypopnea.

Regarding the association between pulmonary function and exercise tolerance, we found that FVC and FEV_1 showed significant positive correlations with the distance covered on the ISWT. This finding demonstrates that smaller lung volumes translate to lower exercise tolerance, underscoring the idea that pulmonary function affects exercise capacity in individuals with OSAS. Impairment of exercise capacity in obese individuals was also shown in another study, in which the authors concluded that being overweight is associated with a loss of self-esteem and lower psychic well-being.[29] Factors such as dyspnea, abnormalities in respiratory mechanics, respiratory muscle dysfunction, and arterial hypoxemia contribute to limiting exercise tolerance in OSAS patients.[14]

In our study, the distance covered on both walk tests was lower than the reference distance for healthy individuals in the Brazilian population,[30-32] indicating that exercise tolerance was below normal in our obese patients with OSAS. The patients in our sample also had comorbidities such as hypertension and type 2 diabetes mellitus. Exercise tolerance is directly related to the good performance of the cardiopulmonary system. Therefore, the impairment of functional exercise capacity in OSAS patients is multifactorial, being associated with obesity, a sedentary lifestyle, cardiovascular diseases, dyspnea, and respiratory abnormalities.[14,15] However, there are conflicting data regarding the impaired exercise capacity resulting from the combination of OSAS with obesity in relation to exercise capacity. A study conducted by Beitler et al.[11] showed that peak oxygen consumption (VO_{2peak}) was significantly lower in obese OSAS patients than in controls, also reporting an association between VO_{2peak} and the AHI. In contrast, Rizzi et al.,[15] in a study of normal-weight OSAS patients, observed no impairment of the functional exercise capacity. However, in a subsequent study—a randomized clinical trial involving obese and normal-weight individuals, with or without OSAS—Rizzi et al.[33] observed a significant difference in exercise tolerance between the obese and non-obese groups regardless of the presence ofOSAS, in terms of CO_2 production and the maximum VO_2. The authors concluded that obesity would be the main condition of low functional capacity, given that the obese patients presented low exercise tolerance, regardless of the presence or absence of OSAS.

Regarding the cardiovascular responses to the 6MWT in the present study, the cardiac parameters measured immediately after the test demonstrated marked

increases in relation to the data collected during the test, results that are in agreement with those obtained by Rizzi et al.[33] in their study of obese patients with OSAS. However, the cardiovascular responses were even more pronounced during and after the ISWT, as was also reported by Gonçalves et al.[34] in a study of healthy individuals. In another study involving obese patients with OSAS, in which cardiopulmonary exercise testing (CPET) with the Bruce protocol was employed,[34] patients with severe apnea were found to show an increase in blood pressure during peak exercise with a return to basal blood pressure levels after exercise. Green et al.[35] stated that the ISWT provokes a physiological response to exercise similar to that observed during CPET.

Although the 6MWT is a standard test in the clinical assessment of effort in patients with OSAS[25] and obese patients,[36] the ISWT has also proven to be feasible and reliable in the assessment of effort tolerance in individuals with OSAS. Green et al.[35] studied patients with heart failure, comparing the responses obtained with CPET, the ISWT, and the 6MWT. They concluded that the ISWT provided a valid index to determine functional capacity in individuals with heart failure and that the predictive power of the ISWT could exceed that of the 6MWT. In a study evaluating patients with moderate or severe OSAS, Billings et al.[37] used the ISWT to compare physical fitness before and after treatment with continuous positive airway pressure. The authors concluded that the ISWT is safe, well tolerated, and easily reproducible in OSAS patients, supporting the idea that it can be used safely in the evaluation of exercise tolerance in such patients.

Our study has limitations, such as the small sample size. However, the number of patients evaluated was within the limits set in the sample calculation. In addition, we did not perform CPET, which is the gold standard test in the analysis of functional capacity and of cardiopulmonary impairment and would have allowed a more reliable evaluation of the cardiovascular parameters, as well as their subsequent correlation with those found on the two other tests. Another limitation was the fact that our study evaluated only obese patients with OSAS and there was no control group of obese patients without OSAS. Furthermore, data regarding cardiovascular comorbidities were not available for the patients in the sample studied. Therefore, studies with greater methodological rigor, such as randomized clinical trials, are needed in order to increase knowledge about the subject in the future.

The results found in the present study show that obese subjects with untreated OSAS presented below-normal lung function, inspiratory muscle strength, and physical capacity. In addition, it was observed that the decline in lung function, but not inspiratory muscle strength, is associated with physical effort tolerance in these patients, which makes it necessary to use therapeutic interventions to improve variables such as physical exercise. We can also emphasize that the ISWT was able to evaluate the exercise tolerance in OSAS, making it quite useful in the clinical investigation of the disease, due to its low cost, reproducibility, and ease of application.

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J Bras Pneumol. 2018;44(4):285-291
http://dx.doi.org/10.1590/S1806-37562017000000154

ORIGINAL ARTICLE

Translation, cross-cultural adaptation, and reliability of the Understanding COPD questionnaire for use in Brazil

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Submitted: 8 May 2017.
Accepted: 7 December 2017.

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ABSTRACT

Objective: To translate the Understanding COPD (UCOPD) questionnaire into Portuguese, adapt it for use in Brazil, and assess its reliability. **Methods:** The UCOPD questionnaire consists of two sections, designated section A and section B. Section A comprises 18 items divided into three domains: "About COPD", "Managing Symptoms of COPD", and "Accessing Help and Support". Section B includes five questions regarding patient satisfaction with the educational component of pulmonary rehabilitation programs. The UCOPD questionnaire was applied twice on the same day by two different raters (with a 10-min interval between applications) and once again 15-20 days later. The Wilcoxon test was used in order to compare the scores among applications. Reliability was assessed by the intraclass correlation coefficient and Bland-Altman plots. **Results:** The study sample consisted of 50 COPD patients (35 men; mean age, 65.3 ± 7.91 years; mean FEV_1, 36.4 ± 16.2% of the predicted value). Inter-rater intraclass correlation coefficients for section A total scores and domain scores ranged from moderate to high. Section A scores and domain scores had no significant differences regarding test-retest reliability ($p < 0.05$). The test-retest and inter-rater Cronbach's alpha coefficients for section A total scores were 0.93 and 0.86, respectively ($p < 0.001$). There were no floor or ceiling effects. **Conclusions:** The Brazilian Portuguese version of the UCOPD questionnaire is reliable.

Keywords: Pulmonary disease, chronic obstructive; reproducibility of results; Health knowledge, attitudes, practice.

INTRODUCTION

Education is one of the key components of pulmonary rehabilitation programs (PRPs) for patients with COPD. In recent years, it has received greater attention because it can teach patients how to cope with their disease and because it can increase the likelihood of their adopting self-management strategies.[1]

Education involves activities that encourage patients and their families to learn more about and, consequently, gain a deeper understanding of the disease, thus improving patient self-efficacy.[1,2] Education plays an important role in promoting behavioral changes,[2,3] which are necessary because patients may not actively engage in appropriate behaviors which could improve their health outcomes.[4] This might be due to a lack of understanding of the importance of appropriate behavior or to a lack of disease-related self-efficacy. Educational interventions can change these outcomes and have proved to be effective in patients with COPD, being associated with improvement in self-management skills,[2] i.e., improved medication use, increased ability to manage disease exacerbations, and increased ability to achieve disease management goals.[5] However, despite its importance, education is seldom evaluated in PRPs because there are only a few instruments available for this purpose. The Understanding COPD (UCOPD) questionnaire,[4] the Bristol COPD Knowledge Questionnaire (BCKQ),[6] the Lung Information Needs Questionnaire (LINQ),[7] and the Mount Sinai Hospital Questionnaire[8] have been developed to assess patient knowledge of COPD. The UCOPD questionnaire stands out because, in addition to evaluating patient understanding of COPD, it assesses self-efficacy, use of self-management skills, and patient satisfaction with a given PRP.[4] However, there is currently no Brazilian Portuguese version of the UCOPD questionnaire. Therefore, given the importance of an instrument that can evaluate the effect of the educational component of PRPs, the objective of the present study was to translate the UCOPD questionnaire into Brazilian Portuguese and determine the reliability of the Brazilian Portuguese version of the questionnaire.

METHODS

Fifty patients with COPD referred to the *Núcleo de Assistência, Ensino e Pesquisa em Reabilitação Pulmonar* of

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Financial support: None.

the *Universidade do Estado de Santa Catarina*, located in the city of Florianópolis, Brazil, were included in the study. The inclusion criteria were as follows: having a clinical diagnosis of COPD confirmed by spirometry in accordance with the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria[9] and self-reporting the ability to read in Brazilian Portuguese.

Patients unable to understand the questionnaire or to follow instructions were excluded (a Mini-Mental State Examination score of 18/19 for patients without previous formal education and a score of 24/25 for patients with previous formal education).[10] In addition, patients with any other severe or limiting respiratory or nonrespiratory disease were excluded. The local research ethics committee approved the study (CAAE protocol no. 11603112.1.0000.0118), and all participants gave written informed consent. The relevant measurement properties of the UCOPD questionnaire were evaluated in accordance with the recommendations of the Consensus-based Standards for the Selection of Health Status Measurement Instruments.[11] The authors of the original version authorized the cross-cultural adaptation of the UCOPD questionnaire.

The cross-cultural adaptation protocol was as recommended by Guillemin et al.[12] First, the English version of the UCOPD questionnaire[4] was translated into Brazilian Portuguese by two independent bilingual translators who are fluent in English and native speakers of Brazilian Portuguese, one of whom had no specific knowledge of health. A summary of the translations was made by a translation review committee, comprising the first author of the original questionnaire, the translators, and health professionals. That version was subsequently back-translated by a health professional who is a native speaker of English and fluent in Portuguese. The back-translator had previously had no contact with the questionnaire.

That first version was applied to 8 patients with COPD in order to identify uncertainties and difficulties regarding the text. Afterwards, issues raised by those patients were discussed by the review committee, and a consensus was reached. The final version of the instrument did not require cross-cultural adaptations or changes in the original structure. Although the name of the questionnaire was translated into Portuguese, a decision was made to keep the original, English-language abbreviation of the name (i.e., UCOPD) in the Brazilian Portuguese version of the questionnaire so as to facilitate recognition of the instrument. Appendix 1 (http://jornaldepneumologia.com.br/detalhe_anexo.asp?id=56) shows the final version of the translated questionnaire.

The Brazilian Portuguese version of the UCOPD questionnaire was tested for inter-rater and test-retest reliability. On the first day, the questionnaire was applied twice by two raters (R1 and R2) in the following order: first by R1 and 10 min later by R2. After 15-20 days, it was reapplied by R2.[13]

The UCOPD questionnaire[4] consists of two sections: section A has 18 items in three domains: "About COPD", "Managing Symptoms of COPD", and "Accessing Help and Support"; section B has five questions regarding patient satisfaction with the educational component of the PRP. The answers to each question are indicated on a ten-centimeter visual analog scale with numerical intervals per centimeter.

The scores for the domains and the total score for section A range from 0% to 100%. The higher the score, the better the understanding, self-efficacy, medication use, and satisfaction. To calculate the scores for each domain, the scores for the individual questions in the domain are added up, divided by the maximum score for the domain, and multiplied by 100. The maximum scores for the domains, as well as total scores for sections A and B, are as follows: About COPD domain (questions 1-7), 70; Managing Symptoms of COPD domain (questions 8-14), 70; Accessing Help and Support domain (questions 15-18), 40; section A total score (questions 1-18), 180; and section B total score (questions 1-5), 50.[4]

For sample characterization, participants underwent spirometry (EasyOne® spirometer; ndd Medical Technologies, Zurich, Switzerland) in accordance with the American Thoracic Society/European Respiratory Society standards.[14] The predicted values were obtained from the equations proposed by Pereira et al.[15] The spirometric and multidimensional GOLD classifications[9] were used in order to stratify the severity of COPD. The Brazilian Portuguese versions of the Saint George's Respiratory Questionnaire (SGRQ)[16] and the COPD Assessment Test (CAT)[17] were applied to all participants, who were also evaluated regarding their physical activity in daily life (PADL) for 12 h on two consecutive week days.[18]

Data are presented as mean ± standard deviation and 95% confidence interval. We used the Wilcoxon test to compare the scores of the UCOPD questionnaire between the applications. The mixed two-way, single-measure intraclass correlation coefficient (ICC) and respective 95% CIs were used in order to analyze the reliability of UCOPD questionnaire, whereas the Cronbach's alpha coefficient was used to analyze the internal consistency of the questionnaire. The classification used for the ICC was as follows: low reproducibility, ICC < 0.40; moderate reproducibility, ICC ≤ 0.75; and high reproducibility, ICC > 0.75.[19]

Bland-Altman plots were used in order to represent the agreement between the UCOPD questionnaire scores, whereas the Spearman's correlation coefficient was used in order to assess the correlation of UCOPD questionnaire scores with SGRQ and CAT scores, as well as with the level of PADL. The standard error of measurement and the minimum detectable difference (MDD) were calculated as described by Terwee et al.[20] For the analysis of the floor and ceiling effects, the proportions of occurrence of the minimum (0%) and maximum (100%) scores for section A of the UCOPD questionnaire were used.[20] The significance level

was 5%. Data analysis was performed with the IBM SPSS Statistics software package, version 20.0 (IBM Corporation, Armonk, NY, USA), and graphics were created using the GraphPad Prism program, version 5.0 (GraphPad Inc., San Diego, CA, USA). In order to estimate the sample size, in accordance with the Consensus-based Standards for the Selection of Health Status Measurement Instruments[21] recommendation, 50 patients were selected (good sample size). Sample size calculation was also based on an expected ICC of 0.50 for moderate reliability,[19] $\alpha = 0.05$, and $\beta = 0.10$, yielding a sample size of 38 patients.[22]

RESULTS

Fifty-five patients with COPD were enrolled in the study. Of those, 2 were excluded for not completing the protocol and 3 because of disease exacerbation during the protocol. Therefore, 50 patients completed the protocol (35 males). Table 1 presents the characteristics of the patients.

The level of education varied among the patients: 7 (14%) had completed college; 4 (8%) had not completed college; 17 (34%) had completed high school; 2 (4%) had not completed high school; 4 (8%) had completed elementary school; 15 (30%) had not completed elementary school; and 1 (2%) had never attended school.

There were no differences in test-retest reliability scores for section A total score and its domains. There were significant differences in About COPD domain scores between R1 and R2 (Table 2). Table 2 shows the scores for section A and its domains, as well as test-retest and inter-rater ICCs, which ranged from satisfactory to excellent. None of the patients scored 0% or 100%.

Table 1. Characteristics of the COPD patients included in the present study (N = 50).[a]

Variable	Result
Age, years	65.3 ± 7.91
BMI, kg/m^2	25.5 ± 4.81
FEV_1/FVC	0.45 ± 0.10
FVC, L	2.31 ± 0.73
FVC, % predicted	61.1 ± 18.0
FEV_1, L	1.07 ± 0.48
FEV_1, % predicted	36.4 ± 16.2
Mini-Mental State Examination score	27.3 ± 2.65
CAT	16.6 ± 7.79
GOLD, stages II-III-IV, n (%)	
II	12 (24)
III	18 (36)
IV	20 (40)
GOLD, stages A-B-C-D, n (%)	
A	02 (04)
B	10 (20)
C	06 (12)
D	32 (64)

BMI: body mass index; CAT: COPD Assessment Test; and GOLD: Global Initiative for Chronic Obstructive Lung Disease. [a]Values expressed as mean ± SD, except where otherwise indicated.

In the agreement analysis, inter-rater Cronbach's alpha coefficients for section A total score and its domains (About COPD, Managing Symptoms of COPD, and Accessing Help and Support) were 0.93, 0.94, 0.83, and 0.94, respectively ($p < 0.001$ for all).

In 11 of the 18 items in section A, ICCs were higher than 0.75 ($p < 0.001$). Items 3, 7, 8, 9, 13, 14, and 15 showed satisfactory reproducibility (an ICC of 0.54-0.68; $p < 0.001$). Of those items, 4 belonged to the Managing Symptoms of COPD domain.

With regard to test-retest reliability, the Cronbach's alpha coefficient for section A total score was 0.86 ($p < 0.001$), and those for About COPD, Managing Symptoms of COPD, and Accessing Help and Support domain scores were 0.83, 0.76, and 0.87, respectively ($p < 0.001$). The ICCs were higher than 0.75 in 8 of the 18 items ($p < 0.001$). However, ICCs ranged from 0.43 to 0.70 for items 3, 4, 7, 8, 9, 10, 12, 14, 15, and 17. Five of the 7 items in the Managing Symptoms of COPD domain had ICCs lower than 0.75. The standard error of measurement was 6, and the MDD was 16.6.

Figure 1 shows the agreement between R1 and R2. There was a wide variability among UCOPD questionnaire applications, which was more pronounced in the test-retest analysis (Figure 2).

UCOPD questionnaire domain scores correlated weakly with CAT and SGRQ scores, as well as with the level of PADL. UCOPD questionnaire section A scores correlated with the total SGRQ score ($r = -0.38$; $p = 0.007$) and SGRQ "impacts" domain scores ($r = -0.46$; $p = 0.001$), as well as with sitting ($r = -0.33$; $p = 0.024$), standing ($r = 0.33$; $p = 0.023$), and walking times ($r = 0.30$; $p = 0.04$). UCOPD questionnaire About COPD domain scores correlated with the total SGRQ score ($r = -0.30$; $p = 0.033$) and SGRQ impacts domain scores ($r = -0.35$; $p = 0.014$), as well as with sitting time ($r = -0.32$; $p = 0.027$). UCOPD questionnaire Managing Symptoms of COPD domain scores correlated with SGRQ impacts domain scores ($r = -0.35$; $p = 0.014$), whereas UCOPD questionnaire Accessing Help and Support domain scores correlated with the CAT score ($r = -0.30$; $p = 0.042$), the total SGRQ score ($r = -0.42$; $p = 0.003$), SGRQ "activity" domain scores ($r = -0.33$; $p = 0.019$), SGRQ impacts domain scores ($r = -0.48$; $p = 0.013$), sitting time ($r = -0.38$; $p = 0.004$), standing time ($r = 0.42$; $p = 0.003$), and walking time ($r = 0.35$; $p = 0.013$), as well as with a level of PADL ≥ 3 metabolic equivalents ($r = 0.33$; $p = 0.021$). No correlations were found between FEV_1 and the total UCOPD questionnaire score or between FEV_1 and UCOPD questionnaire domain scores (values of $p = 0.24$-0.88).

DISCUSSION

The major finding of the present study is that the UCOPD questionnaire is reliable and able to reflect

Table 2. Scores, test-retest intraclass correlation coefficients, and inter-rater intraclass correlation coefficients for the Understanding COPD questionnaire (section A total score and domain scores).[a]

Section A total score and domain scores	Rater 1	Rater 2 test	Rater 2 retest
About COPD (%)	66.1 ± 18.9	71.0 ± 19.5	72.8 ± 18.9*
Managing Symptoms of COPD (%)	67.0 ± 19.0	63.4 ± 20.1	67.3 ± 18.1
Accessing Help and Support (%)	65.2 ± 28.9	64.9 ± 30.3	69.2 ± 27.8
Section A, total (%)	62.3 ± 16.1	62.9 ± 18.4	66.0 ± 16.4
Section A total score and domain scores	Inter-rater ICC (95% CI)		Test-retest ICC (95% CI)
About COPD	0.85 (0.70-0.92)		0.72 (0.56-0.83)
Managing Symptoms of COPD	0.70 (0.53-0.82)		0.61 (0.41-0.76)
Accessing Help and Support	0.89 (0.81-0.93)		0.77 (0.63-0.86)
Section A, total	0.88 (0.79-0.93)		0.74 (0.59-0.88)

ICC: intraclass correlation coefficient. [a]Values expressed as mean ± SD, except where otherwise indicated. *p < 0.05 vs. rater 1.

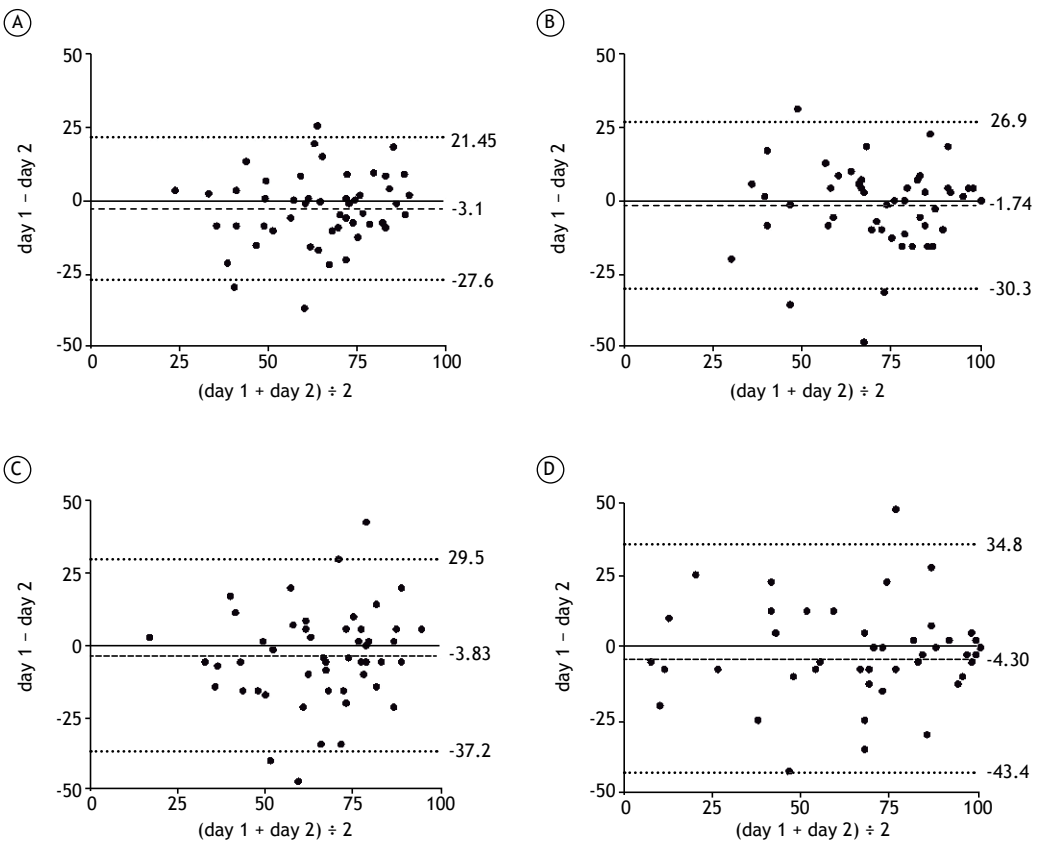

Figure 1. Bland-Altman plots for inter-rater reliability. In A, section A total score; in B, "About COPD" domain scores; in C, "Managing Symptoms of COPD" domain scores; and in D, "Accessing Help and Support" domain scores.

quality of life, health status, and PADL in patients with COPD in Brazil. The test-retest reliability and the inter-rater reliability of the total score for section A of the UCOPD questionnaire were excellent. The reliability of the domains ranged from satisfactory to excellent, the ICCs being lowest for the Managing Symptoms of COPD domain and the test-retest reliability analysis.

In the study of development and validation of the UCOPD questionnaire,[4] the authors found excellent reliability of the domains and section A total score. Interestingly, the Managing Symptoms of COPD domain had the highest ICC among the UCOPD questionnaire domains (ICC = 0.92; 95% CI: 0.81-0.97). Some factors can explain why the results of the present study differed from the aforementioned results. O'Neill et al.[4] included only patients who had a good understanding of written English, and the questionnaire was self-administered. Given that most of the elderly individuals in Brazil have low levels of education,[23] the UCOPD questionnaire was completed by interviewing the participants. Although this is permitted according to the UCOPD questionnaire application instructions, the low education level of the

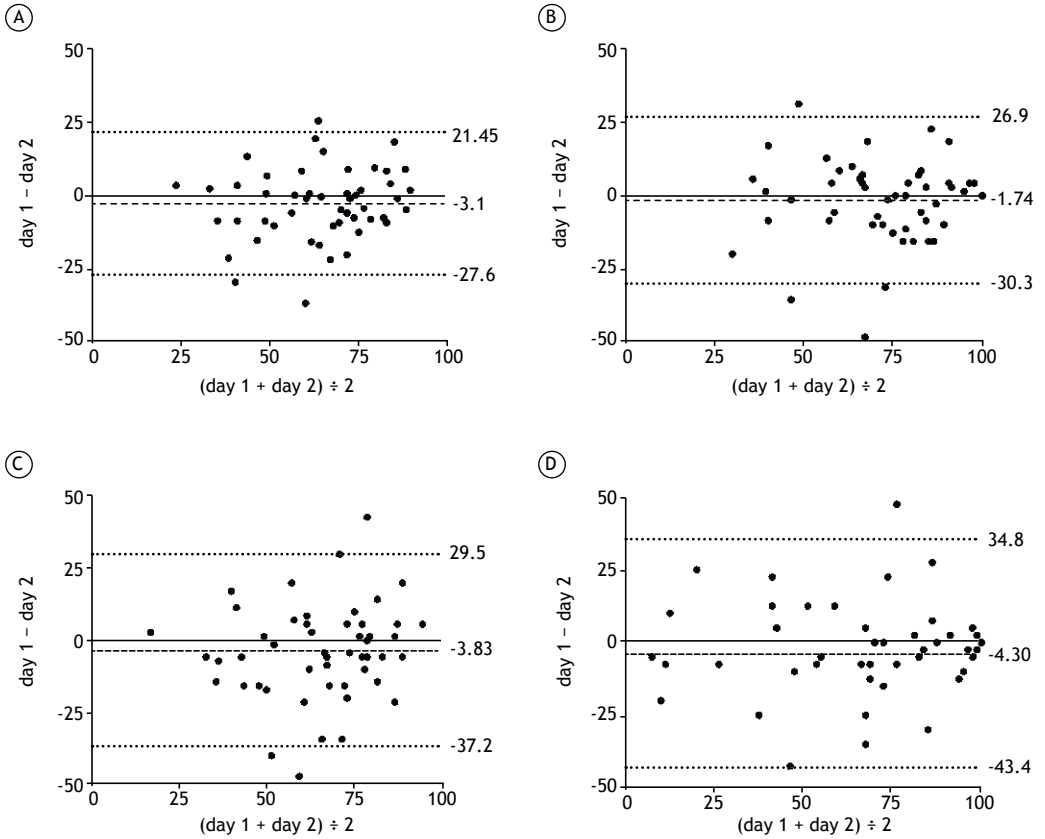

Figure 2. Bland-Altman plots for test-retest reliability. In A, section A total score; in B, "About COPD" domain scores; in C, "Managing Symptoms of COPD" domain scores; and in D, "Accessing Help and Support" domain scores.

majority of the study participants (32% of whom had not completed elementary school) could have affected patient understanding of the Managing Symptoms of COPD domain items and, consequently, contributed to reducing its reliability. However, it was decided not to exclude those patients from the sample. Had they been excluded, the sample would no longer have been representative of the Brazilian population, the external validity of the instrument therefore being compromised.

The reliability of section B of the UCOPD questionnaire was not analyzed in the present study or in the original study.[4] Section B of the UCOPD questionnaire has been reported to have high internal consistency and concordance.[4] In the present study, section B was administered to 7 patients, all of whom had completed a PRP, and the answers were the same for all items. It is worth mentioning that section B is aimed at evaluating patient satisfaction with the education sessions; it is not part of the evaluation of patient knowledge and self-efficacy.

Given the lack of a previously validated instrument to assess knowledge and self-efficacy in COPD patients in Brazil, it was impossible to test the concurrent validity of the UCOPD questionnaire. A correlation of 0.303 ($p = 0.002$) has been obtained between the English-language version of the UCOPD questionnaire and the BCKQ.[4] The association with other outcomes, however, has yet to be tested. Despite weak correlations, it appears that patients with limited knowledge of COPD have impaired quality of life, increased sitting time, and reduced time spent in active postures (walking and standing). It appears that the more patients know about their disease and the more confident they feel about how much they know about it, the more active they become and the better their quality of life is. However, this has yet to be confirmed. Nevertheless, this reinforces the hypothesis that increasing patient knowledge and self-efficacy is an important strategy to promote long-term adherence to active and healthy behaviors.[1,24,25] In addition, this suggests that the UCOPD questionnaire is capable of reflecting other important outcomes, reinforcing its validity.

Although the educational component of PRPs is currently focused on promoting knowledge, self-care, and self-management, as well on increasing self-efficacy, there are only a few instruments that can be used in order to evaluate some or all of these outcomes: the UCOPD questionnaire, the BCKQ,[6] and the LINQ.[7] These instruments were developed in England and are reliable and valid; they can be used in order to assess patient response to educational programs[6] and PRPs.[26] However, to the best of our knowledge, there are currently no data regarding the translation and cross-cultural adaptation of these instruments

in Brazil. In addition, neither the BCKQ nor the LINQ address patient self-efficacy; they are used in order to assess patient knowledge. In contrast, in addition to assessing patient knowledge, the UCOPD questionnaire assesses patient self-efficacy and patient satisfaction with the educational component of PRPs.[4]

Self-efficacy is now regarded as one of the major outcomes to be assessed in patients participating in a PRP, because it appears to be associated with adoption and maintenance of active and healthy behaviors.[1] It is defined as the confidence that an individual has in their ability to deal with a specific task,[3] such as successfully managing their disease. Unlike the BCKQ or the LINQ, the UCOPD questionnaire addresses how confident patients are that they know what COPD is; that they can recognize an exacerbation; that they know when to seek medical attention; that they know how to use their COPD medication; and that they know how to exercise, among other questions. Therefore, it is an interesting tool that can aid in the identification and development of strategies for patients who, despite having good knowledge of their disease, are not confident about applying what they know or being able to manage their health, a lack of confidence that might result in nonadherence to treatment.

Despite cultural differences between Brazil and Northern Ireland, the Brazilian Portuguese version of the UCOPD questionnaire required no major adjustments. The final version of the questionnaire is the same as the first translated version, and its back-translation was approved by the first author of the original questionnaire. The Brazilian Portuguese version of the UCOPD questionnaire was found to be reliable, having no floor or ceiling effect. This finding is important because a floor/ceiling effect could compromise the discriminatory ability of the questionnaire or the detection of change over time/after an intervention.[20]

One potential limitation of the present study is the time elapsed between the two applications of the questionnaire (i.e., 10 min for inter-rater reliability analysis and 15-20 days for test-retest reliability analysis). Although one of the assumptions of the reliability test procedure is that the interval between applications should be short but long enough to avoid respondent memory bias,[27] we found no specific recommendations regarding how long that interval should be. Although the results of the present study were satisfactory, our interval between applications was longer than that in the original study. Therefore, it is possible that patient clinical status changed during that time interval, patient responses being influenced by that. Another possible limitation is that we did not test the responsiveness of the Brazilian Portuguese version of the UCOPD questionnaire to a PRP or other interventions. In addition, there are currently no data such as cut-off points and minimal clinically important difference to assist in interpreting the results of the UCOPD questionnaire. However, this was outside the scope of the present study, further studies therefore being required. Our finding of an MDD of 16.6 reflects the lowest intrapersonal variation; therefore, changes above this point showing a value of $p < 0.05$ can be considered "real".[20]

To the best of our knowledge, this is the first study designed to develop a Brazilian Portuguese version of the UCOPD questionnaire, which is a reliable questionnaire to assess patient knowledge of COPD and patient self-efficacy in managing the disease. Our findings can inform clinical practice, allowing the evaluation of the aforementioned outcomes and contributing to the development of strategies to improve them. In addition, they allow the evaluation of the results of educational programs.

In summary, when translating an outcome measure tool for use in a different country, it is important to ensure that the properties remain robust. The present study demonstrated that the Brazilian Portuguese version of the UCOPD questionnaire is reliable, has internal consistency, and has no floor or ceiling effects that might hinder its use in COPD patients in Brazil. In addition, the questionnaire is able to reflect health status, quality of life, and PADL in such patients. Further studies are needed in order to determine whether the Brazilian Portuguese version of the UCOPD questionnaire is responsive to PRPs.

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J Bras Pneumol. 2018;44(4):292-298
http://dx.doi.org/10.1590/S1806-37562017000000379

ORIGINAL ARTICLE

Hyperhidrosis: prevalence and impact on quality of life

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Submitted: 17 May 2017.
Accepted: 15 December 2017.

Study carried out at the Faculdade de Medicina de Botucatu, Universidade Estadual Paulista, UNESP, Botucatu (SP) Brasil.

ABSTRACT

Objective: To determine the prevalence of primary hyperhidrosis in the city of Botucatu, Brazil, and to evaluate how this disorder affects the quality of life in those suffering from it. **Methods:** A population survey was conducted in order to identify cases of hyperhidrosis among residents in the urban area of the city, selected by systematic cluster sampling. In accordance with the census maps of the city, the sample size should be at least 4,033 participants. Ten interviewers applied a questionnaire that evaluated the presence of excessive sweating and invited the subjects who reported hyperhidrosis to be evaluated by a physician in order to confirm the diagnosis. **Results:** A total of 4,133 residents, in 1,351 households, were surveyed. Excessive sweating was reported by 85 residents (prevalence = 2.07%), of whom 51 (60%) were female. Of those 85 respondents, 51 (60%) agreed to undergo medical evaluation to confirm the diagnosis and only 23 (45%) were diagnosed with primary hyperhidrosis (prevalence = 0.93%). Of the 23 subjects diagnosed with primary hyperhidrosis, 11 (48%) reported poor or very poor quality of life. **Conclusions:** Although the prevalence of self-reported excessive sweating was greater than 2%, the actual prevalence of primary hyperhidrosis in our sample was 0.93% and nearly 50% of the respondents with primary hyperhidrosis reported impaired quality of life.

Keywords: Hyperhidrosis/epidemiology; Hyperhidrosis/diagnosis; Quality of life.

INTRODUCTION

Hyperhidrosis is a disorder characterized by excessive sweating beyond the level physiologically required for thermoregulation.[1,2] Its etiology can be primary (idiopathic)—recent studies having tried to demonstrate a putative genetic link[3,4]—or secondary to other diseases, such as infections, neurological disorders, metabolic disorders, neoplasms, spinal cord injuries, anxiety, and stress.[5,6] For those suffering from it, hyperhidrosis causes profound embarrassment—at the social, psychological, professional, and emotional level. The degree of impairment of quality of life (QoL) in patients with hyperhidrosis is comparable to that seen in patients with chronic diseases, such as severe psoriasis, kidney failure, and advanced-stage rheumatoid arthritis.[7] It is still undetermined whether or not the incidence of hyperhidrosis is actually higher in females; the fact that women more often seek treatment for hyperhidrosis in clinical practice gives a false impression that it is predominant in females.[8,9] The areas commonly affected by primary hyperhidrosis (PH) are the scalp, face, hands, armpits, and feet. Making the distinction between PH and secondary hyperhidrosis (SH) is crucial to defining the most appropriate treatment. Video-assisted thoracoscopic sympathectomy is the standard treatment for PH of the hands and armpits,[10,11] with a clearly high level of satisfaction and a low rate of complications, especially for low nerve blocks.[12,13]

There are few data on the worldwide prevalence of hyperhidrosis, reported values ranging from 0.072% to 9%.[7,14-24] The studies performed to date have used diverse methods, evaluating populations in restricted age groups and with distinct characteristics.

The aim of this study was to establish the prevalence of PH and to determine how it affects the QoL of patients with the condition.

METHODS

Ethics

This study was initiated after approval by the Research Ethics Committee of the College of Medicine of Botucatu – State University of São Paulo (Reference no. 2831/08).

Study population

The study involved the residents of households in the urban area of the city of Botucatu, Brazil. We selected

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Financial support: This study received financial support from the São Paulo Research Foundation (Fundação de Amparo à Pesquisa do Estado de São Paulo, FAPESP).

ISSN 1806-3713

households by systematic cluster sampling, using census maps created by the Brazilian Institute of Geography and Statistics for population counts and household registration.[25]

Sample size calculation

The sample size for the city of Botucatu was calculated considering the prevalence of hyperhidrosis in the United States (2.8%).[15] Considering that the population over 5 years of age in Botucatu consisted of 113,055 residents, and using an accuracy of 0.5%, we calculated a sample size of 4,033 residents.[25]

According to data from the Brazilian Institute of Geography and Statistics, each household in Botucatu has approximately three residents; therefore, at least 1,344 households should be surveyed.

Pilot study

The pilot study involved a total of 30 households in two districts (Vitoriana and Rubião Junior). Field work personnel applied a questionnaire developed by the researchers in order to test it and to determine the best way to approach subjects.

After the end of the pilot study, the interviewers who had been selected for field work underwent theoretical and practical training.

Inclusion criteria

The study included all subjects that agreed to participate and gave written informed consent. The selected resident interviewee was questioned about whether other residents in the household over 5 years of age showed excessive sweating. If so, those residents were also included in the study.

Interview

Ten previously trained interviewers applied a questionnaire that evaluated age, sex, excessive sweating (of the scalp, face, palms, armpits, soles of the feet, other regions, or two or more regions), age at symptom onset, psychosocial effect, predisposing factors, and similar cases within the family. A questionnaire specific for hyperhidrosis was applied to the subjects who reported excessive sweating.[26] The questionnaire consisted of 20 questions evaluating five domains: functional, social, personal, emotional, and special conditions. On each question, subjects were allowed to give only one response (scored from one to five), categorizing QoL as excellent (1), very good (2), good (3), poor (4), or very poor (5) for each situation. Therefore, the overall score could range from 20 (the best possible score, with a score of 1 on each of the 20 questions) to 100 (the worst possible score, with a score of 5 on each of the 20 questions).[26]

Medical evaluation

Subjects identified as having hyperhidrosis were selected to receive a home visit by a thoracic surgeon. For those who preferred, a physician consultation was scheduled at the Botucatu School of Medicine *Hospital das Clínicas*. Subjects were considered to have refused the medical evaluation if three unsuccessful attempts were made.

During the medical evaluation, the diagnosis was confirmed and the hyperhidrosis was classified (as PH or SH). The disorder and its treatment options were explained and, if interested, the patient was invited to schedule a consultation at the thoracic surgery outpatient clinic of the *Hospital das Clínicas*.

All data collected were stored in a specific database (Epi Info, version 6.04) for later descriptive statistical analysis.

We used Cronbach's alpha to test the reliability of the QoL questionnaire and varimax rotation to evaluate the importance of each domain in the final QoL questionnaire score. Principal component analysis for eigenvalues equal to or higher than 0.5 was used in order to extract the factors.

RESULTS

The interviewers visited 1,351 households comprising a total of 4,113 residents, of whom 2,150 (52.3%) were females and 1,963 (47.7%) were males. Ages ranged from 5 to 97 years, with a mean of 38.3 ± 21.2 years. Regarding age and gender distribution (Figure 1), the sample was very similar to the general population of the city.

Of the 4,113 residents in the study population, 85 (2.07%) reported excessive sweating (Figure 2). Of those 85 residents, 51 (60%) were female. In this subgroup, ages ranged from 5 to 72 years, with a mean of 33.9 ± 17.3 years.

The average age at symptom onset was 13.2 ± 9.9 years, and the areas most often affected were the hands (in 45.9%) and feet (in 43.5%). Seventeen subjects (20%) had already sought the help of a health professional, and 15 had sought out a physician and/or two other professionals. The most common psychosocial effect of excessive sweating was embarrassment (33.3%), and the predisposing factor was nervousness (34.1%).

A medical consultation at home or at the outpatient clinic was offered to all subjects who reported excessive sweating. Of those 85 subjects, 51 (60%) agreed to the medical consultation and 43 (40%) refused or did not attend. After evaluation, the prevalence of PH was found to be 0.93%, the diagnosis having been confirmed in 23 subjects (45%), whereas 15 (29.4%) had been diagnosed with SH and 13 (25.5%) were found to have no hyperhidrosis (Figure 3). Of the subjects diagnosed with SH, 13 (87%) were female, and the prevalence was highest in the 50- to 70-year age range; the causes of SH were menopause, obesity, and thyroid disorders. Of the 13 subjects who believed that they had hyperhidrosis but were diagnosed with normal sweating after medical evaluation, 10 (77%) were male.

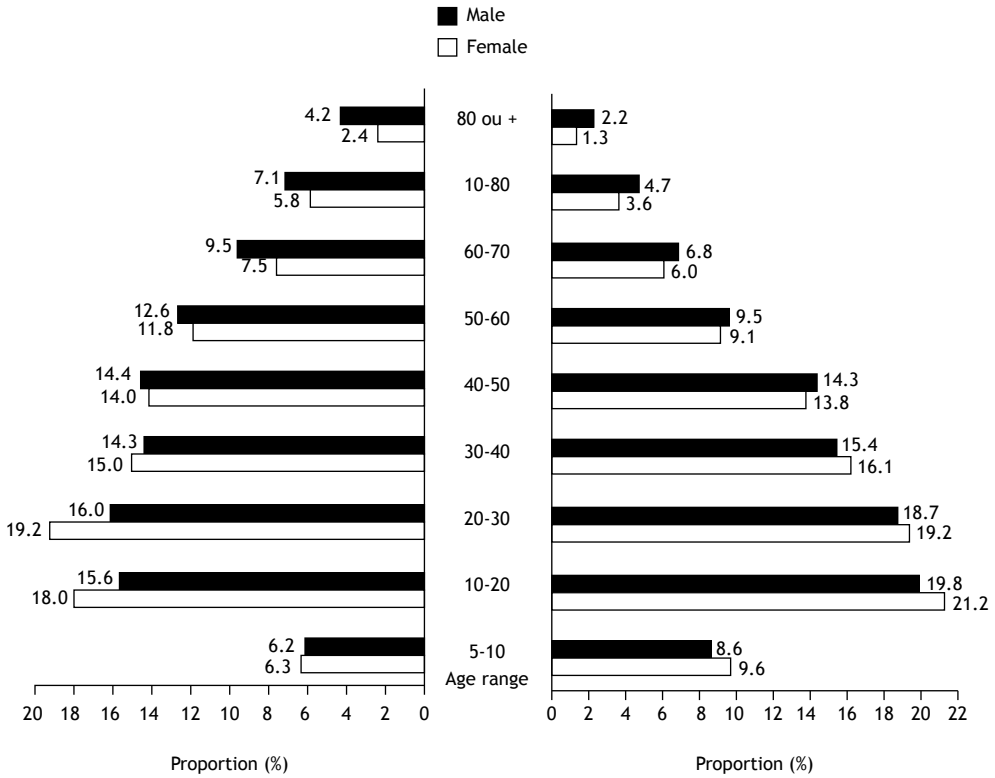

Figure 1. Age and gender distribution of the population over 5 years of age: left side, population of Botucatu (N = 113,055); right side, population sample studied (n = 4,113).

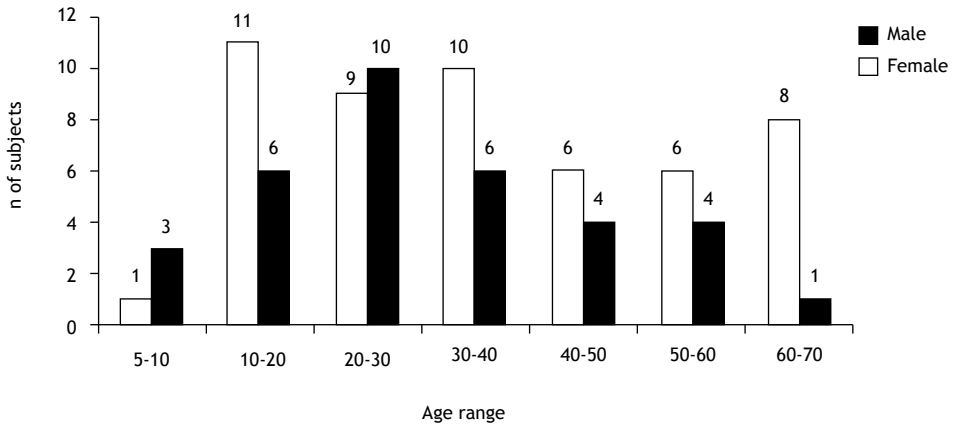

Figure 2. Number of subjects who reported excessive sweating (n = 85), by age range and gender.

Of the subjects diagnosed with PH, 83% were female (Figure 4). The most common occupations were student (in 43%) and house cleaner (in 21%). The age at symptom onset was < 5 years in 4 subjects, 5-10 years in 7, 10-15 years in 3, 15-20 years in 4, and > 20 years in 5.

In subjects with PH, the most common sites of excessive sweating were the hands (in 73.9%), feet (in 60.9%), armpits (in 30.4%), and scalp/face (in 12.9%). The most common psychosocial effect was embarrassment (in 33.3%), followed by shame (in 25.0%) and discomfort (16.7%). The most prevalent predisposing factor was nervousness (39.1%), followed by anxiety (21.7%). A family history of hyperhidrosis was reported by 7 subjects (30.0%). Only 6 subjects (26.1%) had sought the help of a medical professional.

Of the subjects with PH, 48% reported poor or very poor QoL, the same proportion reported good QoL, and only 4.35% reported excellent QoL. Of the domains evaluated (functional-social, personal, emotional, and special conditions), the most affected was the special conditions domain, with high scores especially for situations of tension or worry in enclosed environments, followed by the functional-social domain, with high

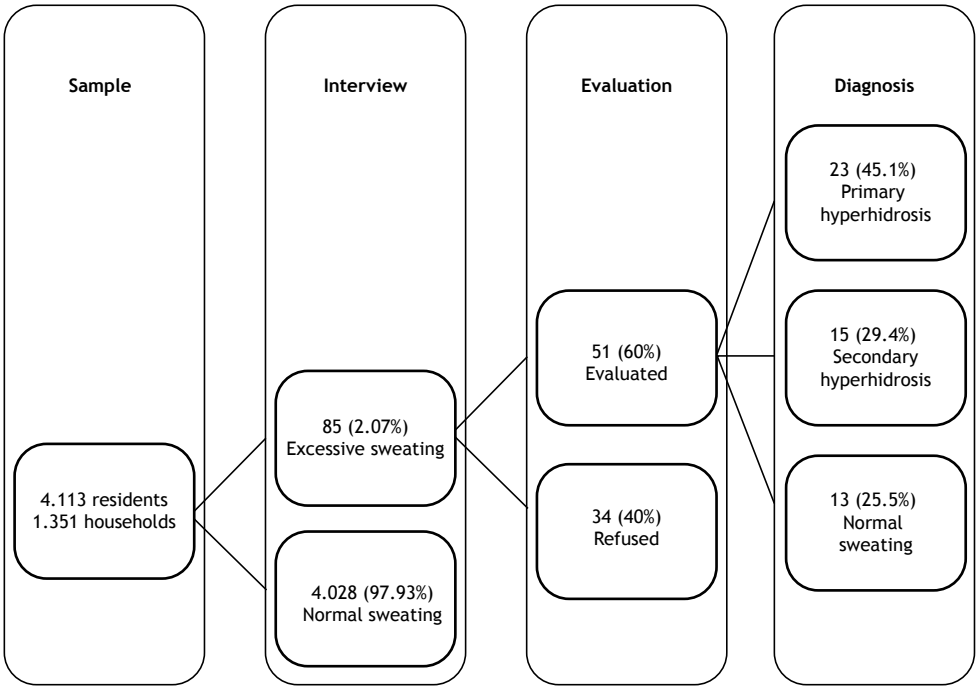

Figure 3. Population interviewed and subjects evaluated by a physician.

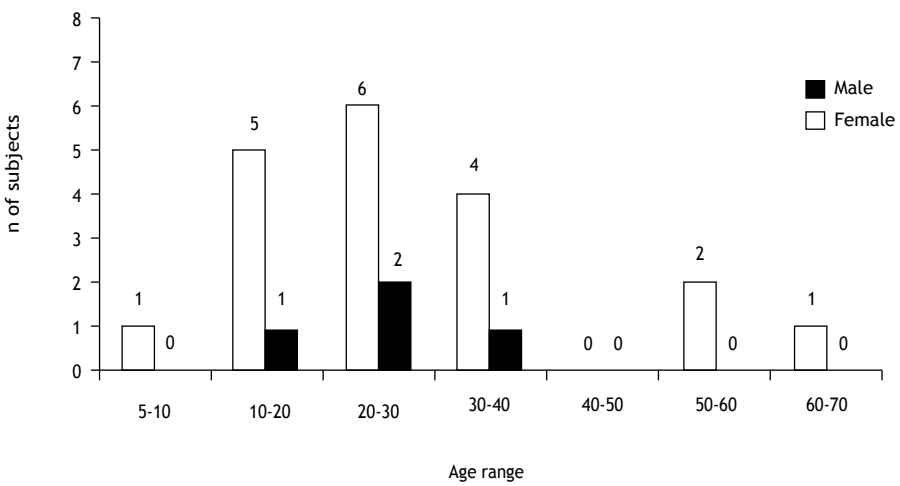

Figure 4. Number of subjects with primary hyperhidrosis (n = 23), by age range and gender.

scores for writing, performing manual tasks, holding objects, and shaking hands. The final mean score for QoL was 52.4 ± 18.7, and 7 subjects had a final score > 60; of those 7 subjects, 4 had a score above 70 and only 2 had a score above 80.

High reliability was observed for the final score of QoL (α = 0.9079), the functional-social domain (α = 0.8624), and the personal domain (α = 0.9033), as evaluated by Cronbach's alpha. The emotional domain (α = 0.5963) and the special conditions domain (α = 0.5883) were considered to be of moderate reliability.

DISCUSSION

Data on the prevalence of hyperhidrosis are quite scarce in the medical literature. We found only 12 studies[7,14-24] that reported statistical data on the prevalence of this disorder; however, the methods used in all those studies raise questions.

The first study on the incidence of hyperhidrosis was performed by Adar et al.[14] The authors reference an epidemiological pilot study involving Israeli youth, among whom the incidence of hyperhidrosis reportedly ranged from 0.6% to 1.0%. Although that study was

cited by several authors, there are no data regarding the methods used to arrive at these values.

In our study, the prevalence of hyperhidrosis after the application of a questionnaire by trained interviewers was above 2%, as observed by Strutton et al.[15] However, after medical evaluation, 25% of the patients that reported excessive sweating actually showed normal sweating and 30% had SH. Consequently, more than half of the subjects that reported excessive sweating did not actually have PH. Therefore, after medical evaluation, the estimated prevalence of PH decreased to less than 1%, as in the study by Adar et al.[14] This demonstrates the importance of medical evaluation for the correct estimation of prevalence. In 2013, Augustin et al.[23] published a study that included 14,336 employees of 52 German companies. In that study, all of the subjects were evaluated by dermatologists and the prevalence rate was 16.3%. However, the study sample included cases of PH and SH, given that 68% of the patients reported generalized hyperhidrosis and only 28% reported hyperhidrosis of the hands, armpits, feet, or other areas.

In the study conducted by Strutton et al.,[15] the prevalence projected for the general population of the United States was 2.8%. In that study, a previously validated questionnaire[15] was applied to a sample of 150,000 subjects, to determine the prevalence of hyperhidrosis. The authors applied the same method used in our study, although the subjects identified as hyperhidrosis patients by the questionnaire were not evaluated by a physician to confirm the diagnosis. Therefore, that sample could have included some subjects with SH or subjects that thought they had hyperhidrosis but in fact sweated a normal amount.

Unfortunately, in our study, some subjects refused medical evaluation, and others were not at home at the scheduled time or did not go to the outpatient clinic on the scheduled day. Patient refusal to undergo medical evaluation could be attributable to several factors, such as fear of being diagnosed with a disease, fear of being induced to undergo a surgical procedure, embarrassment or even resignation regarding the condition, or lack of interest because the sweating does not impair daily activities. There was a similar situation in the Strutton et al. study,[15] in which only 64% of the participants completed the questionnaire required to estimate the prevalence of hyperhidrosis in the general population of the United States.

In a study conducted in Japan, Fujimoto et al.[22] applied questionnaires at companies and in schools. The authors analyzed 5,807 subjects between 5 and 64 years of age and reported a prevalence of 12.76%. Again, the subjects were not examined by a physician and the prevalence might therefore be overestimated.

In a study performed in Taiwan by Chu et al.,[19] the authors reported a prevalence of PH of 0.072%. Data were collected from a database administered by the National Health Insurance Program (of Taiwan), according to code 780.8 of the International Classification of Diseases, 9th revision. In fact, that prevalence rate referred only to the subjects who sought medical treatment and not to the general population. The difference in comparison with the (higher) prevalence reported in other studies can be explained by the fact that not all subjects with PH seek medical treatment. In our study, only 0.41% of subjects in the sample had discussed the problem of excessive sweating with a health professional and, of those, only 0.15% had PH.

The age and gender distribution of the population included in our study was quite representative of the city of Botucatu; that was not observed in other studies.[7,16-25]

Researchers in China published three studies on the prevalence of hyperhidrosis in the country. Tu et al.[17] performed a study in a sample of 13,000 high school and college students between 15 and 22 years of age in the city of Fuzhou. A questionnaire was applied, and the students under suspicion of having PH were later interviewed by a physician. The method used in order to identify subjects with hyperhidrosis was similar to that used in our study; however, the Tu et al. study[17] included only one age range (adolescents), and the prevalence was found to be 4.59%. Another study conducted in China[16] used the same method and age range as the Tu et al. study[17], albeit with a larger study population (33,000 students), and reported a prevalence of 4.36%. A third study[24] reported the results of a nationwide survey performed in the seven regions of continental China. A self-report hyperhidrosis questionnaire was sent to 70,000 college students between 18 and 23 years of age. A total of 67,492 completed questionnaires were evaluated, and the prevalence found was 2.08%. Those three studies showed a selection bias, because the samples were not representative of the general population. The prevalence of PH is known to be higher in the age ranges evaluated (children and adolescents), which might have resulted in its overestimation.

In 2013, Stefaniak et al.[21] evaluated an adult population in Poland, including only students of medicine and odontology, who completed a questionnaire and were later subjected to gravimetry. In their responses on the questionnaire, 16.7% of the students reported suffering from hyperhidrosis, although, after an objective evaluation, only 8% were found to have PH. Therefore, the authors concluded that questionnaires may lead to false-positive results, and that an objective evaluation—which in our study was performed by a physician—is necessary.

Three studies on the prevalence of hyperhidrosis were performed in Brazil.[7,18,20] One was performed in a population sample of the city of Blumenau and found a prevalence of 9%.[18] The study included only 500 subjects ≥ 18 years of age who were randomly approached in the bus terminals of the city. The individuals who were randomly interviewed did not represent a sample statistically large enough to estimate the prevalence of PH in a city of more

than 100,000 inhabitants, and there was no medical interview to confirm the diagnosis; therefore, some subjects with normal sweating or SH may have been included. Furthermore, children and adolescents were excluded from that study.

Westphal et al.,[20] in a study involving 293 students at the Amazonas School of Medicine, reported a prevalence of 5.5%. A questionnaire was prepared to evaluate the presence of hyperhidrosis, and a researcher interviewed the subjects who presumably had PH, to confirm the diagnosis. The authors did not disclose whether the interviewer was a physician, and students who had already been subjected to video-assisted thoracoscopic sympathectomy for the treatment of PH were excluded from the study.

Lima et al.[7] evaluated 447 medical students in the Brazilian state of Sergipe. Hyperhidrosis was found in 14.76% of the students, a high prevalence in comparison with that reported in other studies. The students were interviewed by professors, and only 22.72% had their diagnosis confirmed by a physician. As in our study, the prevalence rate might be lower, because the medical evaluation showed that many subjects sweated a normal amount.

In our study, the prevalence of PH was slightly higher among women, and the proportion of women diagnosed with PH increased significantly after the medical evaluation, because most of the men were shown to sweat a normal amount.[10,27]

In our study, more than 50% of the subjects diagnosed with PH reported excellent or good QoL, in contrast to the study conducted by de Campos et al.,[26] in which 100% of the subjects reported poor or very poor QoL. That discrepancy can be explained by the fact that we conducted an active search for patients with PH, whereas Campos et al.[26] studied patients who sought medical treatment.

We conclude that the estimated prevalence of PH is near 1%, small in comparison with the number of subjects who report excessive sweating. The disorder affects the QoL in nearly 50% of subjects. Additional, methodologically appropriate prevalence studies are needed in order to establish the true worldwide prevalence of hyperhidrosis.

ACKNOWLEDGMENTS

We thank Professor Dr. Luana Carandina for her contribution to our study.

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J Bras Pneumol. 2018;44(4):299-306
http://dx.doi.org/10.1590/S1806-37562017000000276

ORIGINAL ARTICLE

Spirometry in patients screened for coronary artery disease: is it useful?

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Submitted: 10 August 2017.
Accepted: 17 December 2017.

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

ABSTRACT

Objective: To determine the prevalence of spirometric abnormalities in patients screened for coronary artery disease (CAD) and the risk factors for lung function impairment. **Methods:** Patients referred for cardiac CT underwent spirometry and were subsequently divided into two groups, namely normal lung function and abnormal lung function. The prevalence of spirometric abnormalities was calculated for the following subgroups of patients: smokers, patients with metabolic syndrome, elderly patients, and patients with obstructive coronary lesions. All groups and subgroups were compared in terms of the coronary artery calcium score and the Duke CAD severity index. **Results:** A total of 205 patients completed the study. Of those, 147 (72%) had normal lung function and 58 (28%) had abnormal lung function. The median coronary artery calcium score was 1 for the patients with normal lung function and 36 for those with abnormal lung function ($p = 0.01$). The mean Duke CAD severity index was 15 for the former and 27 for the latter ($p < 0.01$). Being a smoker was associated with the highest OR for abnormal lung function, followed by being over 65 years of age and having obstructive coronary lesions. **Conclusions:** The prevalence of spirometric abnormalities appears to be high in patients undergoing cardiac CT for CAD screening. Smokers, elderly individuals, and patients with CAD are at an increased risk of lung function abnormalities and therefore should undergo spirometry.

(ClinicalTrials.gov identifier: NCT01734629 [http://www.clinicaltrials.gov/])

Keywords: Pulmonary disease, chronic obstructive; Spirometry; Coronary disease; Tomography, X-ray computed.

INTRODUCTION

Pulmonary function tests constitute an important tool for evaluating lung disease and dyspnea. Chronic respiratory diseases remain underdiagnosed. In a study conducted in Canada, only 32% of patients with COPD had previously been diagnosed with the disease. In a large epidemiological study conducted in the United States, 15% of adults over 45 years of age were found to have undiagnosed airflow obstruction.[1-3]

In clinical practice, patients suspected of having coronary artery disease (CAD) commonly undergo extensive and expensive testing. Although coexistence of CAD and respiratory disease is common, pulmonary function tests are not commonly performed in heart disease patients. Spirometry is performed in less than 30% of patients examined for dyspnea by a cardiologist.[4]

The use of spirometry in primary care doubles the diagnosis of respiratory disorders, spirometry being safe and accurate for early diagnosis.[5,6] Although spirometry is simple, inexpensive, and highly accurate for detecting lung disease, the possibility of false positives has led a US task force to recommend against the use of spirometry to screen adults for COPD.[7] However, there is recent evidence that the use of spirometry to screen high-risk patients reduces false positives; in addition, new treatment options for patients with COPD have been shown to be effective in changing the natural history of the disease, reinforcing the importance of early diagnosis.[8-10]

Spirometry can aid in assessing cardiovascular risk. A reduction in percent predicted FEV_1 is a risk factor for cardiovascular mortality independent of traditional risk factors, such as hypertension, dyslipidemia, and smoking. Population-based studies and a systematic review including over 80,000 patients showed that reduced FEV_1 is a predictor of mortality.[11-14]

Patients with risk factors for cardiovascular disease, such as smoking and a sedentary lifestyle, are at an increased risk of lung disease and might benefit from spirometry. Many such patients undergo cardiac CT for the detection of CAD.

Cardiac CT is an accurate method for diagnosing CAD. In addition to providing anatomic evaluation, cardiac CT has prognostic implications even in asymptomatic individuals, assisting in predicting cardiovascular events. The coronary artery calcium (CAC) score objectively quantifies CAC and constitutes a method for estimating the risk of cardiovascular events.[15,16]

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Financial support: This study received financial support from the *Fundação de Amparo à Pesquisa do Estado de São Paulo* (FAPESP, São Paulo Research Foundation).

Given the frequent association between COPD and CAD,[14] the increased cardiovascular mortality risk associated with reduced FEV_1, and the fact that pulmonary disease is underdiagnosed, it is likely that many patients undergoing CAD workup have reduced lung function.

Despite being commonly encountered in clinical practice, patients suspected of having CAD but without an established diagnosis of the disease have been the focus of few epidemiological studies. Therefore, the objective of the present study was to determine the prevalence of impaired lung function in this population. A secondary objective was to determine patient characteristics commonly associated with spirometric abnormalities, in order to define a group of patients who might benefit the most from spirometry.

METHODS

This was a cross-sectional study conducted at a tertiary cardiac hospital. Patients over 40 years of age referred for cardiac CT were screened. Those with previously diagnosed CAD, prior myocardial infarction, a history of revascularization, class III or IV angina pectoris,[17] cognitive impairment precluding spirometry, or decompensated heart failure were excluded.[18] The study protocol was approved by the University of São Paulo School of Medicine *Hospital das Clínicas* Research Ethics Committee (Protocol no. 0503/11), located in the city of São Paulo, Brazil, and all participants gave written informed consent.

All screened patients completed a questionnaire assessing demographics, symptoms, smoking status, comorbidities, history of pulmonary disease, and medication use. Dyspnea was quantified by the modified Medical Research Council scale.[19] Waist circumference, hip circumference, and waist-to-hip ratio were measured. Metabolic syndrome was determined on the basis of established criteria.[20]

Cardiac CT was performed with a 64-row CT scanner (Aquilion 64; Toshiba Medical Systems Corporation, Otawara, Japan). The images were analyzed by institutional radiologists blinded to the spirometry results. CAC was quantified by a radiologist using the Agatston method. The Duke CAD severity index was then calculated on the basis of the degree and location of stenosis. Although the Duke CAD severity index was originally developed for coronary angiography, it has been shown to correlate well with coronary CT angiography.[21,22]

All spirometric tests were performed with a KoKo® PFT spirometer (nSpire Health, Inc., Longmont, CO, USA). Spirometry was performed in accordance with the American Thoracic Society/European Respiratory Society criteria.[23] All spirometric variables were expressed as absolute values and as a percentage of the predicted values for the Brazilian population.[24] Participants were divided into two groups on the basis of post-bronchodilator spirometry results: normal lung function, comprising patients with post-bronchodilator FVC, FEV_1, and FEV_1/FVC above the lower limit of normal; and abnormal lung function, comprising patients with post-bronchodilator FVC, FEV_1, or FEV_1/FVC below the lower limit of normal. The patients who presented with abnormal lung function were subdivided into two groups on the basis of their functional impairment: persistent obstructive lung disease, comprising patients with post-bronchodilator FEV_1/FVC below the lower limit of normal; and preserved ratio impaired spirometry (PRISm), comprising patients with post-bronchodilator FVC below the lower limit of normal and normal FEV_1/FVC.[25]

The degree of lung function impairment was determined on the basis of the Brazilian Thoracic Association guidelines for pulmonary function testing.[26] Although the Global Initiative for Chronic Obstructive Lung Disease guidelines define airway obstruction as an FEV_1/FVC ratio of < 0.70, a decision was made to use an FEV_1/FVC ratio below the lower limit of normal in the present study in order to avoid overdiagnosis of obstructive lung disease in the elderly.[27]

Statistical analysis was performed with PASW Statistics for Windows, version 18.0 (SPSS Inc., Chicago, IL, USA). The probability of a type I error was set at 0.05.

The prevalence of spirometric abnormalities was calculated by dividing the number of individuals in the abnormal lung function, persistent obstructive lung disease, and PRISm groups by the total study population. The prevalence of spirometric abnormalities was also calculated for the following subgroups of patients: smokers (current and former), patients with metabolic syndrome, elderly patients, and patients with obstructive coronary lesions.

The normal lung function group was compared with the abnormal lung function group in terms of anthropometric characteristics, smoking status, pulmonary disease, pulmonary symptoms, abdominal circumference, hip circumference, waist-to-hip ratio, spirometric variables, the CAC score, and the Duke CAD severity index. Categorical variables were compared by using the chi-square test. Parametric variables were compared by using the Student's t-test. Nonparametric variables were compared by using the Mann-Whitney test.

The normal lung function group was also compared with the persistent obstructive lung disease and PRISm subgroups by using ANOVA. For cases in which there were significant differences between groups, the Bonferroni test or Dunnett's test was used for multiple comparisons in order to determine which groups differed from one another.

To determine the predictors of impaired lung function, the ORs for having abnormal lung function (including persistent obstructive lung disease and PRISm) were calculated for the following subgroups of patients: smokers and nonsmokers; patients with and without metabolic syndrome; obese and nonobese patients; patients under and over 65 years of age; patients with and without hypertension; patients with and without diabetes; and patients with and without obstructive

coronary lesions. To determine the factors influencing the presence of abnormal lung function, forward stepwise logistic regression analysis was performed, all of the variables showing $p < 0.20$ in the comparison between patients with normal lung function and those with abnormal lung function being included in the initial model. To detect a 25% difference in the prevalence of obstructive coronary lesions between the normal lung function and abnormal lung function groups, with a power of 80% and a type I error of 0.05, the required sample size was calculated to be 50 per group.

RESULTS

Between April of 2011 and December of 2013, 381 patients were invited to participate in the study. Of those, 66 declined to participate, 86 had previously undergone revascularization, 11 were unable to perform spirometry, and 13 were excluded because of a history of myocardial infarction, angina, or decompensated heart failure.

A total of 205 patients completed the study. Of those, 168 underwent coronary CT angiography for symptoms of heart disease, including chest pain and dyspnea. Of the 205 patients who completed the study, 147 (72%) had normal lung function and 58 (28%) had abnormal lung function. Of those, 23 had persistent obstructive lung disease and 35 had PRISm. Figure 1 shows a flow chart of the sample selection process. The CAC score was calculated for all 205 study participants. A total of 188 patients underwent coronary CT angiography and CAC scoringe.

Of the 35 patients with PRISm, 30 had mild spirometric abnormalities, 2 had moderate spirometric abnormalities, and 3 had severe spirometric abnormalities. Of the 23 patients with persistent obstructive lung disease, 19 had mild spirometric abnormalities, 2 had moderate spirometric abnormalities, and 2 had severe spirometric abnormalities.[26]

Figure 2 shows the proportions of patients with normal lung function and abnormal lung function (the latter including those with persistent obstructive lung disease and those with PRISm) in the study sample. There were significant differences between the normal lung function and abnormal lung function groups in terms of the proportions of smokers and nonsmokers, and the proportions of elderly and nonelderly patients ($p < 0.01$). However, there were no significant differences between the two groups regarding the proportions of patients with and without metabolic syndrome ($p = 0.17$).

Of the 188 patients who underwent coronary CT angiography, 142 were found to have no coronary obstruction and 46 were found to have some degree of CAD. There were significant differences between the subgroups of patients with and without coronary obstruction regarding spirometric patterns ($p = 0.04$; Figure 2).

All groups were compared in terms of their major characteristics (Table 1). They were all found to be similar in terms of sex, weight, height, body mass index (BMI), metabolic syndrome, and hip circumference.

Patients with abnormal lung function were found to be older than those with normal lung function ($p < 0.01$). In addition, the proportions of smokers and former smokers were higher among the patients with abnormal lung function than among those with normal lung function, as were the proportions of patients with a history of pulmonary disease and increased waist-to-hip ratio ($p < 0.01$ for all). Abdominal circumference was found to be significantly higher in the abnormal lung function group and in the PRISm subgroup than in the normal lung function group ($p = 0.03$), although not in the persistent obstructive lung disease subgroup.

Of the sample as a whole, 94 (45.8%) had a CAC score of zero. In addition, 9.8% were found to have mild CAC, whereas 44.4% were found to have moderate or severe CAC. The median CAC score for the normal lung function group was 1, being significantly lower than those for the abnormal lung function and PRISm groups (36 and 55, respectively; $p < 0.05$; Figure 3). This difference remained significant even after adjustment for age, BMI, smoking, and metabolic syndrome ($p = 0.04$).

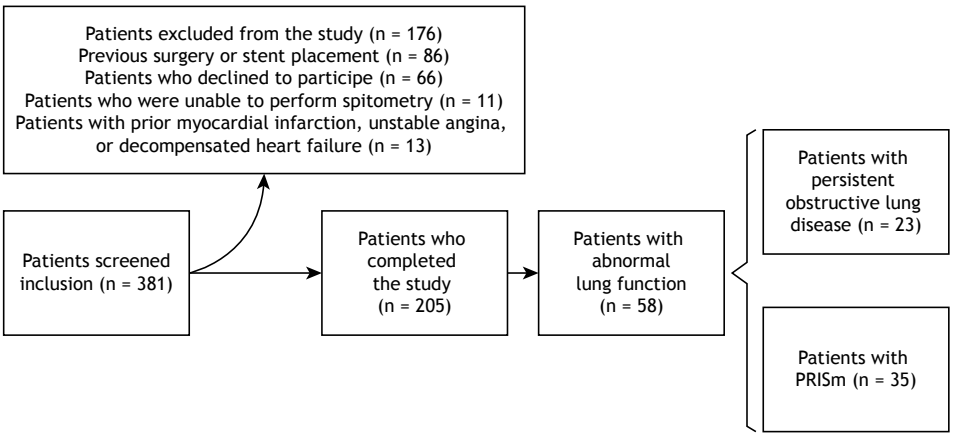

Figure 1. Patient recruitment flow chart. PRISm: preserved ratio impaired spirometry.

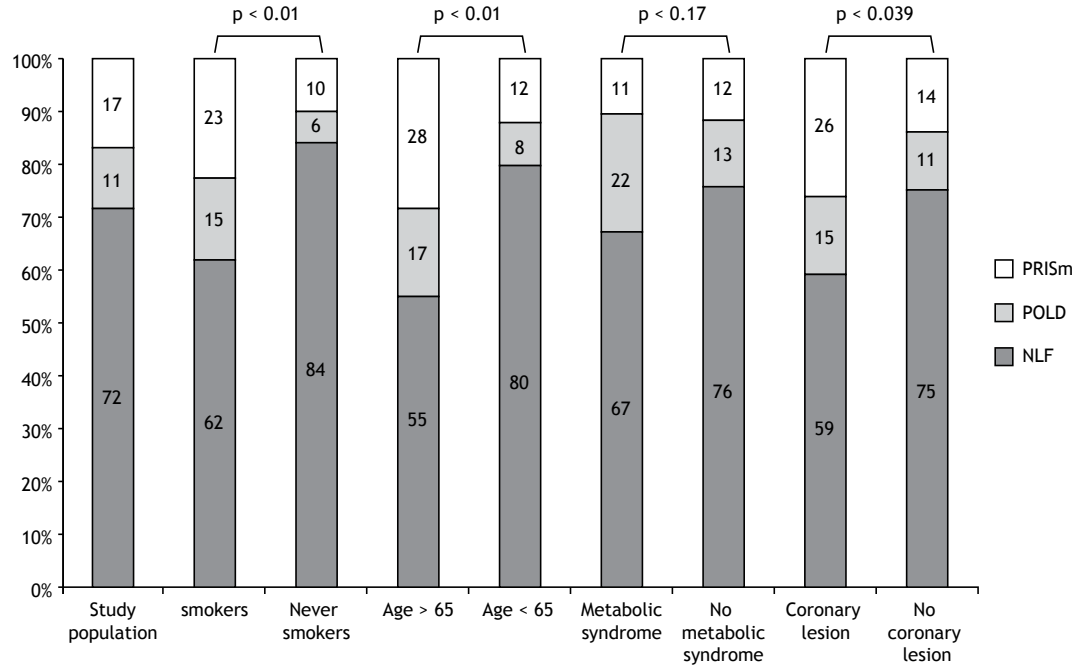

Figure 2. Proportions of patients in each subgroup. Note significant differences between the proportions of smokers and never smokers; elderly and nonelderly patients; and patients with and without coronary lesions. Despite an increased proportion of patients with metabolic syndrome among those with abnormal lung function, the difference in proportions between patients with and without metabolic syndrome was not significant. PRISm: preserved ratio impaired spirometry; POLD: persistent obstructive lung disease; and NLF: normal lung function. Values of p represent the differences in proportions of patients among the subgroups, as assessed by the chi-square test.

The Duke CAD severity index, which reflects the severity of obstruction and the number of diseased vessels, was calculated.[21] Of the sample as a whole, 118 had a Duke CAD severity index of zero. The median Duke CAD severity index for the normal lung function group was 15, being significantly lower than that for the abnormal lung function group (i.e., 27; $p < 0.01$).

The prevalence of chronic respiratory disease was found to be higher in the abnormal lung function group than in the normal lung function group ($p < 0.001$). In the group of patients with abnormal lung function, 11 had a previous diagnosis of chronic pulmonary disease, and 6 were receiving treatment for it. In the group of patients with normal lung function, 7 had a history of chronic pulmonary disease, and only 1 took medication regularly. No differences were found between the abnormal lung function and normal lung function groups regarding the frequency of symptoms (Figure 4). In addition, no differences were found between the two groups regarding the severity of dyspnea, as assessed by the modified Medical Research Council scale ($p = 0.81$). Dyspnea was not significant as a predictor of abnormal lung function.

In order to determine the variables associated with abnormal lung function, we calculated the ORs for presenting with spirometric abnormalities (Table 2). Being a smoker was associated with the highest OR for abnormal lung function, followed by being over 65 years of age and having obstructive coronary lesions. Logistic regression controlling for sex, age, BMI, smoking, obstructive coronary lesions, metabolic syndrome, hypertension, and diabetes mellitus showed that smoking and age were factors independently associated with abnormal lung function.

DISCUSSION

The present study included 205 patients undergoing cardiac CT for CAD screening. None of the participants had previously been diagnosed with cardiovascular disease. Although this patient profile is common in clinical practice, such patients constitute an understudied population. This population was chosen precisely because it is a real-life sample of patients commonly encountered by internists, cardiologists, and pulmonologists. Our finding of abnormal spirometry in 28% of the study participants demonstrates that lung function abnormalities and respiratory disease are often neglected and underdiagnosed in patients screened for cardiac conditions or symptoms.

The 2011 American Board of Internal Medicine Foundation initiative known as Choosing Wisely was introduced in order to alert physicians to excessive testing in many clinical situations, including CAD.[28] In our study population, most of the patients had negative cardiac CT findings, which are indicative of excessive testing. In contrast, spirometry is underused, even in patients with respiratory symptoms.[29]

The prevalence of spirometric abnormalities in the present study was highest in smokers (current and

Table 1. Demographic, clinical, and functional characteristics of the study sample.[a]

Characteristic	Normal lung function	Abnormal lung function	Preserved ratio impaired spirometry	Persistent obstructive lung disease
Sex, M/F	80/67	33/25	22/13	11/12
Age, years	58.40 ± 9.05	64.50 ± 9.80*	64.15 ± 10.16*	64.96 ± 9.50*
Weight, kg	76.64 ± 15.09	80.18 ± 16.80	83.84 ± 17.76	75.36 ± 14.37
Height, m	1.65 ± 0.10	1.66 ± 0.10	1.67 ± 0.10	1.65 ± 0.10
BMI, kg/m^2	28.11 ± 4.66	28.83 ± 5.07	29.73 ± 5.03	27.64 ± 4.98
Smoking status (Smoker/ Former smoker/Nonsmoker)	14/57/76	6/38/14*	1/25/9*	5/13/5*
Metabolic syndrome, yes/no	63/83	31/27	21/14	10/13
Pulmonary disease, yes/no	7/140	11/47*	8/27*	3/20*
Abdominal circumference, cm	100.2 ± 12.4	107.4 ± 12.8*	110.8 ± 11.2*	105.0 ± 14.1
Hip circumference, cm	105.9 ± 10.7	105.0 ± 8.8	106.6 ± 9.0	104.3 ± 9.2
Waist-to-hip ratio	0.94 ± 0.08	1.02 ± 0.07*	1.04 ± 0.08*	1.0 ± 0.07*
FVC, L	3.59 ± 0.90	2.85 ± 0.81*	2.72 ± 0.73*	3.01 ± 0.89*
FVC, % predicted	97.50 ± 12.94	76.8 ± 14.74*	69.66 ± 8.46*	85.96 ± 16.10*
FEV_1, L	2.88 ± 0.67	2.12 ± 0.60*	2.20 ± 0.56*	2.03 ± 0.65*
FEV_1, % predicted	99.20 ± 13.40	73.75 ± 14.94*	72.53 ± 10.14*	73.32 ± 19.58*
FEV_1/FVC, %	80.70 ± 0.05	75.20 ± 0.10*	81.19 ± 0.06*	67.72 ± 0.11*
CAC score[b]	1 (0-86)	36 (0-379)*	55 (0-461)*	3 (0-166)
Coronary obstruction, yes/no	27/106	19/36*	12/20*	7/16

CAC: coronary artery calcium. [a]Data expressed as mean ± SD, except where otherwise indicated. [b]Data expressed as median (interquartile range). *p < 0.05 vs. the normal lung function group.

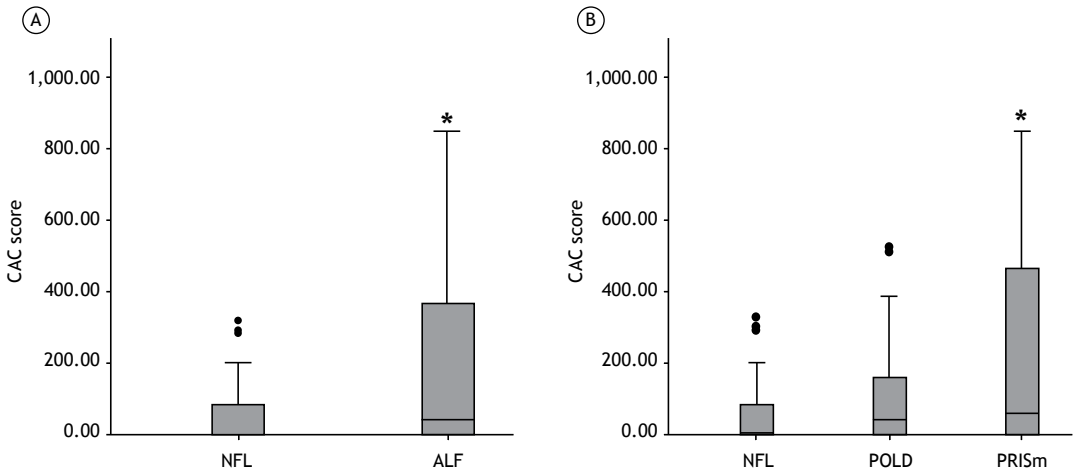

Figure 3. Median dispersion of the coronary artery calcium (CAC) score for patients with normal lung function (NLF) and abnormal lung function (ALF). In A, comparison between the NLF and ALF groups. In B, comparison between the NLF group and the persistent obstructive lung disease (POLD) and preserved ratio impaired spirometry (PRISm) subgroups. The Kruskal-Wallis test showed significant differences among the three groups. *p < 0.05 vs. the NLF group.

former), elderly patients, and patients with CAD, having ranged from 38% to 45%. This finding is consistent with those of a study evaluating CAC in smokers who were at an increased risk for lung cancer but had no previous cardiovascular disease.[30]

In elderly individuals, cardiac patients, and smokers, pulmonary function assessment is usually delayed. Symptoms are underestimated, being attributed to old age, exposure to cigarettes, or cardiovascular disease.[31] The high prevalence of spirometric abnormalities in these subgroups reinforces the importance of a simple, inexpensive test to the clinical management of patients suspected of having CAD.

The prevalence and severity of obstructive coronary lesions (as assessed by the CAC score and the Duke CAD severity index) were higher in the abnormal lung function group than in the normal lung function group. These results can be attributed to the subgroup of patients with PRISm.

Of the sample as a whole, 17.2% had PRISm. Previous epidemiological studies have shown that the prevalence of PRISm is 5.1% in the general population and 12.3% in smokers.[32,33] Mean FVC in the subgroup of PRISm patients in the present study was < 70% predicted, constituting a significant abnormality from a functional point of view. PRISm is classically associated

with interstitial lung disease, neuromuscular disease, obesity, and metabolic syndrome.[34,35] Reduced FVC on spirometry has been associated with increased mortality.[36] In the present study, mean CAC scores were highest in the PRISm subgroup, indicating increased atherosclerosis.

Recent epidemiological studies have attempted to characterize and understand PRISm, and three different clusters have been identified. The first is associated with reduced TLC; the second is related to metabolic disorders; and the third is quite similar to the clinical presentation of COPD.[32] Dyspnea, poorer performance on the six-minute walk test, emphysema, bronchial thickening, and reduced TLC have been identified as predictors of PRISm.[25]

Morbidity and dyspnea have been found to be higher in patients with PRISm than in controls with normal spirometry. Although PRISm has yet to be adequately studied, it is known to increase morbidity and worsen prognosis. Its relationship with respiratory and metabolic diseases can make it an important risk marker in the near future.[37,38]

Of the patients who were found to have abnormal lung function in the present study, 23 (11.2%) had persistent obstructive lung disease. This is consistent with the reported prevalence of persistent obstructive lung disease in the general population in the city of São Paulo.[33] In the present study, airway obstruction was found to be most common in smokers, elderly individuals, and patients with metabolic syndrome. Such patients appear to be at increased risk and therefore constitute a population in which active case finding of and screening for COPD appear to be most effective.

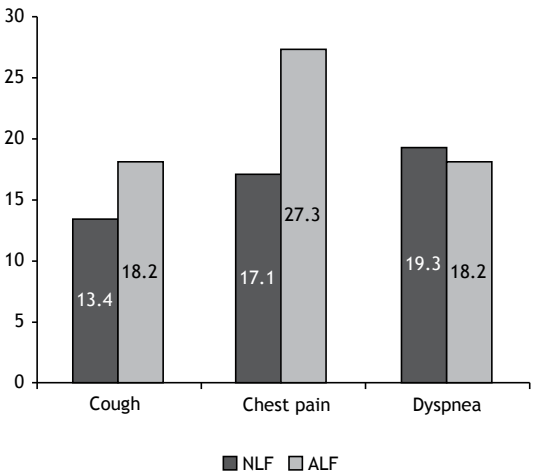

Figure 4. Proportions of patients with respiratory symptoms (cough, chest pain, and dyspnea) in the normal lung function (NLF) and abnormal lung function (ALF) groups. There were no significant differences in symptom frequency between the two groups.

In the present study, symptoms did not predict spirometric abnormalities. This finding supports the idea that pulmonary function changes precede symptoms in respiratory diseases.[39] In addition, the fact that few of our patients had a previous diagnosis of pulmonary disease shows that pulmonary diseases are underdiagnosed in patients suspected of having cardiovascular disease. The respiratory health screening of asymptomatic patients undergoing screening for heart disease can provide valuable information.

The present study has some limitations. Because of the cross-sectional nature of the study, no causality can be established. However, the relationship between pulmonary and cardiovascular disease exists and amplifies the damaging effects of aging, smoking, and other risk factors on the respiratory and cardiovascular systems. Another limitation is that a definitive diagnosis of PRISm cannot be accurately made by spirometry alone, TLC measurement therefore being required.

In conclusion, patients screened for CAD are at an increased risk for lung function impairment, the likelihood of which is higher when the presence of CAD is confirmed. The management of patients with concomitant cardiovascular and pulmonary disease is complex. The high prevalence of lung function abnormalities in patients undergoing cardiac CT for CAD screening and the association between increased atherosclerosis (as assessed by the CAC score) and respiratory disease reinforce the importance of screening for lung disease in patients suspected of having heart disease. Spirometry is encouraged in such patients, and studies evaluating its cost-effectiveness and impact on clinical management are needed.

ACKNOWLEDGMENTS

We would like to thank Rejane Figueiredo for assisting in the statistical analysis; Karla Sabrina Gomes for assisting in patient recruitment; and the staff of the Department of Radiology of the University of São Paulo School of Medicine *Hospital das Clínicas* Heart Institute for their assistance. We would also like to thank Ann Conti Morcos for her assistance in the writing of this manuscript.

Table 2. Crude odds ratios for abnormal spirometry.

Variable	OR	95% CI	p
Smoking	3.21	1.62-6.36	0.0009
Age > 65 years	3.18	1.69-6.01	0.0004
Obstructive coronary lesions	2.07	1.03-4.16	0.04
Metabolic syndrome	1.38	0.74-2.57	0.29
Obesity	0.79	0.40-1.59	0.51
Hypertension	0.91	0.57-1.43	0.75
Diabetes	0.97	0.53-1.77	0.92

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J Bras Pneumol. 2018;44(4):307-314
http://dx.doi.org/10.1590/S1806-37562017000000259

ORIGINAL ARTICLE

CT-guided percutaneous core needle biopsy of pulmonary nodules smaller than 2 cm: technical aspects and factors influencing accuracy

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Submitted: 26 July 2017.
Accepted: 28 January 2018.

Study carried out at the Hospital Israelita Albert Einstein, São Paulo (SP) Brasil.

ABSTRACT

Objective: To evaluate the diagnostic accuracy of CT-guided percutaneous core needle biopsy (CT-CNB) of pulmonary nodules ≤ 2 cm, as well as to identify factors influencing the accuracy of the procedure and its morbidity. **Methods:** This was a retrospective, single-center study of 170 consecutive patients undergoing CT-CNB of small pulmonary nodules (of ≤ 2 cm) between January of 2010 and August of 2015. **Results:** A total of 156 CT-CNBs yielded a definitive diagnosis, the overall diagnostic accuracy being 92.3%. Larger lesions were associated with a higher overall accuracy (OR = 1.30; p = 0.007). Parenchymal hemorrhage occurring during the procedure led to lower accuracy rates (OR = 0.13; p = 0.022). Pneumothorax was the most common complication. A pleura-to-lesion distance > 3 cm was identified as a risk factor for pneumothorax (OR = 16.94), whereas performing a blood patch after biopsy was a protective factor for pneumothorax (OR = 0.18). **Conclusions:** Small nodules (of < 2 cm) represent a technical challenge for diagnosis. CT-CNB is an excellent diagnostic tool, its accuracy being high.

Keywords: Image-guided biopsy; Neoplasms; Lung.

INTRODUCTION

Recent widespread availability of CT and advances in low-dose CT screening techniques have enabled the identification of an increasing number of small pulmonary nodules (of ≤ 2 cm).[1-3] These small nodules represent a diagnostic challenge. In addition, stage IA lesions represent an excellent opportunity to perform lung-sparing resections for non-small cell lung cancer, with excellent 5-year survival and low local recurrence rates.[4]

Lung lesions can be considered benign when imaging findings suggest stability or when consistent clinical and laboratory findings are available. In contrast, lesions that have CT features suggestive of malignancy require further investigation. The options for managing such lesions include surveillance CT imaging, CT-guided biopsy, (navigational or non-navigational) bronchoscopic biopsy, and surgical resection.[5-7] Follow-up CT requires ionizing radiation and provides results after considerable delay. This can cause anxiety in some patients, a more rapid diagnostic method therefore being preferable. CT-guided biopsy can be performed on an outpatient basis and constitutes a viable option in such cases.[8]

CT-guided percutaneous transthoracic core needle biopsy (CNB) is a safe and accurate technique that has been widely used in order to evaluate pulmonary nodules.[9-11] Although some studies have evaluated the accuracy of CT-guided CNB of pulmonary nodules,[12-15] only a few have tested the accuracy of 20-gauge coaxial CNB performed exclusively for lesions of ≤ 2 cm in size.[16,17]

The primary objective of the present study was to evaluate the overall diagnostic accuracy of CT-guided percutaneous 20-gauge CNB of small pulmonary nodules, as well as to identify factors influencing the accuracy of the procedure. A secondary objective was to evaluate morbidity and the factors influencing it.

METHODS

Patients

This was a retrospective, single-center study. The study was approved by the local research ethics committee. Between January of 2010 and August of 2015, 174 CT-guided percutaneous CNBs of small pulmonary

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Financial support: None.

nodules (of ≤ 2 cm) were performed in 170 patients, all of whom gave written informed consent before the procedure.

All 170 patients had undergone CT before recommendation of CT-guided CNB. Platelet count and prothrombin time were determined before the procedure, which was not performed if the platelet count was < 50,000 or if the international normalized ratio was > 1.5. Patients were admitted to the interventional radiology department on the same day of the procedure.

Biopsy procedure

Patients underwent local anesthesia, sedation, or general anesthesia depending on the size and location of the lesion. Lower lobe lesions were most commonly biopsied under general anesthesia, whereas large lesions were most commonly biopsied under local anesthesia. Therefore, the type of anesthesia used varied according to the nodule features and the professional team. The choice of patient position was made in order to facilitate access to the target lesion and avoid target lesion motion, given that lying on the side of the lung to be biopsied reduces the respiratory motion of the lung.

All biopsies were guided by a multislice CT scanner (Somatom Definition AS 40-slice; Siemens Healthcare GmbH, Erlangen, Germany). Each biopsy was performed by one of seven interventional radiologists with more than 5 years of experience.

An initial ultra-low-dose noncontrast chest CT was performed for biopsy planning. The imaging parameters were as follows: tube voltage, 80 kVp; tube current, 8 mA; collimation, 1.2 mm; and slice thickness, 2.4-3.0 mm. The CT scanner gantry laser lights and radiopaque landmarks indicated the site of needle entry on the patient's skin. After needle insertion through the thoracic wall, thin-section CT images were obtained in order to guide the needle. All biopsies were performed by using a coaxial technique with a 19-gauge introducer needle (Argon Medical Devices Inc., Frisco, TX, USA or Cook Medical LCC, Bloomington, IN, USA). With the introducer needle in the correct position, samples were collected through a 20-gauge semiautomatic core needle (SuperCore™; Argon Medical Devices Inc., or Quick-Core®; Cook Medical LCC), which can obtain specimens of 10 or 20 mm in length. Initially, one to three specimens were collected. One of five on-site pathologists with more than 5 years of experience was present for all biopsies. The specimens were gently rolled onto a glass slide and immediately sent for cytopathology (imprint cytology). If the specimen was insufficient, another specimen was taken until a diagnosis was made. When pathology showed that the specimens contained cells consistent with the lesion (sufficient for later analysis), at least three more nodule samples were obtained through the coaxial needle. At the end of the biopsy, all specimens were placed in a container with 10% formalin.

Prior to removal of the coaxial needle, a CT scan of the chest was performed to assess immediate complications. When no pneumothorax was present, a blood patch was performed in the biopsy path, at the discretion of the interventional radiologist, by injecting 1 ml of patient peripheral blood for every 1 cm of needle withdrawn. Immediately after biopsy, a follow-up CT scan of the chest was performed to detect complications. After recovery from anesthesia, all patients were monitored closely, and an expiratory posteroanterior chest X-ray was obtained 1 h after the procedure. After 4-6 h, patients with no complaints or complications were discharged.

Cases of pneumothorax during or after biopsy were classified as mild, moderate, or severe on the basis of the extent of retraction of the lung parenchyma from the chest wall: < 2 cm, mild; 2-4 cm, moderate; and > 4 cm, severe. Symptomatic or increasing pneumothorax despite monitoring or aspiration was treated with placement of a 14-French chest tube (Cook Medical LCC) connected to a Heimlich valve. Hemodynamically stable patients were discharged and returned 2-3 days later for chest tube removal. Parenchymal hemorrhage was classified as mild when it compromised the same lung segment as the nodule; moderate when it compromised distant segments or when associated with small-volume hemoptysis; and severe when associated with large-volume hemoptysis or hemodynamic instability.

Histopathological findings

Final pathology results were used in order to evaluate the accuracy of the CNBs. Because the surgical management of premalignant lesions (such as atypical adenomatous hyperplasia) and malignant lesions is similar, they were grouped together.

CNB findings of malignancy were considered true positives when 1) there was surgical confirmation; 2) the histological findings were consistent with the known primary malignancy; and 3) the subsequent clinical course was consistent with malignancy. Malignant CNB findings were considered false positives when 1) there was no surgical confirmation; and 2) the subsequent clinical course was inconsistent with malignancy. Benign CNB findings were considered true positives when 1) there was surgical confirmation; 2) the lesion disappeared or decreased in size with or without antibiotics; and 3) the lesion remained stable for at least 1 year after biopsy. Benign CNB findings were considered false positives when 1) surgical findings showed malignancy; and 2) the subsequent clinical course was inconsistent with a benign diagnosis. Finally, inadequate or paucicellular CNB specimens were considered false negatives (nondiagnostic). No lesions were classified as true negatives, because the CT findings were conclusive. Patients without a final diagnosis (because of cancer-unrelated death during follow-up, loss to follow-up, or a follow-up period of < 1 year) were excluded. Diagnostic accuracy was

calculated as the sum of all true positives divided by the sum of all included patients.

Statistical analysis

Categorical variables were described as absolute and relative frequencies. Nodule size was described as median and interquartile range. In order to analyze the association between dichotomous outcomes and other study variables, we used generalized estimating equations to take into account the dependence between measurements on each individual. Binomial distribution and exchangeable correlation structure were used. Initially, crude adjustments were made, variables being compared two by two. Associations showing $p < 0.200$ were considered for inclusion in the multiple regression model, and, after a stepwise process of exclusion and inclusion of variables, only variables that had a significant association with the outcome remained in the model. All statistical analyses were performed with the R software, version 3.1.3 (The R Foundation for Statistical Computing, Vienna, Austria), and the level of significance was set at 5%.

A safety analysis was conducted in all of the patients who underwent CNB. An accuracy analysis was conducted in all of the patients in whom the CNB diagnosis was confirmed by surgery or clinical follow-up (≥ 1 year).

RESULTS

A total of 174 CNBs were performed in 170 patients, for whom there were data available for safety analysis. Of the 170 patients analyzed, 89 were male and 81 were female, their mean age being 61.5 years (range, 4-87). The mean lesion size was 1.25 cm (range, 0.4-2.0). Most (80.4%) of the lesions were predominantly solid. Eighteen patients with nonmalignant results were excluded for the following reasons: no follow-up (in 9), less than 1 year of follow-up after biopsy (in 8), and death from other causes during the first year of follow-up (in 1). Lesion size was associated with increased accuracy

Table 1. Variables associated with the overall diagnostic accuracy of CT-guided percutaneous core needle biopsy of small pulmonary nodules.[a]

Variable		Total	Overall diagnostic accuracy		p*
			No	Yes	
		(N = 156)	(n = 12)	(n = 144)	
Nodule density	Predominantly solid	124 (79.5)	7 (58.3)	117 (81.2)	
	Pure ground-glass opacity	32 (20.5)	5 (41.7)	27 (18.8)	0.056
Lesion size	1-10 mm	58 (37.2)	8 (66.7)	50 (34.7)	
	11-20 mm	98 (62.8)	4 (33.3)	94 (65.3)	0.037
Pleura-to-lesion distance	0-10 mm	87 (55.8)	9 (75.0)	78 (54.2)	
	11-30 mm	49 (31.4)	1 (8.3)	48 (33.3)	0.122
	> 30 mm	20 (12.8)	2 (16.7)	18 (12.5)	0.959
Proximity to pulmonary fissures	No	134 (85.9)	11 (91.7)	123 (85.4)	
	Yes	22 (14.1)	1 (8.3)	21 (14.6)	0.583
Length of needle trajectory through the lung parenchyma	0-10 mm	47 (30.1)	5 (41.7)	42 (29.2)	
	11-20 mm	42 (26.9)	3 (25.0)	39 (27.1)	0.553
	21-30 mm	23 (14.7)	1 (8.3)	22 (15.3)	0.385
	> 30 mm	44 (28.2)	3 (25.0)	41 (28.5)	0.484
Type of anesthesia	General anesthesia	117 (75.0)	9 (75.0)	108 (75.0)	
	Conscious sedation or local anesthesia	39 (25.0)	3 (25.0)	36 (25.0)	0.941
Number of specimens obtained	1-2	6 (3.8)	1 (8.3)	5 (3.5)	
	3-4	26 (16.7)	2 (16.7)	24 (16.7)	0.437
	5 or more	124 (79.5)	9 (75.0)	115 (79.9)	0.428
Pneumothorax during the procedure	No	143 (91.7)	10 (83.3)	133 (92.4)	
	Yes	13 (8.3)	2 (16.7)	11 (7.6)	0.447
Alveolar hemorrhage during the procedure	No	141 (90.4)	9 (75.0)	132 (91.7)	
	Yes	15 (9.6)	3 (25.0)	12 (8.3)	0.065
Malignancy	Yes	108 (69.2)	7 (58.3)	101 (70.1)	
	No	48 (30.8)	5 (41.7)	43 (29.9)	0.343
Lesion size, mm[b]		13.00 [9.00-16.00]	8.50 [7.75-12.50]	13.00 [9.75-16.00]	0.006

[a]Values expressed as n (%), except where otherwise indicated. [b]Values expressed as median [interquartile range]. *Logistic regression model.

(p = 0.037), whereas pleura-to-lesion distance, proximity to pulmonary fissures, length of needle trajectory through the lung parenchyma, and number of specimens obtained were not. Table 1 shows all of the variables analyzed for their effect on diagnostic accuracy. Accuracy analysis was possible in 156 CNBs (Figure 1). The histopathological findings of the CNBs are shown in Table 2. The overall diagnostic accuracy of those 156 CNBs was 92.3%. All 144 conclusive CNB results were confirmed as benign or malignant by follow-up imaging or surgery. In the multivariate analysis, larger lesions were associated with higher overall accuracy (OR = 1.30; 95% CI: 1.08-1.57; p = 0.007), whereas parenchymal hemorrhage during the procedure had lower accuracy rates (OR = 0.13; 95% CI: 0.02-0.75; p = 0.022). Some of the features of the 12 biopsied nodules that were misdiagnosed are shown in Table 3.

Pneumothorax was the most common complication, having occurred in 25 (16.0%) of 156 CNBs. Pneumothorax was mild in 5 cases, moderate in 13, and severe in 7. Of the 25 pneumothoraces, 10 decreased in size or remained stable, whereas 15 moderate-to-severe pneumothoraces required chest tube placement. Of those, 1 occurred before biopsy, i.e., during intubation, being associated with massive mediastinal emphysema secondary to tracheal injury, and 3 were delayed pneumothoraces, which were identified 24 h after the procedure.

In the multivariate analysis, a pleura-to-lesion distance > 3 cm was identified as a risk factor for pneumothorax (OR = 16.94; 95% CI: 2.39-120.26), whereas performing a blood patch after biopsy (n = 88/156; 56.4%) was a protective factor for pneumothorax (OR = 0.18; 95% CI: 0.04-0.86).

With regard to bleeding complications of the procedure, alveolar hemorrhage occurred in 15 CNBs (9.6%), being mild in 10 and moderate in 5. In addition, there was 1 case of mild hemothorax. No additional treatment was required in any of the aforementioned cases. In the multivariate analysis, there were no risk factors associated with bleeding complications.

Uncommon complications included myocardial infarction, in 1 patient, and cerebral air embolism, in 1 patient (Figure 2). The former was due to the anesthetics, and the patient made a full recovery; the latter was possibly due to positive pressure ventilation during biopsy, and the patient developed cognitive dysfunction despite having received specialized treatment.

DISCUSSION

Recent advances in imaging techniques and screening protocols have allowed the identification of an increasingly large number of small nodules in many parts of the body, such as the prostate, breasts, and lungs.[16] CT-CNB plays a key role in the evaluation of small pulmonary nodules. Several studies using different guidance techniques and needle sizes have shown that CNB has a high diagnostic accuracy.[9,15-21]

In the present study, 170 patients underwent CT-guided 20-gauge CNB. Eighteen patients were lost to follow-up or were followed for less than 1 year, which is one of the limitations of the study. The diagnostic accuracy of CT-CNB in the present study was 92.3%. This finding is similar to those of other studies reporting the diagnostic accuracy of CNBs of nodules smaller than 2 cm (i.e., 87-95%).[12,16,17] Unlike most other studies, in which accuracy was measured for malignancy only, our study measured "overall accuracy", which includes accuracy for benign CNB results. This is especially important in Brazil, where tuberculosis remains a health problem. CNB can provide a definitive diagnosis in cases of infection or benign disease, avoiding an unnecessary pulmonary resection and its associated morbidity.

There are several reasons why diagnostic accuracy was high in the present study. First, we used a coaxial technique, which allows multiple biopsies once the lesion has been targeted. Second, we performed CNB rather than fine-needle biopsy. Third, we had an experienced pathologist in our team. Finally, we used a biopsy protocol that consisted of an additional three biopsies after adequate diagnostic tissue had been obtained (as determined by the pathologist).

The coaxial technique is the most widely recommended technique for percutaneous lung biopsy[16] because it has been shown to reduce procedure time and complications. In addition, larger specimens can be collected with core needles that are inserted into the coaxial introducer, thus facilitating histopathology.[22] Finally, the presence of an experienced pathologist is extremely helpful because it ensures that the biopsy is performed in the target lesion and that the specimen collected is sufficient for diagnosis, especially when the lesion has a necrotic component.

With regard to the coaxial introducer and core needles, we always use 19- and 20-gauge needles, respectively. For percutaneous biopsies, the smallest gauge needle that can obtain sufficient tissue for diagnosis should be used. It has been reported that a larger gauge needle translates to a higher risk of complications.[8] We found that, for small pulmonary nodules, 20-gauge core needles can be used not only for histopathology and immunohistochemistry but also for simultaneous molecular and genetic analyses. This finding is important because of the ever-growing trend toward personalized cancer therapies.

Pneumothorax and bleeding were the most common complications in our sample, with an incidence of 14.3% and 7.4%, respectively. A chest tube was placed in 8.7% of the patients in our sample. These results are similar to those of previous studies.[12,16] According to the guidelines proposed by Gupta et al.,[8] all except one of the complications observed in the present study were minor. The only major complication was

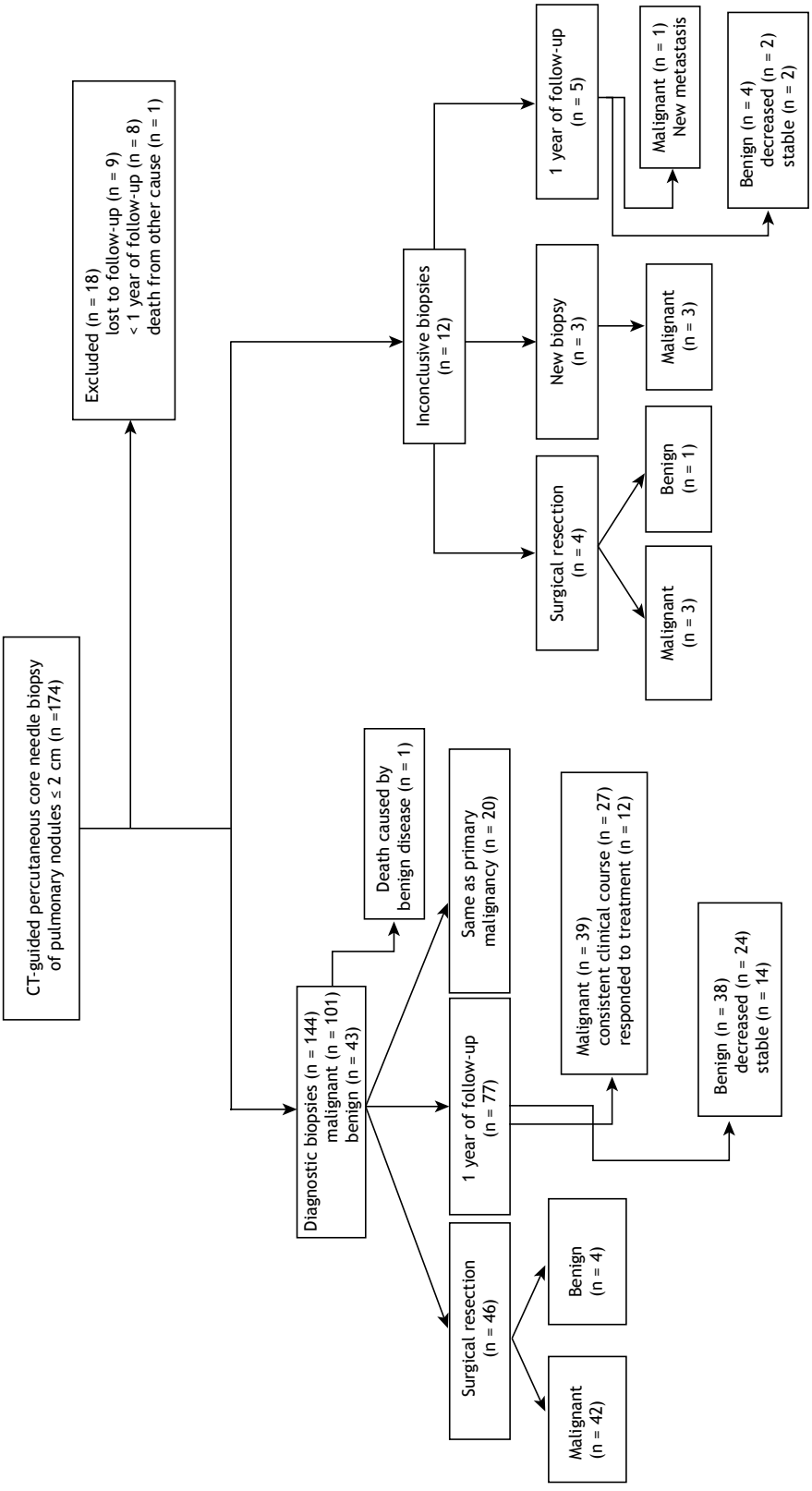

Figure 1. Flow chart of 174 patients undergoing CT-guided percutaneous core needle biopsy of pulmonary nodules of ≤ 2 cm in size, together with the final diagnosis.

Table 2. Histopathological findings of 156 biopsied lesions.

Biopsy diagnosis	Patients, n (%)
Malignant/premalignant	100 (64.1)
Primary adenocarcinoma	48
Metastatic adenocarcinoma	21
Other metastasis	13
Carcinoid tumor	7
Primary squamous cell carcinoma	6
Atypical adenomatous hyperplasia	5
Benign	44 (28.2)
Fungal infection	12
Organizing pneumonia	10
Caseating granuloma	5
Noncaseating granuloma	5
Other non-specific chronic inflammation	5
Hamartoma	4
Abscess	1
Fibrosis	1
Pulmonary infarction	1
Inconclusive/insufficient material	12 (7.7)
Total	156 (100)

Table 3. Features of the nodules that were initially misdiagnosed, together with the final diagnosis.

Case	Size, mm	Density	Distance from the pleura, mm	Specimen, n	Complications during biopsy	Final diagnosis
1	4	subsolid	3	> 7	none	Benign - unknown
2	7	solid	2	> 7	mild pneumothorax	Benign - unknown
3	7	subsolid	6	6	none	Primary adenocarcinoma
4	8	subsolid	8	7	none	Primary adenocarcinoma
5	8	solid	7	> 7	none	Metastasis
6	8	subsolid	2	> 7	none	Benign - fibrosis
7	9	solid	4	1	mild bleeding	Metastasis
8	10	solid	2	> 7	moderate pneumothorax	Metastasis
9	12	solid	0	3	hemodynamic instability*	Metastasis
10	14	solid	31	3	moderate bleeding	Benign - unknown
11	14	subsolid	15	> 7	moderate bleeding	Benign - unknown
12	14	solid	35	7	none	Carcinoid tumor

*The patient presented with myocardial infarction during biopsy, which was immediately interrupted.

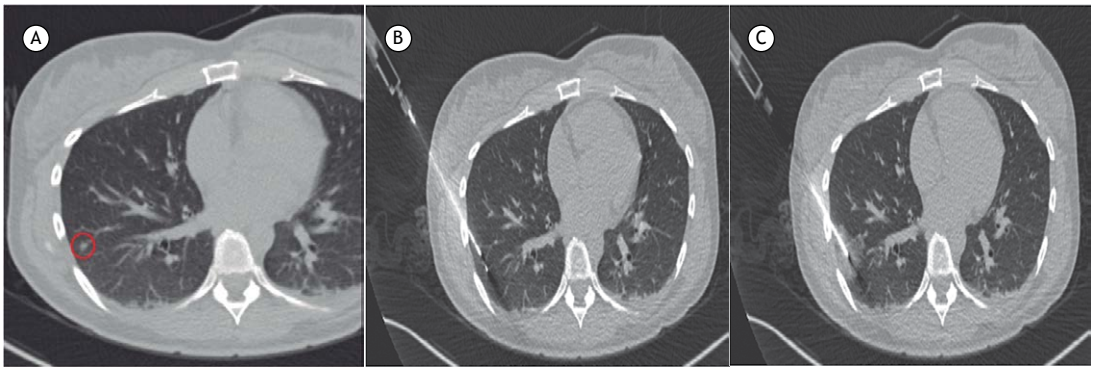

Figure 2. In A, pulmonary nodule with slightly jagged edges, measuring 0.6 cm and located in the lateral basal segment of the right lower lobe. In B, coaxial needle placement guided by CT. In C, alveolar hemorrhage after collection of the first specimen.

cerebral air embolism (in 1 patient), a relatively rare complication.[23]

Several factors have been found to affect the accuracy of CT-guided CNB of pulmonary lesions, including lesion size ≤ 1 cm,[9] lesion size ≤ 1.5 cm,[24] lower lobe lesions,[9] ≤ 2 specimens,[9] and malignant lesions.[9] In studies analyzing the aforementioned factors in patients with nodules of ≤ 2.0 cm in size, the only factor that was found to have a positive influence on the diagnostic accuracy of CT-CNB was a lesion size ≥ 0.8 cm.[17] In the present study, two factors were found to have influenced the overall diagnostic accuracy of CT-CNB: lesion size and parenchymal hemorrhage. To the best of our knowledge, ours is the first study in which parenchymal hemorrhage was associated with a lower diagnostic accuracy.

Some studies have shown that smaller lesions lead to lower biopsy accuracy,[9-12] whereas others have not.[1,25] In the present study, a smaller lesion translated to a lower diagnostic accuracy. Given that biopsies of pulmonary nodules smaller than 1 cm are challenging, our choice of patient position was made so as to minimize target lesion motion and provide greater stability to the coaxial and biopsy needles. This is particularly advantageous for nodules of < 1 cm in size.

Parenchymal hemorrhage was another factor that negatively influenced the overall diagnostic accuracy. We found that parenchymal hemorrhage usually occurs after the first sample collection and results in poor visualization on subsequent imaging and biopsy. On CT, alveolar hemorrhage has an attenuation coefficient that is very similar to that of a pulmonary nodule, which is therefore obscured by it. An attempt should therefore be made to obtain the best possible specimen at the first collection, with CT confirmation of the cutting needle crossing the largest diameter of the target lesion.

In conclusion, the overall diagnostic accuracy of CT-guided percutaneous 20-gauge CNB of pulmonary nodules smaller than 2 cm is high. Lesion size and parenchymal hemorrhage are associated with reduced accuracy. Pneumothorax is the most common complication of CT-CNB, being associated with a pleura-to-lesion distance > 3 cm, whereas performing a blood patch after biopsy appears to be a protective factor in selected cases.

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J Bras Pneumol. 2018;44(4):315-320
http://dx.doi.org/10.1590/S1806-37562017000000121

ORIGINAL ARTICLE

Validation of a bioelectrical impedance analysis system for body composition assessment in patients with COPD

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Submitted: 30 April 2017.
Accepted: 15 December 2017.

Study carried out at the Núcleo de Assistência, Ensino e Pesquisa em Reabilitação Pulmonar, Universidade do Estado de Santa Catarina – UDESC – Florianópolis (SC) Brasil.

ABSTRACT

Objective: To investigate the validity of an eight-contact electrode bioelectrical impedance analysis (BIA) system within a household scale for assessing whole body composition in COPD patients. **Methods:** Seventeen patients with COPD (mean age = 67 ± 8 years; mean FEV_1 = 38.6 ± 16.1% of predicted; and mean body mass index = 24.7 ± 5.4 kg/m^2) underwent dual-energy X-ray absorptiometry (DEXA) and an eight-contact electrode BIA system for body composition assessment. **Results:** There was a strong inter-method correlation for fat mass (r = 0.95), fat-free mass (r = 0.93), and lean mass (r = 0.93), but the correlation was moderate for bone mineral content (r = 0.73; p < 0.01 for all). In the agreement analysis, the values between DEXA and the BIA system differed by only 0.15 kg (−6.39 to 6.70 kg), 0.26 kg (−5.96 to 6.49 kg), −0.13 kg (−0.76 to 0.50 kg), and −0.55 kg (−6.71 to 5.61 kg) for fat-free mass, lean mass, bone mineral content, and fat mass, respectively. **Conclusions:** The eight-contact electrode BIA system showed to be a valid tool in the assessment of whole body composition in our sample of patients with COPD.

Keywords: Pulmonary disease, chronic obstructive; Body composition; Electric impedance.

INTRODUCTION

Weight loss and depletion of muscle mass are common systemic manifestations in COPD[1] and have been associated with the disease prognosis. It is known that body mass index (BMI) is related to the number of hospitalizations[2] and length of hospital stay[3] for acute exacerbation in patients with COPD, with an impact on mortality.[4,5] The fat-free mass (FFM) index, however, seems to be a stronger predictor of mortality[6] and disease severity[7] than does BMI in those patients, justifying the routine assessment of their body composition.

The use of dual-energy X-ray absorptiometry (DEXA) is recommended to assess body composition in COPD patients.[8,9] This system distinguishes the body composition in three compartments by a difference in the attenuation of X-rays among body tissues. In comparison with DEXA, conventional bioelectrical impedance analysis (BIA) system, with four adhesive gel electrodes, has satisfactory clinical accuracy in estimating body composition in patients with COPD.[10] The BIA system, which is based on differential opposition to the electrical current among body tissues, has been used to assess body composition in COPD patients in various studies.[11-13]

The measurement of lean mass (LM) by an eight-contact electrode BIA system has already been validated against DEXA in people ranging in age from 6 to 64 years.[14] Additionally, this simple, practical, and convenient system was used in an epidemiological study in which FFM and FFM index were determined in men and women of white ethnicity ranging from 45 to 69 years of age.[15] However, to the best of our knowledge, the assessment of body composition using this system has yet to be studied in patients with COPD. In those patients, factors other than age contribute to muscle atrophy, such as disuse, inflammation, oxidative stress, hypoxemia, hypercapnia, low levels of anabolic hormones or growth factors, impaired energy balance, corticosteroid use, and vitamin D deficiency.[16] Thereby, the objective of the present study was to investigate the validity of an eight-contact

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Financial support: This study received financial support from the *Fundação de Amparo à Pesquisa do Estado de Santa Catarina*/Brazilian *Conselho Nacional de Desenvolvimento Científico e Tecnológico* (FAPESC/CNPq, Foundation for the Support of Research in the State of Santa Catarina/National Council for Scientific and Technological Development; Grant no. 3509/2010-2).

electrode BIA system within a household scale for assessing whole body composition in COPD patients, using DEXA as the standard method.

METHODS

This was a cross-sectional study conducted between July and December of 2011. The study sample was selected by convenience and included COPD patients classified as the Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages 2, 3, or 4 (presence of a post-bronchodilator FEV_1/FVC ratio < 0.70 and FEV_1 < 80% of the predicted value),[17] of both genders, who had a smoking history ≥ 20 pack-years, had been clinically stable four weeks prior to study entry, and were ≥ 40 years of age. Exclusion criteria were current smoking and presence of associated diseases, such as cardiomyopathy, musculoskeletal diseases, cancer, tuberculosis, or asthma. A total of 17 clinically stable COPD patients (14 men) from public or private pulmonary outpatient clinics agreed to participate in the study. The study was approved by the Research Ethics Committees of the *Universidade do Estado de Santa Catarina* and the *Universidade Federal de Santa Catarina* (Protocol numbers 85/2010 and 865.2010, respectively). All participants gave written informed consent.

Pulmonary function

Lung function was assessed using a previously calibrated spirometer (EasyOne®; ndd Medical Technologies, Zurich, Switzerland). Spirometry was performed before and after the inhalation of 400 μg of albuterol in accordance with the American Thoracic Society/European Respiratory Society standards.[18] The predicted values were calculated based on equations proposed by Pereira et al.[19]

Nutritional status

During the assessment of nutritional status, the individuals remained barefoot and unadorned, wearing only an apron. Height was measured with a wall-mounted stadiometer (Standard; Sanny, São Bernardo do Campo, Brazil) in accordance with the standardization proposed by Gordon et al.[20] Weight and body composition variables were measured with a household segmental body composition monitor (BC-558 Ironman; Tanita Corp., Tokyo, Japan). That body composition monitor operates at 50 kHz and contains eight contact electrodes, two pairs of electrodes being coupled to a metal platform for the feet and two pairs for hand grasping. The metal platform is attached to a force transducer for the measurement of weight, and the eight contact electrodes are connected to a digital circuit. The measurement of body composition variables by the eight-contact electrode BIA system was performed as per the instructions of the manufacturer and as recommended by Kyle et al.[21] Measurements were taken ten minutes after the patients had been positioned in orthostatic position, in order to minimize errors caused by acute changes in body fluid distribution.[22] Data on total body composition—body fat percentage, muscle mass, and bone mass—were collected.

On the same day, body composition was also assessed by whole-body DEXA scanning, which was conducted by a medical radiology technician certified by the Brazilian Society of Clinical Densitometry. The subjects laid still in the supine position during the evaluation. A Lunar Prodigy Advance bone densitometer (GE Healthcare, Madison, WI, USA) was previously calibrated in accordance with the manufacturer's recommendations and used with the enCORE software, version 12.30 (GE Healthcare) for the acquisition of the following body composition variables: bone mineral content (BMC); LM, fat mass (FM); and FFM (in kg for all). For the inter-method analysis, the following was considered: FM = (total body weight × FM%)/100; FFM = total body weight − FM; LM = muscle mass; and BMC = bone mass.

Statistical analysis

The data were reported as means ± SD. The Shapiro-Wilk test was used to analyze data normality. A paired t-test was used in order to compare the means of the body composition variables obtained via BIA and DEXA. Pearson's correlation coefficient was used in order to test the association between the variables obtained by the two assessment methods, whereas Bland & Altman scatter plots were used to assess agreement between the methods. Statistical significance was set at $p < 0.05$. All statistical analyses were performed with the IBM SPSS Statistics software package, version 20.0 (IBM Corporation, Armonk, NY, USA).

RESULTS

The sample comprised 17 subjects (14 men) classified as GOLD stage 2 (moderate COPD; n = 4), 3 (severe COPD; n = 6), and 4 (very severe COPD; n = 7). Regarding medications, 14 (80%) of the subjects reported the use of long-acting β_2 agonists combined with corticosteroids; 11 (67%) used long-acting anticholinergics; 9 (53%) used long-acting β_2 agonists; 3 (20%) used short-acting β_2 agonists combined with anticholinergics; and 1 (7%) used short-acting xanthines. The characteristics of the sample are shown in Table 1.

There were no significant differences between body composition variables obtained by DEXA and by BIA (Table 2), both correlating positively. The variables measured by BIA (FFM, LM, and FM) showed strong correlations with the respective variables measured by DEXA, whereas the BMC values showed a moderate correlation between the methods (Figure 1).

Figure 2 shows the agreement between body composition variables measured by DEXA and by BIA. The inter-method differences (IMDs) and the limits of agreement (LOA) for FFM, LM, BMC, and FM values were 0.15 kg (−6.39 to 6.70 kg), 0.26 kg (−5.96 to 6.49 kg), −0.13 kg (−0.76 to 0.50 kg), and −0.55 kg

Table 1. Characteristics of the study group.

Characteristic	Mean ± SD	Range
Age, years	67 ± 8	56-79
Smoking history, pack-years	50 (24-74)[a]	21-150
FEV_1/FVC[b]	0.45 ± 0.11	0.26-0.65
FEV_1, L[b]	1.17 ± 0.48	0.54-2.04
FEV_1, % predicted[b]	38.6 ± 16.1	15-65
FVC, L[b]	2.53 ± 0.61	1.51-3.49
FVC, % predicted[b]	64.5 ± 16.0	42-103
BMI, kg/m^2	24.7 ± 5.4	16.9-33.9

BMI: body mass index. [a]Value expressed as median (interquartile range). [b]Post-bronchodilator values.

(−6.71 to 5.61 kg), respectively. The body composition variables were within the LOA, except for the BMC value of one patient.

DISCUSSION

The aim of the present study was to investigate the validity of an eight-contact electrode BIA system for the assessment of total body composition in a sample of patients with moderate to very severe COPD, using DEXA as the standard evaluation method. Measurements of FFM, LM, and FM obtained by the two methods showed strong positive correlations. In

Table 2. Body composition of the study group.

Variable	DEXA		BIA		p
	Mean ± SD	Range	Mean ± SD	Range	
FFM, kg	50.7 ± 8.5	35.1-64.3	50.6 ± 8.6	38.9-63.0	0.848
LM, kg	48.3 ± 8.2	33.6-61.4	48.0 ± 8.2	36.9-59.9	0.730
BMC, kg	2.43 ± 0.46	1.59-3.35	2.56 ± 0.39	2.00-3.10	0.107
FM, kg	20.7 ± 9.4	5.06-33.9	21.3 ± 8.3	9.89-35.3	0.471

DEXA: dual-energy X-ray absorptiometry; BIA: bioelectrical impedance analysis; FFM: fat free mass; LM: lean mass; BMC: bone mineral content; and FM: fat mass.

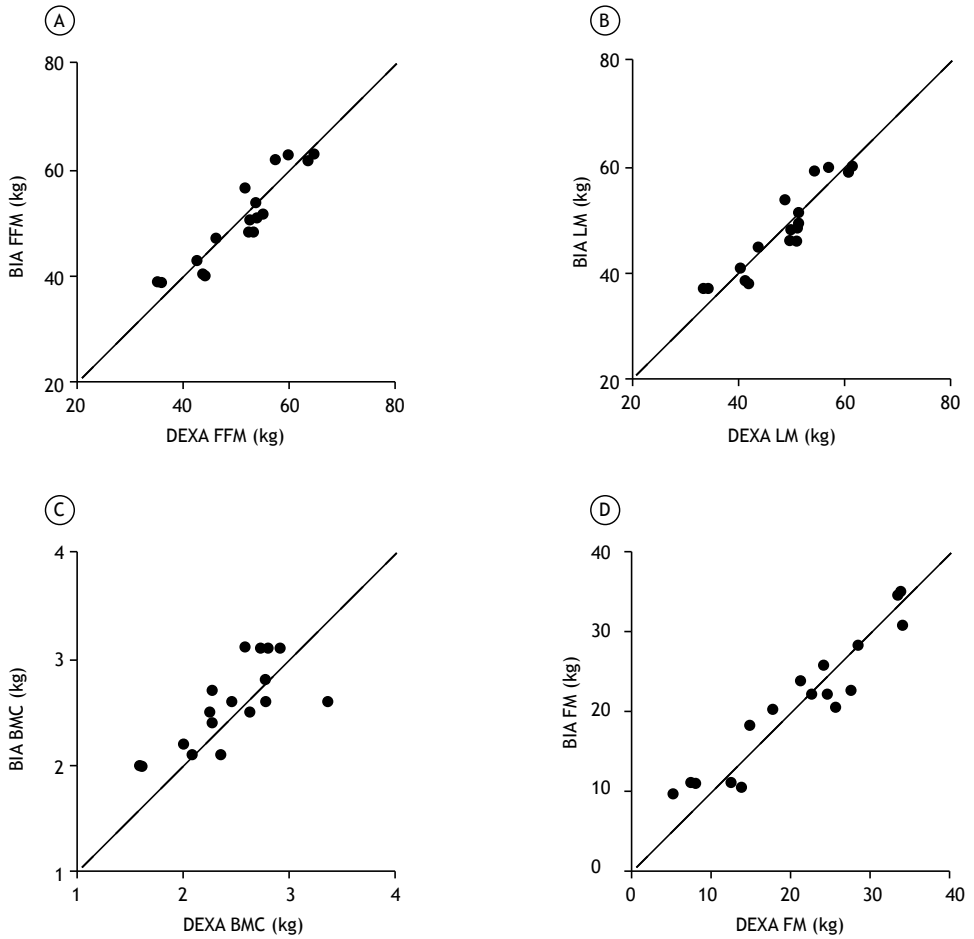

Figure 1. Correlation between body composition variables assessed by dual-energy X-ray absorptiometry and the eight-contact electrode bioelectrical impedance analysis system. DEXA: dual-energy X-ray absorptiometry; BIA: bioelectrical impedance analysis; FFM: fat free mass; LM: lean mass; BMC: bone mineral content; and FM: fat mass.

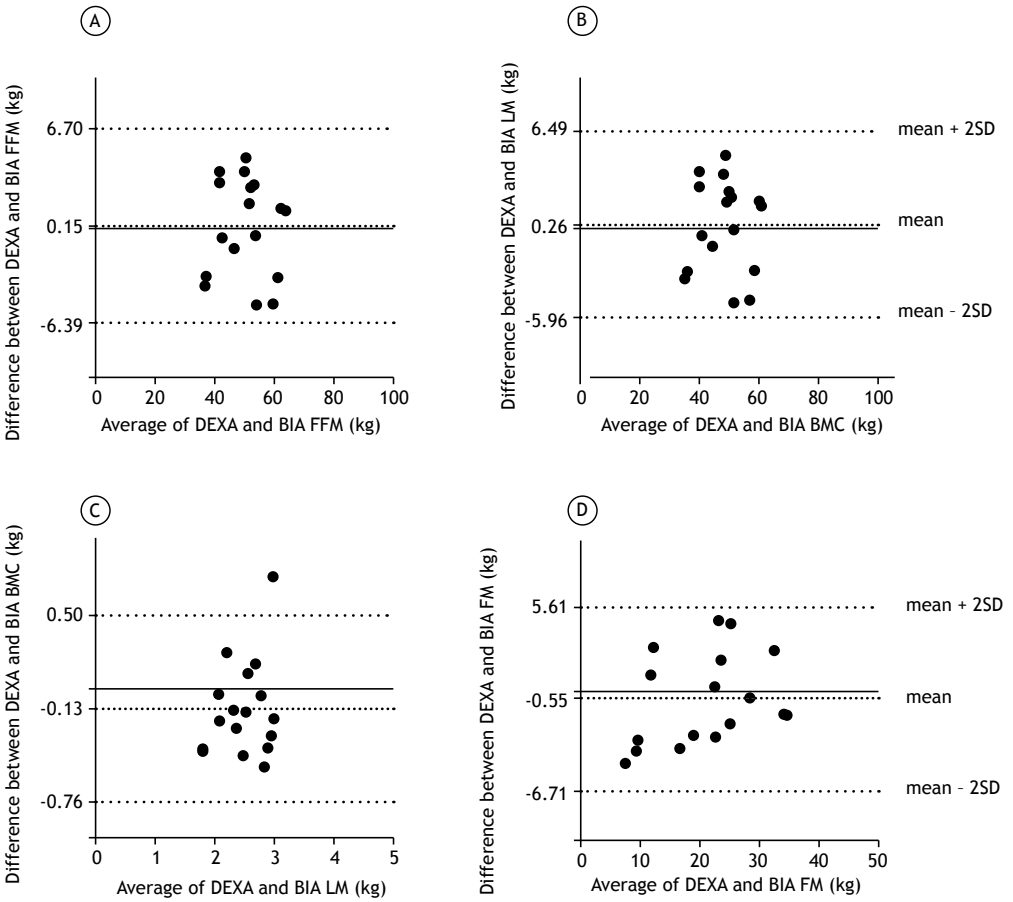

Figure 2. Mean differences and limits of agreement between body composition variables assessed by dual-energy X-ray absorptiometry and the eight-contact electrode bioelectrical impedance analysis system. DEXA: dual-energy X-ray absorptiometry; BIA: bioelectrical impedance analysis; FFM: fat free mass; LM: lean mass; BMC: bone mineral content; and FM: fat mass.

the agreement analysis, slight IMDs were observed between the body composition variables obtained by DEXA and the BIA system, with no statistical differences. To our knowledge, the validity of that BIA system for assessing body composition in COPD patients has never been investigated before. However, previous studies have used DEXA as the criterion method for analyzing the ability of various equations to estimate body composition by conventional BIA systems as an evaluation method for those patients.[10,23-26]

In the current study, a strong inter-method correlation was found for FFM, LM, and FM values. Lerario et al.[10] also observed a strong correlation between FFM values measured by DEXA and by a conventional BIA system in patients with COPD ($r = 0.95$; $p < 0.001$). That had been previously shown by Kyle et al.[24] in patients with chronic respiratory failure ($r = 0.952$; $p < 0.0001$). Pichard et al.[23] studied the association between DEXA and several equations for the estimation of body composition by using a conventional BIA system in patients with chronic respiratory failure. Those authors found a minimum correlation coefficient of 0.66 ($p < 0.001$) for FFM and FM. In heavy smokers, Rom et al.[27] showed a strong correlation between BMC ($r = 0.81$), LM ($r = 0.94$), and FM ($r = 0.97$) measured by an eight-contact electrode BIA system and DEXA).

When analyzing the agreement between the methods in the present study, we found that the eight-contact electrode BIA system slightly underestimated FFM values when compared with those by DEXA. Corroborating this result, underestimated values for FFM obtained by conventional BIA systems compared with those measured by DEXA in COPD patients were also observed in other studies.[10,25,26] The bias ranged between 0.57 and 4.1 kg, which is greater than that observed in the current study.[10,25,26] However, FFM values were overestimated by BIA when compared with DEXA in other studies involving patients with chronic respiratory failure, with biases between 0.1 and 8.0 kg.[23,24]

In the present study, the eight-contact electrode BIA system underestimated LM when it was compared with DEXA. It is known that FFM is primarily composed by LM, and, therefore, when there is FFM underestimation, LM underestimation is also expected. Overestimated FM values were obtained by the eight-contact electrode BIA system when they were compared with those by DEXA. However, Rom et al.[27] found underestimated FM values obtained by an eight-contact electrode

BIA system when compared with those obtained by DEXA (IMDs = 0.19 kg) in heavy smokers. In healthy elderly Europeans, Mally et al.[28] found that an eight-contact electrode BIA system underestimated LM (IMDs = 1.0 kg) and overestimated FM (IMDs = −5.8 kg) when compared with the values obtained by DEXA in men, which confirms the results observed in the current study, since our sample was composed mostly by males. In the present study, we also found that the eight-contact electrode BIA system slightly overestimated BMC values when compared with those by DEXA and that the BMC values measured by the two methods showed a moderate correlation. BMC is a component of FFM, and it appears to be decreased in COPD patients.[29] It is known that DEXA enables the identification of bone mineral loss in these patients[8] and is considered the gold standard for bone mass determination. This suggests that the eight-contact electrode BIA system is not as accurate a method as DEXA for the evaluation of the skeletal status of patients with COPD.

Although DEXA is not considered the gold standard for body composition evaluation,[30] it has been recommended as a reference method for this purpose in COPD patients.[8,9] Its high cost and demand on training and technological resources, however, limit its use in clinical practice. Because BIA has lower costs and is easy to use, it has been chosen as a method for assessing body composition in patients with COPD in some studies.[11,12] The eight-contact electrode BIA system associated with household scales dispenses with the use of adhesive gel electrodes, has lower costs than does a conventional BIA monitor, and enables easy and immediate assessment of body composition and weight. We found that the eight-contact electrode BIA system, in addition to its simplicity, practicality, and convenience, can be used as an alternative to more complex methods for routine assessment of body composition in patients with COPD in clinical practice and epidemiological studies.

The exclusion of patients with mild airflow obstruction in our sample can be identified as a limiting factor, making the extrapolation of the observed results not possible for those patients. Moreover, the small sample size, recruited by convenience from public and private pulmonary clinics, reduces the external validity of the study because the sample might not be representative of the general COPD population in terms of body composition. In addition, the analysis of groups according to the severity of airflow obstruction, gender, or nutritional status cannot be made in our study. Despite the small sample size, the statistical power for all correlations observed between the body composition variables obtained by DEXA and by the eight-contact electrode BIA system was greater than 90%. Further investigations using a larger and randomly selected sample of patients with COPD are recommended in order to confirm our results. Another limitation that could be pointed out is that the responsiveness of the BIA system to an intervention was not evaluated because of the cross-sectional design of the present study.

In conclusion, the eight-contact electrode BIA system is a simple and useful tool for the assessment of whole body composition in clinically stable patients with moderate to very severe COPD, and the difference in LOA does not seem to have an impact on the validity of the method.

ACKNOWLEDGMENTS

We would like to thank Leila Marques John Steidle, Pablo Moritz, Tatjana Almeida Prado, Camilo Fernandes, and Fatima Almeida Saitn Martin (pulmonologists) for referring their patients to our study. We would also like to thank Ivo Sebastian Garzel Junior (radiologist) and Sonitec® clinic of medical diagnostic imaging for performing the DEXA scans.

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J Bras Pneumol. 2018;44(4):321-333
http://dx.doi.org/10.1590/S1806-37562017000000185

REVIEW ARTICLE

Patient-ventilator asynchrony

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Submitted: 30 May 2017.
Accepted: 3 September 2017.

Study carried out in the Departamento de Medicina Clínica, Universidade Federal do Ceará, Fortaleza (CE) Brasil.

ABSTRACT

Patient-ventilator asynchrony (PVA) is a mismatch between the patient, regarding time, flow, volume, or pressure demands of the patient respiratory system, and the ventilator, which supplies such demands, during mechanical ventilation (MV). It is a common phenomenon, with incidence rates ranging from 10% to 85%. PVA might be due to factors related to the patient, to the ventilator, or both. The most common PVA types are those related to triggering, such as ineffective effort, auto-triggering, and double triggering; those related to premature or delayed cycling; and those related to insufficient or excessive flow. Each of these types can be detected by visual inspection of volume, flow, and pressure waveforms on the mechanical ventilator display. Specific ventilatory strategies can be used in combination with clinical management, such as controlling patient pain, anxiety, fever, etc. Deep sedation should be avoided whenever possible. PVA has been associated with unwanted outcomes, such as discomfort, dyspnea, worsening of pulmonary gas exchange, increased work of breathing, diaphragmatic injury, sleep impairment, and increased use of sedation or neuromuscular blockade, as well as increases in the duration of MV, weaning time, and mortality. Proportional assist ventilation and neurally adjusted ventilatory assist are modalities of partial ventilatory support that reduce PVA and have shown promise. This article reviews the literature on the types and causes of PVA, as well as the methods used in its evaluation, its potential implications in the recovery process of critically ill patients, and strategies for its resolution.

Keywords: Respiration, artificial; Respiratory insufficiency; Interactive ventilatory support.

INTRODUCTION

Definition and epidemiology

Mechanical ventilation (MV) is one of the most commonly used interventions in the ICU, being indispensable to maintaining the life of critically ill patients with acute respiratory failure.[1] The main objectives of MV include maintaining adequate levels of gas exchange and decreasing respiratory effort, until the clinical condition that was the indication for MV is resolved or compensated.[2] To that end, the goal should be optimal patient-ventilator interaction, with a balance between patient inspiratory effort and ventilator triggering, between ventilatory demand and delivery of flow and tidal volume, and between interruption of patient inspiration and cycling of the device. Patient-ventilator asynchrony can be defined as a mismatch between the patient, regarding time, flow, volume, or pressure demands of the patient respiratory system, and the ventilator, which supplies such demands, during MV.[3] Asynchrony events can range from subtle changes, the detection of which demands strong suspicion and refined monitoring, to an evident "struggle" between the patient and the ventilator.

Patient-ventilator asynchrony has incidence rates ranging from 10% to 85%.[4-8] This great variation can be explained by the fact that different factors affect the incidence and detection of patient-ventilator asynchrony (Chart 1). To quantify this phenomenon, some authors have proposed the asynchrony index (AI), defined as the number of asynchrony events divided by the total respiratory rate, that is, the sum of ventilator cycles and ineffective efforts, and expressed as a percentage. In one pioneering study,[5] nearly one fourth of the patients had an AI above 10% when the incidence of events over only 30 min of continuous monitoring of intubated patients was evaluated.

RISK FACTORS

Patient-related factors

Regardless of the etiology of the respiratory failure leading to the need for MV, the greater clinical severity of the patient favors the occurrence of asynchrony, especially during the initial phases of ventilatory support. Sepsis, acidosis, anxiety, and fever are some of the factors that increase ventilatory demand and hinder the balance between the flow and volume demanded by the patient and those delivered by the ventilator, contributing to the occurrence of asynchrony.[9] In patients who are unstable, sedation and analgesia are often required until stabilization is achieved. The underlying diagnosis is also very relevant. COPD has been considered the most commonly associated

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Financial support: None.

condition with asynchrony, especially in the presence of auto-positive end-expiratory pressure (auto-PEEP), which hinders ventilator triggering and favors the frequent occurrence of ineffective efforts.[10] Respiratory mechanics influences the type of patient-ventilator asynchrony, depending on neural inspiratory time and on ventilator settings.[10,11] An obstructive respiratory mechanics profile appears to be more associated with delayed cycling asynchrony, aggravated by short neural inspiratory time, whereas a restrictive respiratory mechanics profile with longer neural inspiratory time favors premature cycling events during pressure support ventilation (PSV) and proportional assist ventilation plus (PAV+).[11] In fact, depending on the ventilatory mode, COPD patients can also have cycle asynchrony. This occurs, for instance, when patients receive PSV, whose cycling is linked to the percent reduction in inspiratory flow.[12,13] Another condition that favors certain types of asynchrony is acute respiratory distress syndrome (ARDS). Patients with this condition should be ventilated with low tidal volumes and low continuous positive airway pressures.[2] Although these settings are lung protective, they are often not tolerated by the patient and cause asynchrony.[14] Double triggering is one the most common types of asynchrony and can result in the delivery of converging respiratory cycles, which means that MV is no longer protective. This hypothesis has been proposed to explain the satisfactory results with the use of neuromuscular blockade in the first days of ventilation in patients with severe ARDS, perhaps because it prevents this type of asynchrony and ensures protective ventilation.[15]

Ventilator-related factors

The choice of ventilatory mode and the choice of ventilator settings are factors that affect the incidence of asynchrony. A study involving 62 patients, 11 on volume-controlled ventilation (VCV) and 51 on PSV, detected 2.1 asynchrony events per minute, on average, the incidence being significantly higher in those on VCV than in those on PSV (4.3 ± 4.8 events/min vs. 1.9 ± 3.8 events/min).[5] In conventional modes—VCV, pressure-controlled ventilation (PCV), and PSV—pneumatic triggering can be a source of asynchrony, especially in patients on auto-PEEP, such as those with COPD.[16] The VCV mode is more commonly associated with asynchrony resulting from inadequate flow or tidal volume, such as double triggering, given that these parameters are set by the operator and are not always adequate to the demand of the patient.[17] Switching to modes in which the flow and volume vary in response to patient effort, such as PSV and PCV, can improve comfort.[18] However, choosing a ventilatory mode that allows the patient to have a certain control over inspiratory flow, such as PCV or PSV, does not ensure optimal patient-ventilator interaction. For the application of PCV and PSV, the choice of the level of support to be delivered is essential and should be individualized.

TYPES OF ASYNCHRONY, DIAGNOSES, AND STRATEGIES

By analyzing volume, flow, and pressure waveforms on the mechanical ventilator display, it is possible to detect the most common types of patient-ventilator asynchrony, which are those related to triggering, those related to cycling, and those related to flow. Chart 2 presents the types of patient-ventilator asynchrony and comments on ventilator- and patient-related factors, as well as therapeutic strategies for each situation.

Triggering asynchronies include ineffective triggering or effort, auto-triggering, and double triggering. They are called so because they result from problems in the triggering or initiation of the respiratory cycle by the ventilator in response to patient respiratory muscle effort. Ineffective triggering consists in failure to recognize patient inspiratory muscle effort. Figure 1 illustrates two different scenarios in which ineffective efforts can occur. Ineffective efforts might be due to factors related to the ventilator, such as inappropriate sensitivity setting or malfunctioning sensitivity; to the patient, such as respiratory muscle weakness (whether or not it is related to sedation) or neuromuscular blockade (due to auto-PEEP); or to both. Clinically, patient inspiratory effort can be sensed by touching the chest or abdomen, observing that movement of the chest or abdomen is not accompanied by a ventilator-delivered breath.[2]

To resolve ineffective triggering, the sensitivity should be set as high as possible, thus avoiding, however, auto-triggering and switching from pressure triggering to flow triggering, which is more sensitive. When auto-PEEP associated with dynamic hyperinflation is observed, one can attempt to increase PEEP cautiously—monitoring the resolution or attenuation of asynchrony, rarely exceeding 10 cmH_2O, or reducing the pressure support

Chart 1. Factors that affect the occurrence and detection of patient-ventilator asynchrony.

Factors related to the occurrence of asynchrony	Factors related to the detection of asynchrony
Indication for MV	Observation time
Severity of respiratory failure	Length of the observation periods
Ventilatory modes	Timing of observation during MV (e.g., first days and phase of weaning)
Ventilator settings	Detection method (e.g., clinical assessment, waveform monitoring, esophageal balloon measurement, and detection of the electrical activity of the diaphragm)
Level of sedation	Definition of asynchrony and of its significance

MV: mechanical ventilation.

Chart 2. Common types of patient-ventilator asynchrony, associated factors, and therapeutic strategies.

Asynchrony	Determining factors	Therapeutic strategies
Triggering		
Ineffective triggering	Ventilator:	
	Inappropriate sensitivity setting or malfunction of the sensitivity mechanism	Adjustment/correction of sensitivity problems (flow more sensitive than pressure)
	Prolonged inspiratory time	Decrease inspiratory time by adjusting settings for each mode (VCV, PCV, and PSV)
	Patient:	
	Respiratory muscle weakness	Reduce or discontinue neural drive depressants, sedation, or NMBA
	Decreased neural drive	
	Dynamic hyperinflation (auto-PEEP)	Minimize hyperinflation and titrate extrinsic PEEP (values lower than auto-PEEP values), decrease PS levels (PSV mode)
Double triggering	Ventilator:	
	Inspiratory time too short relative to neural inspiratory time	Increase inspiratory time (VCV or PCV) or decrease the cycling threshold percentage of peak flow (PSV)
	Low tidal volume in VCV	Deep sedation ± NMBA in early severe ARDS Modes that allow variation in tidal volume, such as PCV
Reverse triggering	Muscle effort resulting from mechanical inflation	Reduce sedation, NMBA in early severe ARDS
Auto-triggering	Ventilator:	
	"Excessive" sensitivity	Optimize the sensitivity setting
	System leak	Correct leak
	Condensate in the ventilator circuit	Remove condensate
	Patient:	
	Transmission of pressure or flow oscillations because of cardiac activity	Optimize the sensitivity setting
Cycling		
Premature cycling	Ventilator:	
	Inspiratory time is too short relative to patient inspiratory time	In VCV, decrease inspiratory flow or increase tidal volume In PCV, increase inspiratory time
	Patient:	
	Restrictive respiratory mechanics in PSV, as in pulmonary fibrosis	In PSV, decrease the cycling threshold percentage criterion or increase PS
Delayed cycling	Ventilator:	
	Inspiratory time is too long relative to patient inspiratory time	In VCV, increase inspiratory flow In PCV, decrease inspiratory time
	Patient:	
	Obstructive respiratory mechanics in PSV, as in COPD	In PSV, increase the cycling threshold percentage criterion, or decrease PS, or decrease rise time
Flow		
Insufficient flow	Ventilator:	
	In VCV, the flow setting is too low	In VCV, increase inspiratory flow or switch to PCV or PSV (free flow)
	In PCV and PSV, the applied pressure is too low, long rise time	
	Patient:	
	Excessive ventilatory demand, increased neural drive	Reduce neural drive and metabolic demand: control fever, pain, metabolic acidosis, and anxiety
Excessive flow	Ventilator:	
	In VCV, the flow setting is too high	In VCV, decrease inspiratory flow
	In PCV and PSV, the applied pressure is too high, rise time is too short (overshoot)	In PCV and PSV, decrease applied pressure, increase rise time

VCV: volume-controlled ventilation; PCV: pressure-controlled ventilation; PSV: pressure support ventilation; NMBA: neuromuscular blocking agent; (auto-)PEEP: (auto-)positive end-expiratory pressure; PS: pressure support; and ARDS: acute respiratory distress syndrome.

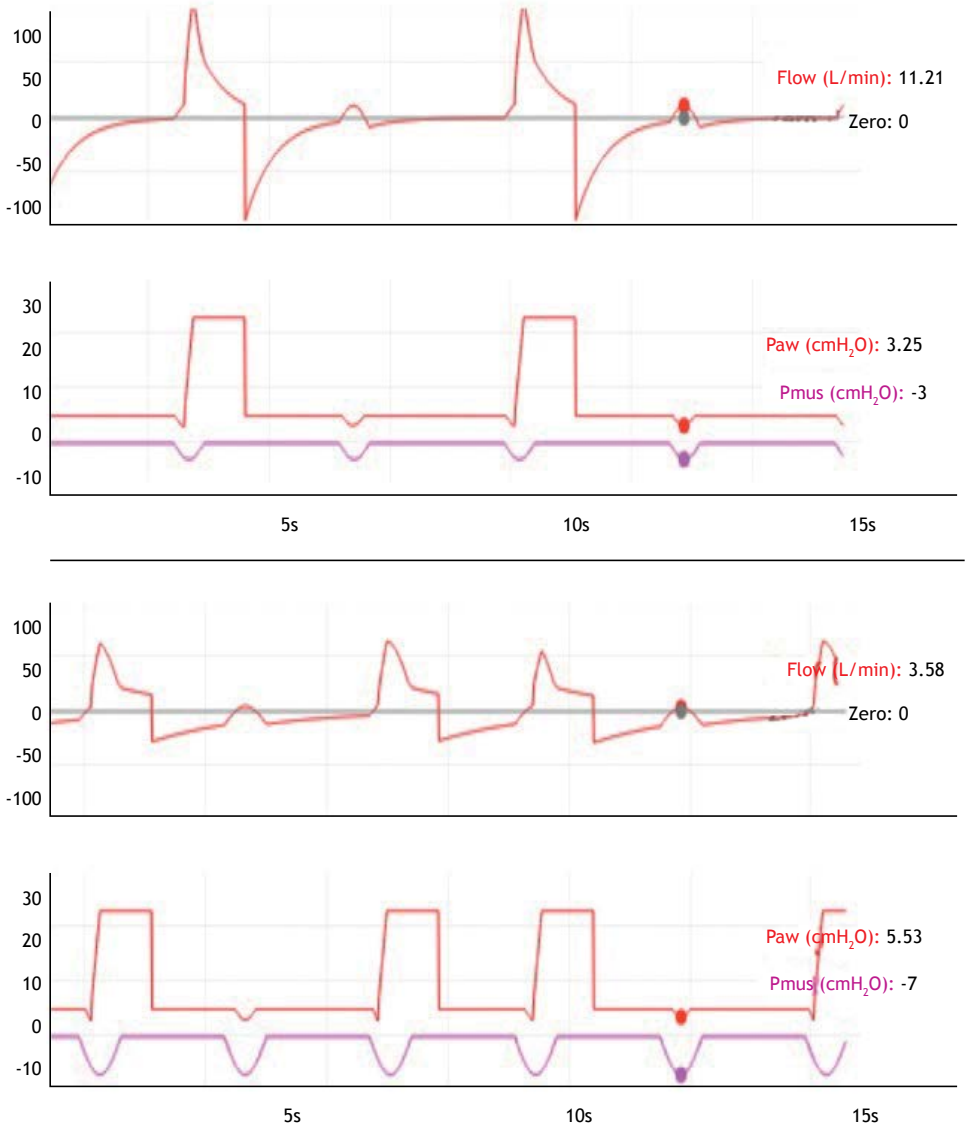

Figure 1. Flow and pressure waveforms, respectively, illustrating two simulated types of ineffective triggering. The first two waveforms represent a patient without problems in respiratory mechanics, with a weak spontaneous effort (Pmus) because of respiratory muscle weakness or decreased neural drive. The bottom two waveforms represent a patient with airflow obstruction and difficulty in triggering some breaths because of the presence of auto-positive end-expiratory pressure, even with a muscle effort that is "physiological" but unable to trigger ventilator breaths. In both cases, pressure-controlled ventilation (pressure sensitivity of −2 cmH_2O) was used. The dots on the waveforms indicate ineffective efforts. Paw: airway pressure; and Pmus: muscle pressure. Source: Xlung®.

level in PCV and PSV (if tidal volume is high)—or to decrease inspiratory time in VCV.

Auto-triggering is the opposite of ineffective triggering: the ventilator triggers a breath when it improperly recognizes a flow or pressure variation in the circuit as being patient spontaneous respiratory muscle effort. In other words, the ventilator sensitivity system is "tricked" by artifacts, such as leaks with depressurization of the circuit or flow or pressure oscillations due to the presence of condensate in the circuit, or by transmission of intrathoracic pressure variations because of cardiac activity due to systolic ejection. Figure 2 illustrates two common situations that generate auto-triggering.

Double triggering consists of the ventilator delivering two consecutive breaths in response to patient respiratory muscle effort, that is, it occurs when patient effort triggers two breaths in a row. In such cases, patient neural inspiratory time is longer than the ventilator inspiratory time. The first trigger is from patient effort.

Reverse triggering occurs when patient inspiratory muscle effort results from reflex mechanisms triggered by mechanical insufflation with a ventilator-controlled

breath. This form of patient-ventilator interaction, which is still unclear and potentially common, may go unnoticed clinically; it is necessary to monitor esophageal pressure, because the muscle effort does not originate in the respiratory center of the patient but rather in a patient-delivered breath. The term "entrainment" has also been used to describe this phenomenon.[19] Figure 3 illustrates two types of asynchrony: double triggering and reverse triggering. In both cases, there is stacking of tidal volumes, resulting in distension of the lung parenchyma, with a corresponding increase in alveolar and airway pressures, and posing a risk of ventilator-induced lung injury, particularly in patients with ARDS.[2,17-19] The main therapeutic strategy in such cases consists of increasing inspiratory time (in VCV and PCV), and, in PSV mode, it consists of increasing inspiratory time by decreasing the cycling percentage of peak flow.

Premature cycling occurs when the ventilator ends the inspiratory flow sooner than desired by the patient, that is, the ventilator inspiratory time is shorter than patient neural inspiratory time. Delayed cycling is due to the reverse: the ventilator delivers a breath with a longer inspiratory time than is desired by the patient, that is, the ventilator inspiratory time is longer than patient neural inspiratory time. In VCV and PCV, the ventilator operator

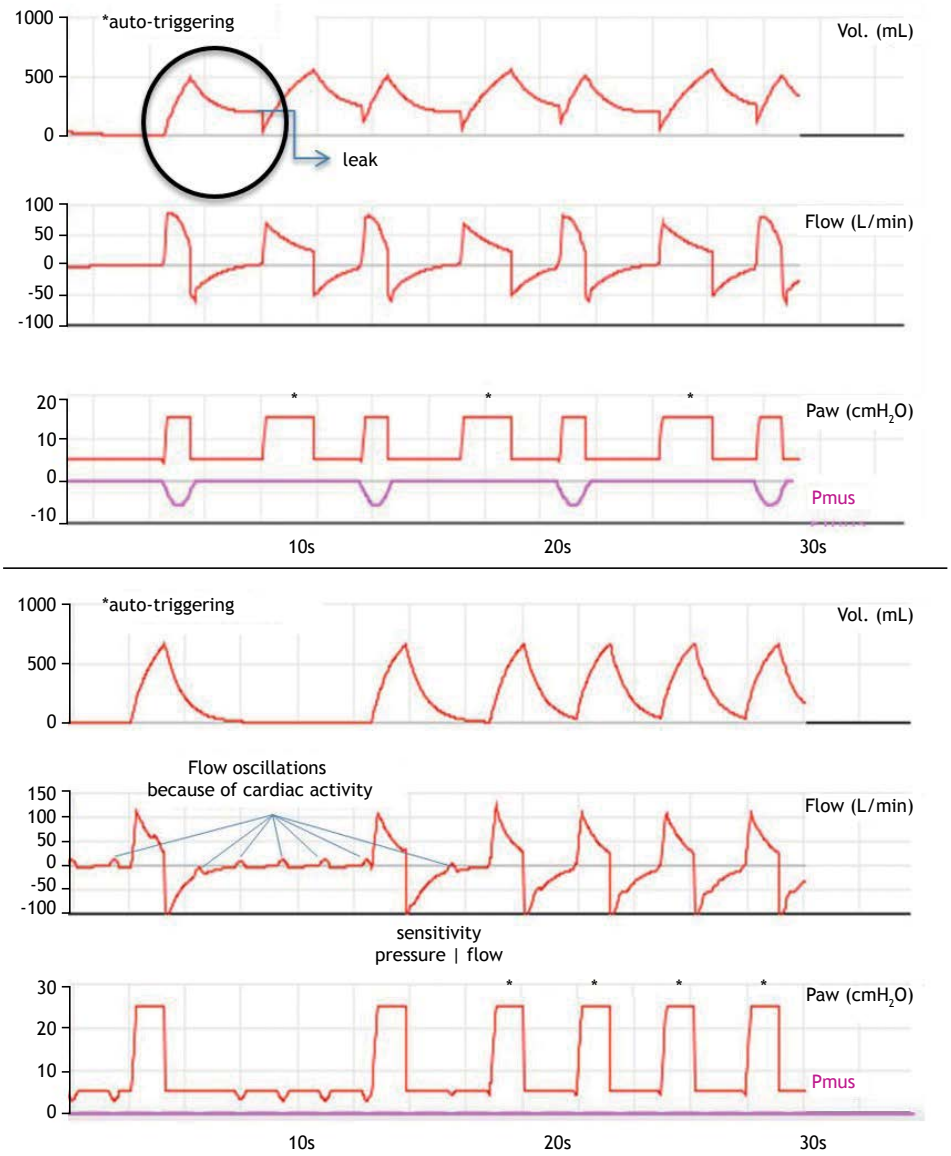

Figure 2. Volume, flow and pressure waveforms, respectively, illustrating two simulated types of auto-triggering. The first three waveforms represent a patient on pressure-support ventilation with flow sensitivity. The system with a leak causes the onset of flow-triggered breaths, without patient effort (Pmus = 0). The bottom three waveforms represent a patient on pressure-controlled ventilation,* without respiratory muscle effort, but showing regular flow and pressure oscillations, with a respiratory rate of approximately 80 breaths/min, corresponding to his/her heart rate. Pressure sensitivity was changed to flow sensitivity. The increase in the total respiratory rate was due to triggers induced by transmission of flow oscillations because of cardiac activity. Vol.: volume; and Paw: airway pressure. Source: Xlung®.

can attempt to correct these asynchronies by directly adjusting the inspiratory time setting and assessing patient adaptation by interpreting the MV waveforms on the ventilator display. In PSV mode, the main strategy is to adjust the cycling threshold percentage of peak flow, which can usually be set between 5% and 70%. To correct premature cycling, the threshold should be decreased, and, to correct delayed cycling, the threshold should be increased. In COPD patients, because of their increased airway resistance, the decrease in the flow delivered by PSV is slower, delaying ventilator cycling. This asynchrony can be corrected or minimized by adjusting the cycling level, which is usually preset at 25%, to higher values, such as 40-50%. Another approach can be to change the applied pressure support over PEEP. When this parameter is increased, inspiratory time usually increases as well, and vice-versa. Figure 4 illustrates premature cycling and delayed cycling, as well as the effects that changes in the cycling criterion have on these asynchronies.

Flow asynchrony can be of two types: insufficient inspiratory flow and excessive inspiratory flow. In instances of the first type, the flow received by the patient is lower than his/her ventilatory demand, typically occurring when the flow is set by the operator and cannot be increased by patient spontaneous

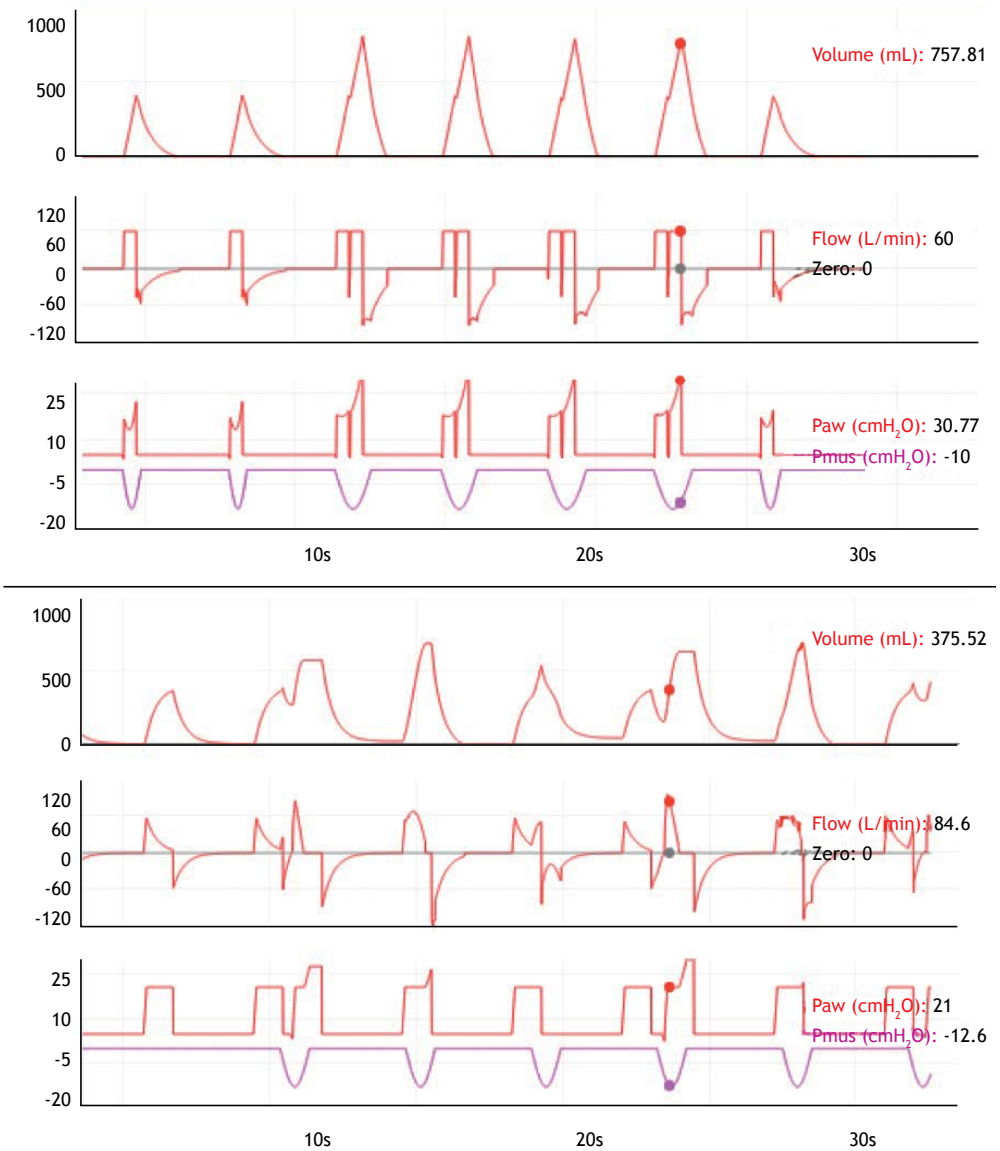

Figure 3. Volume, flow, and pressure waveforms, respectively, illustrating two simulations of asynchrony. The first three waveforms represent a case in which, because of patient neural inspiratory time, which is longer than the ventilator inspiratory time, the first breath is always triggered by the patient, during volume-controlled ventilation. The dots indicate stacked tidal volume caused by double triggering. The bottom three waveforms represent a case of reverse triggering due to respiratory muscle effort triggered by reflex mechanisms resulting from a ventilator-delivered breath, during pressure-controlled ventilation. Note, in both cases, stacked tidal volume and increased airway pressure during asynchrony. The dots indicate reverse triggering. Paw: airway pressure; and Pmus: muscle pressure. Source: Xlung®.

efforts, as occurs during VCV. However, insufficient inspiratory flow can also occur during PCV and PSV when the levels set are insufficient to deliver the flow "desired" by the patient. The therapeutic approach can include a reduction in ventilatory demand: correction of fever, anxiety, pain, acidosis, etc.; or an increase in flow delivery by means of appropriate adjustments for each mode (Chart 2), observing patient comfort and use of accessory respiratory muscles, as well as the conformation of the pressure waveform. In patients on VCV, switching to PCV or PSV, which have free flow, can be a good alternative. In addition, in PCV and PSV, an adjustment in rise time directly affects flow delivery soon after the respiratory cycle is triggered; the shorter the rise time, the higher the flow delivery and the faster the initial pressurization of the system; a short rise time is recommended in patients with clinical signs of air hunger. Excessive flow asynchrony occurs because of an exaggerated delivery of inspiratory flow. In some cases, excessive pressurization may occur, characterizing an overshoot of the flow in PCV or PSV. The best option consists of reducing flow delivery by reducing the set value in VCV or by reducing the applied pressure over PEEP or increasing the rise time in PCV and PSV. Figure 5 illustrates flow asynchrony and volume asynchrony during VCV, as well as their correction during PCV.

ADVERSE EFFECTS OF PATIENT-VENTILATOR ASYNCHRONY

General

Patient-ventilator asynchrony causes a series of adverse clinical effects and is associated with unwanted

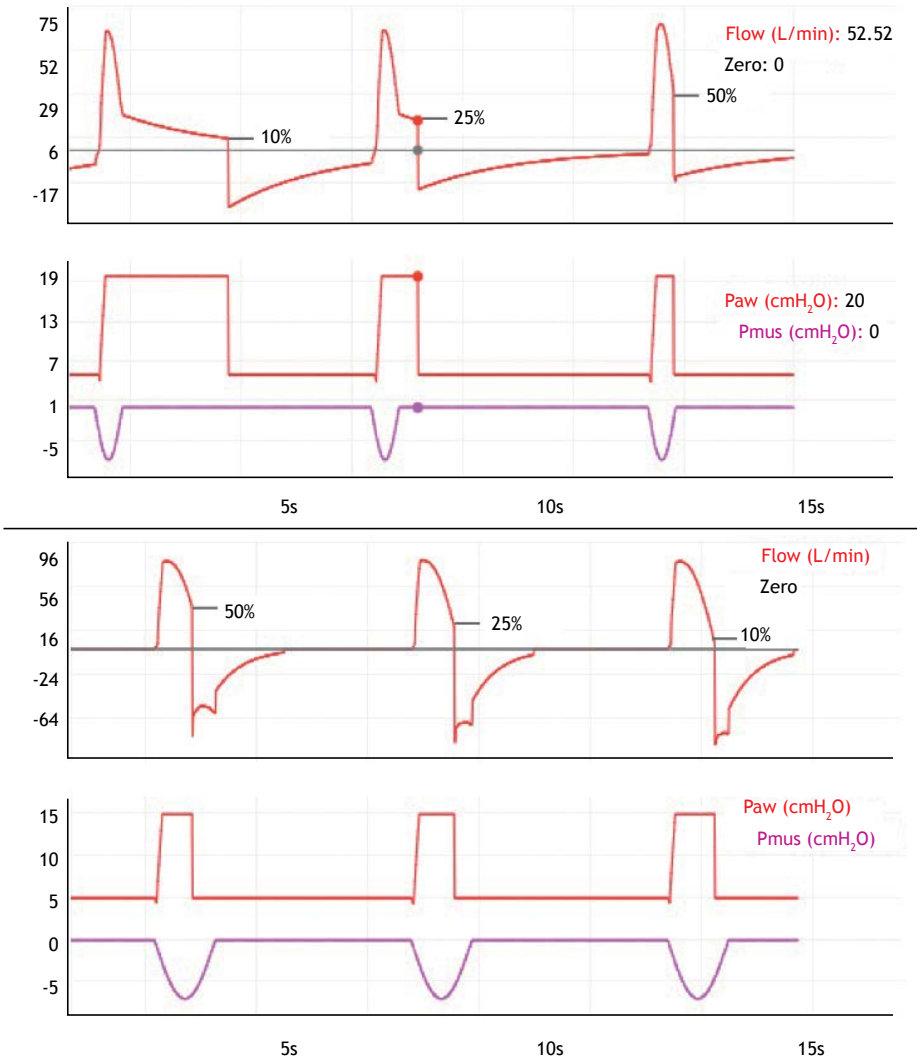

Figure 4. Flow and pressure waveforms, respectively, illustrating two types of cycling asynchrony simulated during pressure support ventilation. The first two waveforms represent a patient with COPD. Asynchrony is corrected by increasing the threshold percentage of peak inspiratory flow for termination of inspiration. The bottom two waveforms represent a patient with restrictive lung disease experiencing premature cycling. Asynchrony is attenuated by decreasing the cycling threshold percentage of peak flow. The dots indicate cycling during pressure support ventilation. Paw: airway pressure; and Pmus: muscle pressure. Source: Xlung®.

outcomes, such as discomfort, dyspnea, worsening of pulmonary gas exchange, increased respiratory effort, diaphragmatic injury, decreased quantity and quality of sleep, increased use of sedation, increased use of neuromuscular blockade, an increased duration of MV, and increased mortality.[20-23] Symptoms of "air hunger" or "excessive inspiratory effort", that is, dyspnea, although rarely studied, are very common during MV. In one study, the use of VCV was associated with these symptoms (OR = 4.77; 95% CI: 1.6-4.3), and an increase in flow or tidal volume attenuated them in 10 of 45 patients (22%).[24] Not surprisingly, because VCV has stricter settings for delivery of flow and tidal volume, it is associated with greater discomfort in non-sedated patients, which could also be reflected in the incidence of asynchrony, although this last observation requires further evidence.[24,25] Asynchrony events can impair oxygenation. A decrease in AI—from 3.36% during PSV to 1.73% during neurally adjusted ventilatory assist (NAVA)—was associated with an increase in the PaO_2/FiO_2 ratio (203 mmHg vs. 254 mmHg).[26] Both excessive and insufficient ventilatory support can cause respiratory muscle damage. In instances of the former, damage includes muscle fiber atrophy or apoptosis, and, in instances of the latter, damage includes increased work of breathing and eventually fatigue. Optimal patient-ventilator interaction, without asynchrony, would theoretically be ideal for the respiratory muscles. It is also possible that certain types of asynchrony, such as ineffective effort, especially when it occurs in the mid-expiratory phase, cause damage to diaphragm muscle fibers by generating eccentric or plyometric contractions during stretching of these fibers in this phase of the respiratory cycle.[27,28]

Use of sedation

Patients on MV are commonly sedated so that they can adapt to ventilatory support.[29] However, observational studies have shown an association between deep sedation and a higher incidence of asynchrony.[22,30] In one study, adult patients receiving PSV during deep sedation with propofol during wakefulness had, under sedation, a higher rate of asynchrony (21.8% vs. 5.9%); decreased respiratory drive, as measured by electrical activity of the diaphragm (Edi; 9.9 μV vs. 3.1 μV); worsening of pulmonary gas exchange (increased $PaCO_2$); and reduced tidal volume (0.39 L vs. 0.44 L).[31] Deep sedation is currently considered a predictor of ineffective effort asynchrony.[29,32] In addition to sedation level, drug type is a factor that affects the incidence of asynchrony. In a multicenter study, AI was lower when using dexmedetomidine as a sedative during MV compared with propofol (2.68% vs. 9.10%), even when targeting light sedation.[33] Increasing intravenous sedation to reduce asynchrony appears to be an ineffective, if not harmful, strategy. Ventilator adjustments, such as changing the ventilatory mode or increasing inspiratory time to one second, were more effective in reducing asynchrony than was increasing sedation.[34] Therefore, in patients experiencing asynchrony, continuous intravenous sedation should only be instituted or increased after optimization of ventilator settings combined with management of common clinical problems, such as pain, anxiety, and delirium, or with prompt administration of a bolus in cases of an evident "struggle" between the patient and the ventilator, for safety reasons.

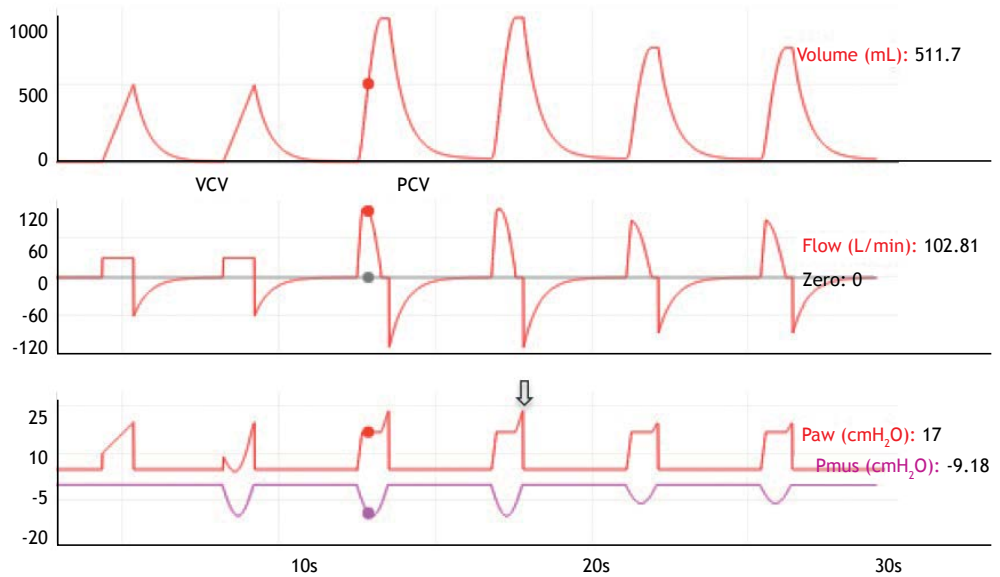

Figure 5. Volume, flow, and pressure waveforms, respectively, illustrating simulation of correction of flow asynchrony and volume asynchrony (air hunger), evident in the second breath, during VCV. The application of PCV from the third breath onward enabled delivery of flow and tidal volume. The patient responded with decreased muscle contraction (Pmus) from the fourth breath onward. Note a slight airway pressure overshoot at the end of breath during PCV (arrow), attenuated by better adaptation of the patient. The dots indicate free-flow delivery during PCV. VCV: volume-controlled ventilation; PCV: pressure-controlled ventilation; Paw: airway pressure;; and Pmus: muscle pressure. Source: Xlung®.

Sleep impairment

ICU patients on MV are highly susceptible to sleep fragmentation and decreased sleep time because of the presence of alarms, the use of inappropriate ventilator settings, and patient-ventilator asynchrony.[1,2] However, the relationship between patient-ventilator asynchrony and sleep quality is controversial.[35-37] In one study, total sleep time and sleep efficiency were higher during MV than during spontaneous breathing in tracheostomized patients on prolonged MV. Some patients had respiratory events (central apnea and double triggering asynchrony) that accounted for 11% of the sleep fragmentation index during MV. It is possible that, once asynchrony has been corrected by making appropriate ventilator adjustments, there is even greater advantage in using MV than spontaneous breathing.[38] One study compared PAV+ and PSV during sleep.[8] Although there was a significant reduction of asynchrony events/h with PAV+ relative to PSV (5 events/h vs. 40 events/h), this effect did not lead to a significant improvement in sleep quality, and PAV+ was associated with increased sleep fragmentation (18.8 events/h vs. 18.1 events/h) and with a lower rapid-eye-movement sleep percentage (0.0% vs. 5.8%).[8] Current findings are insufficient to determine if, how, and the extent to which, patient-ventilator asynchrony affects sleep.

Duration of MV and mortality

In a pioneering study,[4] the presence of ineffective efforts, as detected over an observation period of only 2 min within the first week of admission to a weaning center, was identified in 19 of 174 patients (11%). In this group of patients, this presence was associated with a lower rate of weaning success (16% vs. 57%). Patients in this group were older, were more likely to have been diagnosed with COPD, had higher $PaCO_2$, and had lower MIP; it was not possible to confirm the relationship between patient-ventilator asynchrony and impaired weaning.[4] In another study,[5] it was observed that patients with an AI ≥ 10%, as determined over a 30-min observation period aimed at detecting four types of asynchrony, had longer duration of MV than did those with an AI < 10% (25 days vs. 7 days). Among the former, there was a higher proportion of patients who required tracheostomy (33% vs. 4%). Mortality in the ≥10% AI group was 47% vs. 32% in the <10% AI group, a difference without statistical significance ($p = 0.36$). However, patients with patient-ventilator asynchrony had different clinical characteristics, a higher proportion of them having COPD, as well as higher bicarbonate and pH levels; a cause-and-effect relationship was not established between patient-ventilator asynchrony and impaired weaning.[5]

In another study,[32] 60 patients were evaluated over 20 min within the first 24 h of ventilatory support, regarding the occurrence of ineffective efforts. Fourteen patients (23%) were identified as having an AI ≥ 10%, all of whom had demographic and clinical characteristics similar to those of patients with an AI < 10%. Compared with patients in the <10% AI group, those in the ≥10% AI group had longer duration of MV (6 days vs. 2 days; $p = 0.007$), fewer ventilator-free days (21 days vs. 25 days; $p = 0.02$), and longer ICU stays (8.3 days vs. 4.2 days; $p = 0.01$). Mortality did not differ significantly between the groups (5.3 vs. 9.2%; $p = 0.39$).[32] One of the major limitations of studies on the incidence of patient-ventilator asynchronies and their effects on clinical outcomes is the fact that the observation period is too short. To overcome this limitation, a group of researchers investigated patient-ventilator asynchrony through analysis of asynchronies detected by dedicated software throughout the period when a group of patients was on MV.[22] The following types of asynchrony were monitored; ineffective efforts; double triggering; aborted inspirations; premature cycling; and delayed cycling. Of a total of 50 patients who remained on MV for more than 24 h, those with an AI ≥ 10% showed a tendency toward having longer duration of MV than did those with an AI < 10% (16 days vs. 6 days; $p = 0.061$). ICU mortality was significantly higher among the former than among the latter (67% vs. 14%; $p = 0.011$), as was in-hospital mortality (67% vs. 23%; $p = 0.044$). The longer observation period, which is a major difference relative to other studies and covered more than 80% of the total duration of MV, was the strength of that study.[22] This allowed the determination of the true incidence of patient-ventilator asynchrony and may have been the reason why an association was identified between this incidence and higher mortality. In contrast, the fact that patient-ventilator asynchronies were identified automatically through the use of dedicated software, which is not yet available for confirming these findings in other centers, constitutes a limitation; it should be highlighted that the association found between the incidence of patient-ventilator asynchrony and higher mortality does not definitively establish a causal relationship between patient-ventilator asynchrony and duration of MV or between patient-ventilator asynchrony and mortality.[22]

PAV AND NAVA

PAV and NAVA are two new ventilatory modes that have been developed to reduce the occurrence of patient-ventilator asynchrony.[23,39,40] Both are currently classified as proportional modes, because they require the patient to make some inspiratory effort and deliver partial support in proportion to patient effort. This is what mainly distinguishes these two modes from other pressure support modes, such as PSV, in which airway pressure is set and adjusted in the ventilator and is not changed by patient effort. In NAVA and PAV, although through different algorithms, airway pressure varies in proportion to patient effort: the greater the effort, the greater the inspiratory assistance, which translates to increased airway pressure.[2]

In NAVA mode, inspiratory support is proportional to Edi, which is estimated by an esophageal catheter inserted through the subject's nose specifically for

the application of NAVA. In PAV mode and, more specifically, in its latest commercial version, PAV+, inspiratory support is delivered in proportion to the work of breathing performed by the patient, estimated by applying end-inspiratory micropauses that allow estimation of the resistance and static elastance of the respiratory system by using the equation of motion.[40]

In NAVA mode, after positioning of the catheter, Edi is measured breath by breath and used for triggering, to deliver inspiratory support in proportion to patient effort, and for cycling. Triggering occurs when Edi increases by 0.5 μV above baseline activity, and cycling occurs when Edi decreases to 70% of its peak. The inspiratory support delivered by the ventilator is adjusted by the NAVA level, or NAVA gain, a factor by which Edi is multiplied to determine the pressure that will be applied to the airways.[41] Therefore, patient effort, estimated by the Edi waveform, determines triggering, pressurization, and cycling in NAVA, and the only parameter that has to be set by the clinician is the NAVA level. For instance, if the NAVA level is set to 2 $cmH_2O/\mu V$, and if, in a given breath, peak Edi is 10 μV, peak airway pressure will be 10 × 2, that is, 20 cmH_2O.

In PAV+ mode, once respiratory system elastance and airway resistance have been estimated, the ventilator measures instantaneous inspiratory flow and volume and uses the equation of movement to determine the pressure that will be applied to the airways. Therefore, the percentage of the total work of breathing that will be performed by the ventilator is adjusted, and the ventilator delivers inspiratory flow in proportion to patient effort to perform the determined percentage of the total work of breathing. In addition, the ventilator continuously displays the work of breathing performed by the patient, breath by breath, thereby guiding the adjustment of the percentage of assistance delivered.[39,40] For instance, if inspiratory support is set to 60% of the total work of breathing and the patient is performing a low work of breathing, the percentage of assistance should be reduced until the work of breathing performed by the patient is within an appropriate range, which not only prevents over assistance but also prevents fatigue. Cycling in PAV+ mode is flow based and is set to an absolute value, usually being preset at 3 L/min.

NAVA and PAV reduce patient-ventilator asynchrony when compared with PSV.[39,40] NAVA is particularly effective in reducing trigger asynchrony, given that this type of asynchrony occurs when the ventilator detects the onset of Edi, and several studies have shown that NAVA reduces the incidence of ineffective efforts.[42-45] In contrast, NAVA can increase the incidence of double triggering, and, therefore, the incidence of this type of asynchrony can be monitored during its use.[4,44,46] The only clinical study that has evaluated clinical outcomes failed to show any superiority of NAVA over PSV,[47] although there are other ongoing studies. PAV+ has also been compared with PSV, showing better patient control of tidal volume, better quality of sleep, and reduction of asynchrony events.[8,48-50] PAV+ can be used in COPD patients experiencing asynchrony during PSV, as long as care is taken to avoid leaks, which can lead to errors in estimating elastance and resistance, impairing the proper functioning of PAV+.[2]

Single-circuit ventilators or ventilators originally designed for noninvasive ventilation have flow generators and use a single circuit for inspiration and expiration, with exhalation holes in the circuit, which is open to the environment. They use automatic trigger and cycle algorithms and interact well with patients; in addition, these devices appear to reduce auto-trigger asynchrony and to optimize trigger synchrony.[11]

INNOVATIVE TECHNOLOGIES AND PROCESSES

Two new approaches in the diagnosis and treatment of patient-ventilator asynchrony have gained prominence in recent years. The first one is the development of methods for the automatic detection of asynchrony. As previously discussed, the incidence of asynchrony is greatly underestimated, because bedside detection of asynchrony is poor. The sensitivity of residents and intensivists for detecting asynchrony by observing ventilator waveforms is usually low and is affected by their level of training.[7] A study of health professionals found that specific training on MV improves the ability of these professionals to detect asynchrony on the basis of observation of waveforms on the mechanical ventilator display; however, this detection ability was not affected by length of experience or health professional type (nurse, physician, or physical therapist).[51] Therefore, the development of automatic detection methods could improve the diagnosis of asynchrony, inform health professionals, and potentially be used in the future to suggest ventilator adjustments or even to provide the basis for automation of ventilator adjustments.[52] Several algorithms that can detect wasted efforts, double triggering, or asynchrony in general have been developed, but their bedside application is still restricted to research protocols.[52-56] The algorithms for detecting wasted efforts, which are common in COPD patients, and double triggering,[20] which can be harmful in ARDS patients, have been shown to be particularly accurate and comparable to offline detection based on ventilator waveforms, which is itself much superior to online detection, at the bedside.

Another approach is the use of strategies of minimal or no sedation for patients with asynchrony, as discussed previously. These strategies have yet to be tested in larger clinical trials because they affect various domains of critically ill patients on MV. It is of note that, in our experience, i.v. fentanyl, especially when administered continuously and for a long time for the purposes of analgesia and sedation, can cause generalized muscle stiffness, an adverse effect that can lead to difficult-to-resolve asynchronies.

TRAINING HEALTH PROFESSIONALS IN THE DIAGNOSIS AND TREATMENT OF PATIENT-VENTILATOR ASYNCHRONY

The provision of education on MV is considered insufficient given the needs of clinical practice. This is due to the lack of a specific curricular approach to the subject for physicians and health professionals during their education.[57,58] In a study conducted in Brazil,[57] medical students, residents, and emergency physicians considered their knowledge of MV management to be inadequate, according to data from a self-assessment tool. This implies a need for educational programs and training on MV for medical students and even for experienced physicians.[57] Although training in MV is essential for the diagnosis of asynchrony, practical education on MV still requires further dissemination and a systematized approach.[51] Logistical problems; limited space in ICUs and emergency rooms; limited clinical settings; potential risks to patients, faculty, and students; and difficulties in performing arterial blood gas analysis and imaging tests and analyzing their results are some of the obstacles found in MV education.[59,60] Therefore, educational programs and training specifically addressing MV, based on realistic or virtual online simulation, are considered promising tools, but, to that end, studies and technological development are needed.[59,60]

FINAL CONSIDERATIONS

The most common types of patient-ventilator asynchrony are those related to triggering, such as ineffective effort, auto-triggering, and double triggering; those related to premature or delayed cycling; are those related to insufficient or excessive flow. Because patient-ventilator asynchrony is a common phenomenon and is associated with negative clinical outcomes in patients on MV, it is essential that ICU staff actively seek the diagnosis and prompt resolution of this problem. New ventilatory modes, such as NAVA and PAV+, as well as software for automated detection and quantification of asynchronies, have shown promise but have yet to be made more accessible. Training programs addressing patient-ventilator asynchrony in MV should be stimulated and disseminated on a large scale.

ACKNOWLEDGMENTS

We thank postgraduate student Juliana Arcanjo Lino for her contribution. We also thank Xlung for granting access to their platform (www.xlung.net) for digital simulation of MV waveforms.

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J Bras Pneumol. 2018;44(4):334-334
http://dx.doi.org/10.1590/S1806-37562018000000117

Presence of gas in an unusual place: spontaneous pneumomediastinum (Hamman's syndrome)

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A 19-year-old male patient complained of coughing without expectoration, mild dyspnea, and retrosternal pain for three days, with no history of trauma. At physical examination, the patient presented with mild dyspnea, with no evidence of bruising or open cutaneous wounds, mildly painful crackles on bilateral supraclavicular and anterior cervical palpation, and no abnormalities on lung auscultation or laboratory test results. Chest HRCT scans revealed the presence of gas foci in the mediastinum that extended to the neck (Figure 1, arrows), which was compatible with spontaneous pneumomediastinum (Hamman's syndrome). This is a benign, usually self-limiting disease[1] that is more common in male patients from 17 to 25 years of age and slender body type[2] and is characterized by the presence of air in the mediastinum that is unrelated to trauma[3]; the prognosis is usually excellent with conservative treatment, i.e., symptomatic treatment based on analgesia, oxygen therapy, and rest.

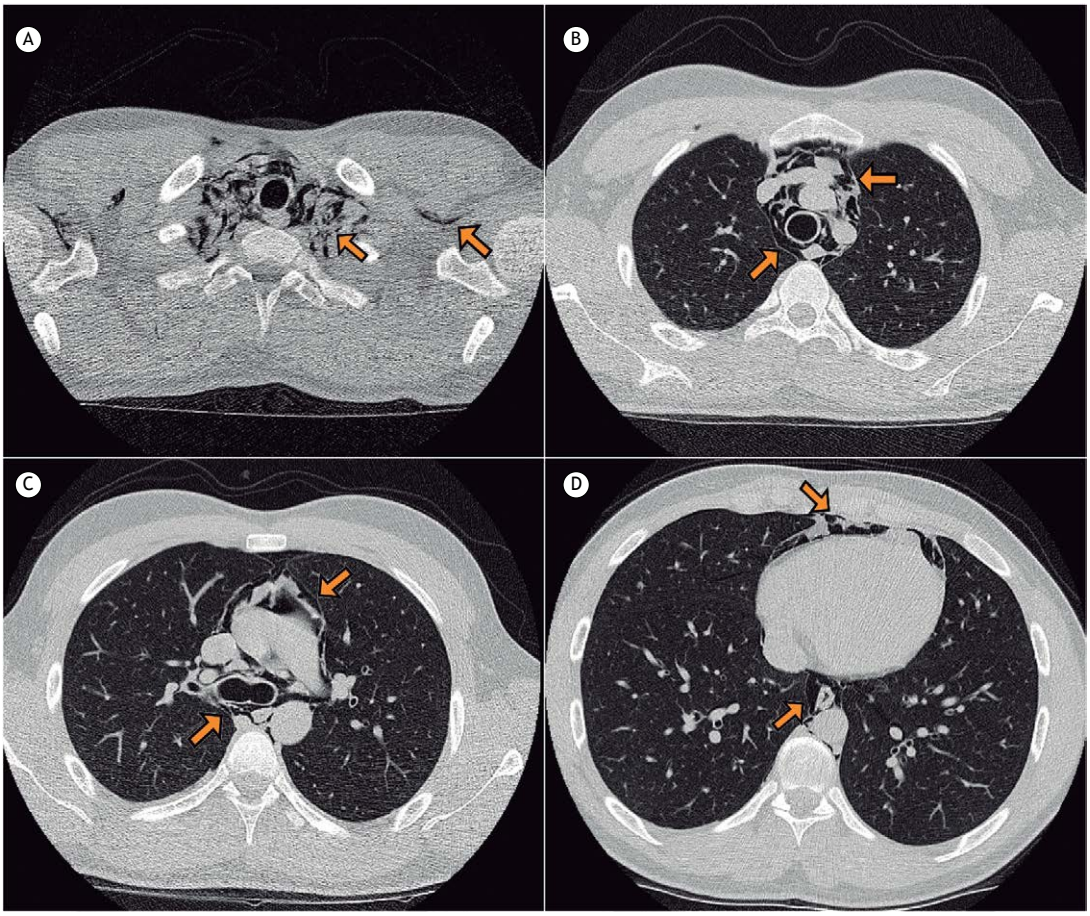

Figure 1. HRCT scans using axial sections, filter and lung window settings, showing the presence of laminar images with marked hypoattenuation representing gas (arrows) in deep topographies in the cervicothoracic transition and axillary regions (in A), as well as in mediastinal, paraesophageal, and paracardiac sites (in B, C and D, respectively).

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ISSN 1806-3713

J Bras Pneumol. 2018;44(4):335-336
http://dx.doi.org/10.1590/S1806-37562017000000175

Hyperimmunoglobulin E syndrome (Job syndrome): chest CT findings

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TO THE EDITOR:

A 38-year-old male patient presented with a history of recurrent respiratory and skin infections since childhood. Fourteen years prior, he had been admitted with an acute respiratory infection, and an elevated IgE level (> 3,000 IU/mL) was observed. Hyperimmunoglobulin E syndrome (HIES) was diagnosed. Since then, the patient has been followed on an outpatient basis, with recurrent paranasal sinusitis and respiratory infections caused by *Staphylococcus aureus*, *Haemophilus influenzae*, and *Pseudomonas aeruginosa*, among others. He has undergone periodic low-dose chest CTs. The most recent CT scans demonstrated thin-walled cavities, predominating in the upper lobes, and non-homogeneous consolidations in the left lung, as well as bronchiectasis. The patient was then diagnosed with recurrent *S. aureus* pneumonia and treated with antibiotics (Figure 1).

HIES, also known as Job syndrome, is a rare multisystem immunodeficiency disease characterized by high serum IgE levels, eczema, and recurrent skin and lung infections. Dysfunction of T-helper 17 lymphocytes plays a crucial role in the immune response to infections caused by pathogens such as extracellular bacteria and fungi. A hallmark of the syndrome is an elevated serum IgE concentration, exceeding 2,000 U/mL and frequently greater than 5,000 U/mL. A value of 2,000 U/mL is considered to be the cut-off point, which has proved to be helpful in establishing a definitive diagnosis of the syndrome.[1-4]

Two distinct forms of the disorder (autosomal-dominant and autosomal-recessive) have been recognized. The autosomal-dominant form is associated with a cluster of facial, dental, skeletal, and connective tissue abnormalities, which are not seen in the recessive type.[1,5] Aside from skin lesions, the most commonly occurring complications include upper airway infection, manifested as paranasal sinusitis, exudative otitis media, otitis externa, mastoiditis, or respiratory tract infection.[1,4]

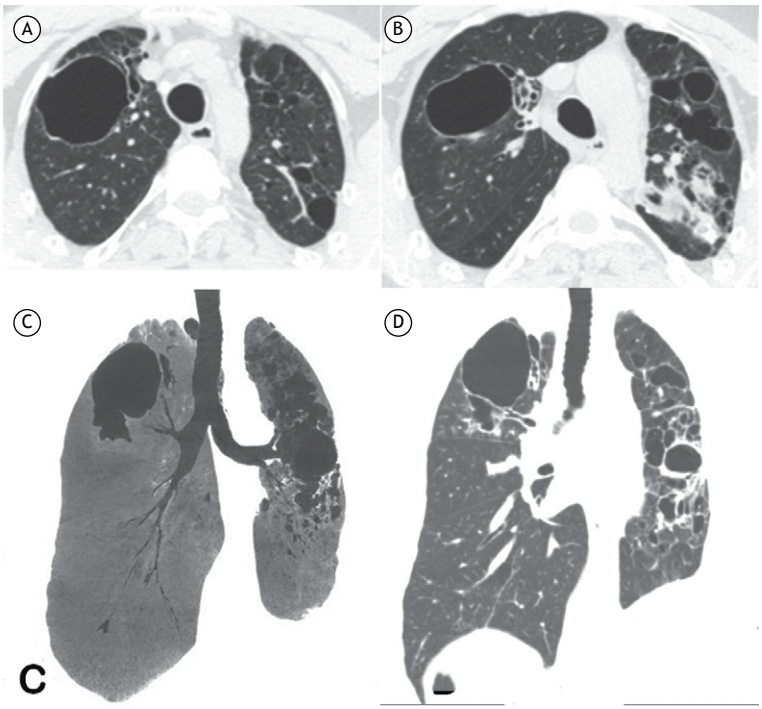

Figure 1. Axial CT scans of the upper lobes (in A and B) and a coronal reconstruction (in C) show bilateral thin-walled cavities and non-homogeneous consolidations in the left lung as well as bronchiectasis. A coronal reconstruction performed 10 months prior (in D) demonstrated similar findings.

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Severe recurrent respiratory infections are usually caused by *S. aureus*, including methicillin-resistant strains, and, less frequently, by *H. influenzae* and *Streptococcus pneumoniae*. Pneumonia is typically complicated by lung abscesses, bronchiectasis, bronchopleural fistulas, and the formation of pneumatoceles. Complications associated with pulmonary infection are among the most common causes of death in the course of HIES. In children, late diagnosis significantly worsens respiratory function and reduces the chance for normal development. The bronchopulmonary lesions are predisposing factors for colonization by opportunistic microorganisms, such as *P. aeruginosa* and *Aspergillus fumigatus*. The latter can lead not only to invasive aspergillosis, requiring intensive therapy, but also to the formation of aspergilloma. Pulmonary sequelae lead invariably to the development of chronic respiratory insufficiency and are the main cause of mortality in HIES.[1,2,4] Other complications include facial, musculoskeletal, neurological, and vascular abnormalities. In addition, the risk of development of neoplastic diseases, such as Hodgkin and non-Hodgkin lymphomas, as well as acute myeloid leukemia, should not be overlooked in patients with HIES.[4,5]

The main goals of HIES management are aggressive treatment of infections and good skin care. A further point of note is that aberrant tissue healing following pulmonary infection can result in parenchymal abnormalities that allow bacterial and fungal colonization leading to infection. Pulmonary surgery appears to be associated with a greater risk of complications and should be considered carefully and undertaken only in a center with specific experience with the disease.[5]

In conclusion, HIES, a multisystem disorder with a diverse somatic picture and a variable clinical course depending on the variant of the disease, poses a great challenge for clinicians in terms of establishing a diagnosis in suspected cases. The introduction of comprehensive management, including prophylactic treatment, can reduce the frequency of recurrence. Patients with HIES require management with an interdisciplinary approach to prevent irreversible and life-threatening pulmonary complications.

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J Bras Pneumol. 2018;44(4):337-338
http://dx.doi.org/10.1590/S1806-37562017000000306

Left main coronary artery compression in a patient with portopulmonary hypertension

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TO THE EDITOR,

We report the case of a 54-year-old male patient with a diagnosis of portopulmonary hypertension (POPH) secondary to alcoholic liver cirrhosis (Child-Pugh class C and Model for End-Stage Liver Disease = 16). The patient was referred to the Outpatient Clinic for Disorders of the Pulmonary Circulation of the Federal University of Minas Gerais *Hospital das Clínicas*, located in the city of Belo Horizonte, Brazil, for assessment to inform decision-making about liver transplantation. At the initial evaluation, he complained of retrosternal pain that was brought on by moderate physical exertion and resolved with rest, without syncope or presyncope. Physical examination revealed a regular cardiac rhythm and fixed splitting of the second heart sound over the pulmonary area, and pulmonary auscultation was unremarkable. An echocardiogram revealed mild enlargement of the right atrium and right ventricle, with an estimated pulmonary artery systolic pressure of 40 mmHg. His spirometry results were as follows: FEV_1 = 3.80 L (101% of predicted); FVC = 4.95 L (104% of predicted); FEV_1/FVC ratio = 0.77 (97% of predicted); and a negative bronchodilator test. Lung radionuclide imaging findings suggested a low probability of pulmonary thromboembolism. A computed tomography scan of the chest showed normal attenuation of the lung parenchyma, with no pleural effusion, masses, or lymph node enlargement. Right heart catheterization revealed a mean pulmonary artery pressure of 48 mmHg, pulmonary artery resistance of 6.22 Woods units, a diastolic gradient of 25 mmHg, and a cardiac index of 3.17 L/min/m^2. On the basis of these findings, the patient received a confirmed diagnosis of POPH, with limitation corresponding to functional class II, and stable angina, class III, due to extrinsic compression of the left main coronary artery (LMCA).

The patient was then hospitalized to undergo further diagnostic assessment and therapeutic planning. Coronary computed tomography angiography (Figures 1A and 1B) showed severe ostial LMCA stenosis that was probably due to extrinsic compression by the main pulmonary artery (MPA). Coronary cineangiography (Figure 1C) revealed severe stenosis in the proximal third (80%) of the LMCA.

The patient underwent percutaneous angioplasty with placement of a drug-eluting stent into the LMCA (Figure 1D), followed by antiplatelet therapy with acetylsalicylic acid and clopidogrel. He was started on sildenafil 20 mg three times daily to treat pulmonary arterial hypertension (PAH). The patient experienced significant improvement in symptoms and functional capacity.

Angina symptoms are usually associated with coronary atherosclerosis, although they may be due to other conditions such as inflammatory diseases and extrinsic compression of coronary arteries.[1] Of those conditions, LMCA compression by a dilated MPA has been reported as a potentially reversible cause of angina and ventricular dysfunction in patients with PAH. This type of compression is primarily related to congenital heart disease or idiopathic PAH; however, other forms of PAH, such as POPH, can trigger it. Unlike atherosclerotic coronary disease, which is more prevalent in elderly patients, extrinsic compression of the LMCA seems to affect younger patients.[2]

Extrinsic compression of the LMCA can cause chest pain, left ventricular dysfunction, ischemia, and sudden death. Its implications in terms of function and prognosis remain poorly characterized, but malignant arrhythmias and ventricular dysfunction can contribute to increasing the incidence of sudden death in patients with PAH.[3] LMCA compression seems to be related to MPA diameter (greater than 49 mm) and to the ratio of MPA diameter to aorta diameter, as measured by echocardiography.[4]

The current literature on PAH has emphasized the need to generate and investigate a second diagnostic hypothesis for angina or angina-like symptoms in patients with PAH. In the case reported here, the patient underwent coronary computed tomography angiography and coronary cineangiography to elucidate the cause of his angina symptoms. Currently, coronary cineangiography is the gold standard test for making this diagnosis. When viewed with contrast, the LMCA appears narrowed at its origin and has a dilated tubular appearance distal to the obstruction (Figure 1).[2] Noninvasive techniques, such as coronary computed tomography angiography, cardiac magnetic resonance imaging, and transesophageal echocardiography, can demonstrate the origin and proximal course of the coronary arteries.

LMCA compression in patients with PAH is a treatable cause of angina and left ventricular ischemia. However, despite the fact that numerous treatment options have been described for LMCA compression, there is still controversy regarding optimal therapy for this condition.

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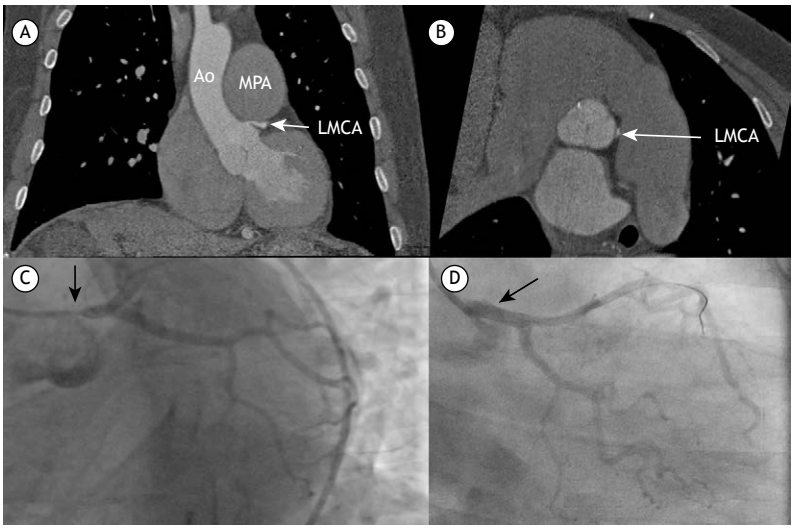

Figure 1. Coronal (in A) and axial (in B) images from coronary computed tomography angiography showing extrinsic compression of the left main coronary artery (LMCA) by the main pulmonary artery (MPA). In C, coronary cineangiography showing severe stenosis in the proximal third of the LMCA (arrow). In D, coronary cineangiography showing the LMCA after stenting (arrow). Ao: aorta.

Treatment options include percutaneous coronary intervention (PCI), coronary artery bypass grafting, and heart-lung transplantation.[3] Although coronary artery bypass grafting remains the treatment of choice for LMCA revascularization, PCI may be considered in patients with anatomic conditions associated with a low risk of PCI procedural complications or in patients with clinical conditions that predict an increased risk of adverse surgical outcomes. In 2017, Galiè et al.[5] presented data on the prevalence of extrinsic compression of the LMCA by a dilated MPA in patients with PAH and angina, as well as the results of PCI. Of 765 patients with PAH, 121 (16%) presented with symptoms that were consistent with angina pectoris. Of those 121 patients, 94 (78%) had abnormal computed tomography angiography findings. Significant LMCA stenosis was detected by coronary angiography in 48 (40%) of the 121 symptomatic patients. A total of 45 patients underwent PCI with stenting, with symptom relief occurring in 91% of the patients, and 5 (11%) developed restenosis.[5] In the case reported here, the patient underwent percutaneous angioplasty with drug-eluting stenting in the LMCA, followed by antiplatelet therapy with acetylsalicylic acid and clopidogrel. For treating PAH, he was started on sildenafil at a dose of 20 mg three times daily. The patient experienced significant improvement in symptoms and functional capacity.

In conclusion, retrosternal pain caused by extrinsic compression of the LMCA by a dilated MPA should be considered in the differential diagnosis of angina or left ventricular dysfunction in patients with PAH. Percutaneous stent implantation can yield good angiographic and clinical outcomes. Further studies are needed in order to determine the impact of PCI on the prognosis of such patients.

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Artigo: Patient-ventilator asynchrony.

Publicação: J. bras. pneumol., ahead of print Epub 16-Jul-2018.

DOI: http://dx.doi.org/10.1590/s1806-37562017000000185

On page 3, **where is written**:

"In PSV, increase the cycling threshold percentage criterion, or decrease PS, or **increase** rise time"

It should be read:

"In PSV, increase the cycling threshold percentage criterion, or decrease PS, or **decrease** rise time"

On page 3, **where is written**:

"In PCV and PSV, decrease applied pressure, **decrease** rise time"

It should be read:

"In PCV and PSV, decrease applied pressure, **increase** rise time"

On page 6, Figure 3, **where is written**:

"Pmus (cmH20): −10??????"

It should be read:

"Pmus (cmH20): −10"

Manuscript: Tuberculosis treatment

Publication: J Bras Pneumol. 2017;43(6):472-486.

DOI: http://dx.doi.org/10.1590/s1806-37562016000000388

On page 479, Chart 5, **where is written:**

"[a]The number preceding the acronym indicates duration of treatment in weeks."

It should be read:

"[a]The number preceding the acronym indicates duration of treatment in months."

ISSN 1806-3713

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

Abstracts

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

Chapter in a Book

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

Official Publications

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

Theses

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

Electronic publications

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

Homepages/URLs

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

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