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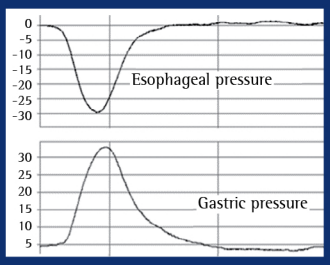
HIGHLIGHT

Respiratory muscle assessment



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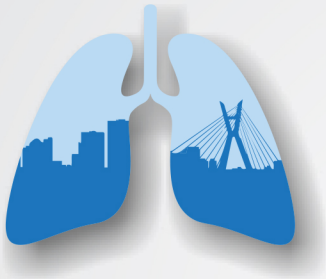

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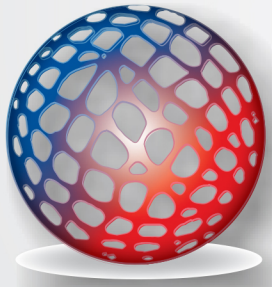

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Sumário/Contents

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Sumário / Contents

Relevance of anamnesis and of biomarkers in the assessment of smoking among patients with airway disease

Importância da anamnese e dos biomarcadores na avaliação de tabagismo nas doenças de vias aéreas

Ubiratan de Paula Santos[1]

"The prevalence of smoking in patients with chronic obstructive pulmonary disease or asthma is high—the relevance of anamnesis and of the use of biomarkers in clinical practice."

— Ubiratan de Paula Santos.

Smoking is the leading preventable risk factor for death. It is estimated to have been responsible for 6.3 million deaths globally in 2010.[1] Studies have suggested that smokers live, on average, 10 years shorter than nonsmokers and that one in every two smokers will die from a tobacco-related disease.[2,3] The reason for such an impact is the presence, in the smoke inhaled from burning tobacco, of approximately 5,300 chemicals, including 250 toxic components, 72 carcinogens (600 trillion molecules of carcinogens per cigarette smoked), and 4×10^9 fine particles/cm³ of inhaled smoke.[4] Among the major impairments associated with smoking are airway and interstitial respiratory diseases, especially COPD and more than 10 types of cancer, including head and neck cancer[5] and lung cancer, which is ranked 1st in the global ranking of cancer deaths,[6] smoking being responsible for more than 80% of cases. In addition to these known morbidities, evidence from new studies suggest that smoking increases the risk of death from renal failure, intestinal ischemia, breast cancer, and prostate cancer,[7] thereby broadening the spectrum and dimension of the effects of smoking. In other diseases such as asthma, although various studies have suggested that smoking is a causal factor, there is still controversy over it; however, evidence confirms that smoking or exposure to environmental tobacco smoke makes asthma control difficult and makes exacerbations more frequent.[8] Because of greater knowledge of the risks and because of the measures adopted by countries, the prevalence of smokers has been gradually declining, especially in Brazil, with a reduction in the prevalence of smokers, in the population aged 18 years or older, from 35.4% to 16.8% between 1989 and 2010.[9]

In this issue, the Brazilian Journal of Pulmonology publishes an interesting study[10] involving patients with COPD or asthma and a control group of healthy smokers and nonsmokers, comparing smoking markers to determine the accuracy of the self-report of smoking status. The data are impressive: 29% of the patients with asthma or COPD who self-reported being nonsmokers had high urinary cotinine values and high exhaled CO values. If we consider urinary cotinine levels alone, whose cut-off value of 200 ng/mL is used in order to discriminate smokers from nonsmokers, they were too high to be explained only by the exposure to environmental tobacco smoke, and the prevalence of self-reported nonsmokers who had high levels of this marker reached 38% (29% and 47% of the patients with asthma and COPD, respectively). As indicated in the article,[10] the values observed for false information were higher than those observed in other studies, which can be explained, in part, by differences in the prevalence of smokers in the local populations during the various study periods. Research conducted in various countries has shown that the prevalence of smokers among patients with COPD[11,12] or asthma[12,13] is similar to that observed among smokers in general. In the study by Stelmach et al.,[10] since it was carried out at a specialized care hospital, we should also consider the possibility of patients fearing discontinuation of follow-up as one of the factors influencing such a large number of false reports.

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The study[10] results strongly suggest that, in the approach to patients with asthma or COPD, the question on smoking status be reiterated and this status be assessed (including with the use of biomarkers) at each visit, especially in patients with more frequent exacerbations, and that help be offered to those who wish to quit smoking. Although cotinine is a more accurate marker of tobacco smoke exposure than is the measure of exhaled CO, the latter can be used for this purpose, since it is inexpensive, it is measured instantaneously, and its values do not differ significantly between smokers with COPD and those without.[14] A study conducted in the United Kingdom revealed that only 13% of smokers received prescriptions for smoking cessation treatment, although those with COPD were particularly likely to be prescribed such treatment.[15] In addition, another study by the same group[16] revealed a high (17%) prevalence of exposure to environmental tobacco smoke in asthma patients, and such exposure is known to be associated with exacerbations.[8] Although studies have suggested that, with the aid of medications, patients with chronic disease have rates of cessation similar to those of patients without chronic disease,[11] it is possible that patients with chronic lung disease who continue smoking have more difficulty in quitting smoking, requiring greater support as compared with smokers without such comorbidities, including greater screening for psychological morbidities associated with smoking,[17] which can influence cessation success.

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Respiratory muscles: myths and secrets

Musculatura respiratória: mitos e segredos

Eloara Vieira Machado Ferreira[1]

Why is it so important that pulmonologists are familiar with respiratory muscle assessment?

Respiratory muscle weakness is associated with increased respiratory workload and reduced or interrupted (central or peripheral) neural stimulation. In healthy individuals (in whom central respiratory drive is normal), the respiratory muscle strength required in order to drive the respiratory system must be greater than the sum of the work imposed by the lungs, rib cage, and airways.[1] An imbalance between the respiratory workload and respiratory muscle strength results in progressive respiratory muscle weakness, which can progress to alveolar hypoventilation and respiratory failure depending on its severity. In most cases, the inspiratory muscles (the most important of which is the diaphragm) are affected first, because of their active role in breathing.[2]

Several diseases, particularly neuromuscular diseases, can affect the respiratory muscles. However, systemic inflammation (autoimmune rheumatic diseases), heart failure, and pulmonary impairment, observed in obstructive diseases with lung hyperinflation, in restrictive diseases, and in cases of rib cage deformities, can also adversely affect the respiratory muscles.[3] Therefore, respiratory muscle assessment can be one of the steps in the investigation of dyspnea of unknown cause or in the investigation of the clinical and functional dissociation in patients with chronic respiratory failure.

In the initial evaluation of respiratory muscle strength, easily applied and widely available methods should be prioritized, overall evaluation of respiratory muscles being given priority over a more specific respiratory muscle assessment. Therefore, MIP and MEP measurements play a central role in the diagnostic evaluation of respiratory muscle strength. Values of MIP and MEP within the normal range rule out respiratory muscle weakness. However, low MIP and MEP values do not unequivocally confirm the presence of respiratory muscle weakness, because they might be related to technical problems or underexertion; therefore, further investigation is required in order to confirm the diagnosis. Steier et al.[4] showed that the use of MIP and MEP alone in the evaluation of patients with neuromuscular disease or patients with dyspnea of unknown cause can lead to overdiagnosis of respiratory muscle weakness, whereas a combination of methods reduces false-positive results by 30%.

In the current issue of the Brazilian Journal of Pulmonology, Caruso et al.[5] present the various methods of respiratory muscle assessment. The division of the methods into volitional and nonvolitional respiratory muscle tests and their progressive sequencing (ranging from simple, noninvasive tests to tests that are more complex) facilitate the understanding of the tests and aid in choosing the test that is most suitable for the suspected diagnosis. It is of note that the authors addressed the increased use of diaphragmatic ultrasound in determining inspiratory muscle weakness. The advantage of ultrasound is that it requires equipment that is widely available, although it requires an operator who is familiar with the technique. Ultrasound can be used in order to evaluate diaphragmatic structure and function and can be performed in an outpatient or hospital setting.[5] However, certain diseases require methods that are more complex for an accurate diagnosis, including electrical or magnetic phrenic nerve stimulation and (surface or needle) electromyography, the latter being able to evaluate the diaphragm and different inspiratory and expiratory muscles separately.[2]

It should be noted that respiratory muscle assessment can be performed in the pediatric population. However, volitional respiratory muscle testing is not feasible in infancy and early childhood in particular. Therefore, invasive techniques such as sniff transdiaphragmatic pressure during crying spells and sniff nasal inspiratory pressure are required and can be performed in children over 4 years of age.[6]

Despite being outside the scope of the study by Caruso et al.,[5] tests such as pulmonary function

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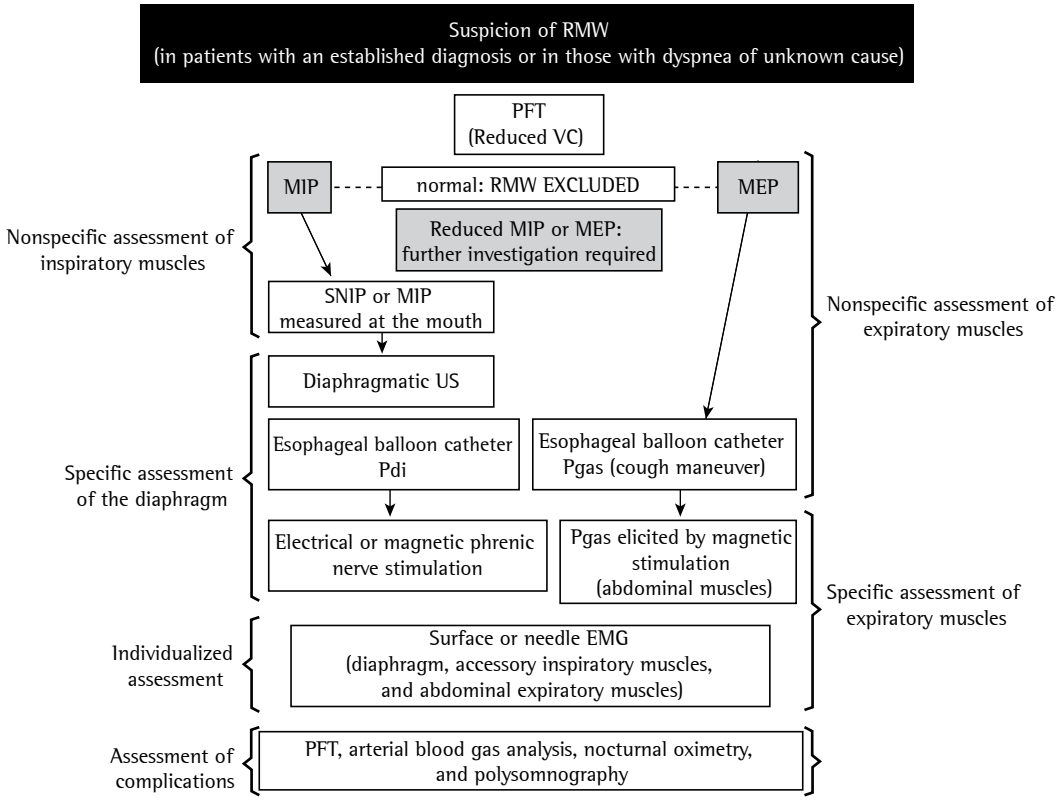

Figure 1 - Diagnostic algorithm for respiratory muscle weakness. RMW: respiratory muscle weakness; PFT: pulmonary function testing; SNIP: sniff nasal inspiratory pressure; US: ultrasound; Pdi: transdiaphragmatic pressure; Pgas: gastric pressure; and EMG: electromyography.

testing, arterial blood gas analysis, nocturnal oximetry, and polysomnography are important in the initial investigation and monitoring of disease progression, as well as in informing decisions regarding noninvasive ventilation.[7,8] A diagnosis of inspiratory muscle weakness is unlikely in patients who present with preserved VC and are suspected of having the condition. In such patients, inspiratory capacity is reduced, resulting in reduced TLC with virtually unchanged functional residual capacity.[9] The onset of nocturnal hypoventilation with hypoxemia and the presence of hypercapnia indicate disease severity and a risk of respiratory failure.[9,10]

Regarding the answer to the initial question, it is essential that pulmonologists understand the pathophysiological mechanisms involved in respiratory muscle impairment; that they are familiar with the wide range of differential diagnoses (especially when investigating dyspnea); and that they are able to intervene when serial evaluations reveal signs of complications. In addition, it is crucial that pulmonologists do not take a simplistic approach to respiratory muscle assessment by requesting MIP and MEP measurements to determine the presence or absence of respiratory muscle weakness. Therefore, on the basis of the various methods presented by Caruso et al.,[5] I herein propose a diagnostic algorithm for respiratory muscle weakness (Figure 1).

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Diagnostic methods to assess inspiratory and expiratory muscle strength*

Métodos diagnósticos para avaliação da força muscular inspiratória e expiratória

Pedro Caruso, André Luis Pereira de Albuquerque, Pauliane Vieira Santana, Leticia Zumpano Cardenas, Jeferson George Ferreira, Elena Prina, Patrícia Fernandes Trevizan, Mayra Caleffi Pereira, Vinicius Iamonti, Renata Pletsch, Marcelo Ceneviva Macchione, Carlos Roberto Ribeiro Carvalho

Abstract

Impairment of (inspiratory and expiratory) respiratory muscles is a common clinical finding, not only in patients with neuromuscular disease but also in patients with primary disease of the lung parenchyma or airways. Although such impairment is common, its recognition is usually delayed because its signs and symptoms are nonspecific and late. This delayed recognition, or even the lack thereof, occurs because the diagnostic tests used in the assessment of respiratory muscle strength are not widely known and available. There are various methods of assessing respiratory muscle strength during the inspiratory and expiratory phases. These methods are divided into two categories: volitional tests (which require patient understanding and cooperation); and non-volitional tests. Volitional tests, such as those that measure maximal inspiratory and expiratory pressures, are the most commonly used because they are readily available. Non-volitional tests depend on magnetic stimulation of the phrenic nerve accompanied by the measurement of inspiratory mouth pressure, inspiratory esophageal pressure, or inspiratory transdiaphragmatic pressure. Another method that has come to be widely used is ultrasound imaging of the diaphragm. We believe that pulmonologists involved in the care of patients with respiratory diseases should be familiar with the tests used in order to assess respiratory muscle function.Therefore, the aim of the present article is to describe the advantages, disadvantages, procedures, and clinical applicability of the main tests used in the assessment of respiratory muscle strength.

Keywords: Respiratory muscles; Muscle weakness; Diaphragm; Respiratory function tests; Diagnostic tests, routine.

Resumo

O acometimento da musculatura ventilatória (inspiratória e expiratória) é um achado clínico frequente, não somente nos pacientes com doenças neuromusculares, mas também nos pacientes com doenças primárias do parênquima pulmonar ou das vias aéreas. Embora esse acometimento seja frequente, seu reconhecimento costuma ser demorado porque seus sinais e sintomas são inespecíficos e tardios. Esse reconhecimento tardio, ou mesmo a falta de reconhecimento, é acentuado porque os exames diagnósticos usados para a avaliação da musculatura respiratória não são plenamente conhecidos e disponíveis. Usando diferentes métodos, a avaliação da força muscular ventilatória é feita para a fase inspiratória e expiratória. Os métodos usados dividem-se em volitivos (que exigem compreensão e colaboração do paciente) e não volitivos. Os volitivos, como a medida da pressão inspiratória e expiratória máximas, são os mais empregados por serem facilmente disponíveis. Os não volitivos dependem da estimulação magnética do nervo frênico associada a medida da pressão inspiratória na boca, no esôfago ou transdiafragmática. Finalmente, outro método que vem se tornando frequente é a ultrassonografia diafragmática. Acreditamos que o pneumologista envolvido nos cuidados a pacientes com doenças respiratórias deve conhecer os exames usados na avaliação da musculatura ventilatória. Por isso, o objetivo do presente artigo é descrever as vantagens, desvantagens, procedimentos de mensuração e aplicabilidade clínica dos principais exames utilizados para avaliação da força muscular ventilatória.

Descritores: Músculos respiratórios; Força muscular; Diafragma; Testes de função respiratória, Testes diagnósticos de rotina.

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Introduction

Impairment of (inspiratory and expiratory) respiratory muscles is a common clinical finding, not only in patients with neuromuscular disease but also in those with respiratory diseases affecting the lung parenchyma or airways.[1,2]

Inspiratory muscle weakness can cause dyspnea[2] and exertion intolerance. However, diagnosis is usually delayed, because most screening protocols for dyspnea do not include assessment of respiratory muscle strength. In addition, when assessment of respiratory muscle strength is performed, it includes tests that yield a high percentage of false negatives, because they depend on patient cooperation (volitional tests). Therefore, for the appropriate investigation and possible confirmation of respiratory muscle weakness as a cause of respiratory failure, it is of paramount importance to be familiar with non-volitional measures and even with techniques that are more invasive, such as the measurement of transdiaphragmatic pressure.

The aim of the present article is to describe the advantages, disadvantages, procedures, and clinical applicability of the main diagnostic methods to assess respiratory muscle strength. Although we discuss the main measures of respiratory muscle strength, we do not specifically address the diagnosis of muscle fatigue. We also do not describe other related tests that are not specific or sensitive for confirming the diagnosis of respiratory muscle weakness, such as spirometry and arterial blood gas analysis.

Volitional tests for measuring inspiratory muscle strength

Maximal inspiratory pressure

Maximal inspiratory pressure (MIP) is the most widely used measure of respiratory muscle strength in patients with suspected respiratory muscle weakness.[3] It is determined by measuring upper airway pressure (mouth for outpatients and trachea for intubated or tracheostomized patients) during a maximal voluntary inspiratory effort. The measured pressure is a composite of the pressure generated by the inspiratory muscles and the elastic recoil pressure of the lungs and chest wall.

Advantages

It uses low-cost, portable equipment; it is easy and rapid to perform; it is noninvasive; and it has well-established reference values, in different populations (lower limit of normal of 60 cmH_2O for females and 80 cmH_2O for males).[4-6] In addition, since the relationship between lung volumes and inspiratory muscle strength is not linear,[7] the measurement of MIP can diagnose inspiratory muscle weakness earlier than would be possible based on changes in lung volumes.

Disadvantages

The maneuver is not intuitive and depends on patient cooperation. Therefore, a low value might not mean weakness, but rather a lack of cooperation. MIP has high coefficients of intraindividual and interindividual variation (10 to 13%)[8] and low accuracy for predicting successful extubation in mechanically ventilated patients.[9]

How to measure

MIP is measured from RV or from functional residual capacity (FRC). Since there is an inverse relationship between lung volume and inspiratory muscle strength,[6] measurements from RV yield module values that are 30% higher than those obtained from measurements from FRC. Although measurements from RV yield higher values, some physicians and researchers use measurements from FRC because they more reproducible and more easily performed by patients. However, when measurements from FRC are made, it is necessary that FRC volume be known, because this volume will affect the pressure generated.

The measurement of MIP can be made with an analog or digital pressure manometer.[10] Digital devices are preferred over analog devices, given that the highest MIP value occurs briefly and may go unnoticed on an analog display (Figure 1). Measurements are usually made with patients in a sitting position, with or without nose clips. Patients are asked to exhale to RV and then perform a maximal inspiratory effort, sustaining it for 1 to 2 seconds. To prevent overestimation of values because of glottal closure and pressure by the mouth muscles, there should be a 2-mm-wide opening in the mouthpiece, which can be a rigid tubular mouthpiece or a rubber mouthpiece. The latter gives slightly higher values.[11]

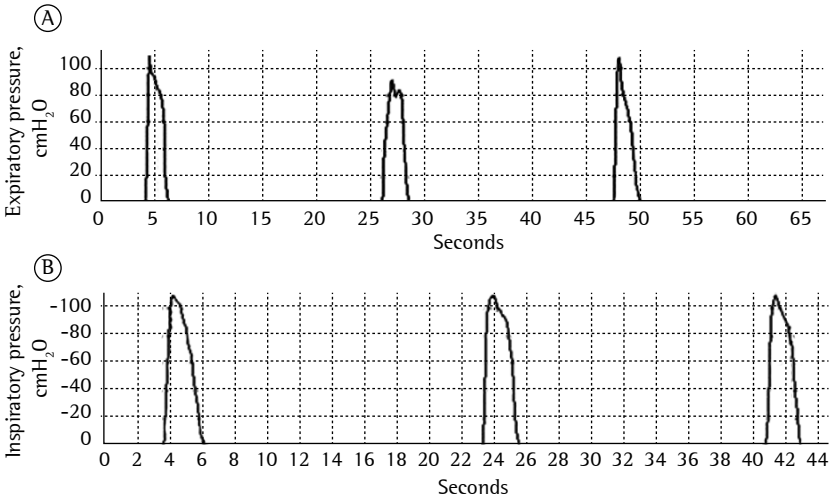

Figure 1 - Measurement of MEP and MIP with a digital pressure manometer (model MVD 300; Globalmed, Porto Alegre, Brazil). In A, positive MEP values. In B, negative MIP values.

In critically ill intubated patients who are uncooperative, the optimal measurement of MIP is made with a one-way valve (it permits exhalation, but occludes during inspiration) attached to the tube and takes 25 seconds (Figure 2).[12]

In any method, the maneuver should be repeated 3 to 8 times, and the highest value recorded will be used for analysis. The reproducibility of the MIP measurement, with or without a one-way valve, is 10%.

Clinical applicability

Determining MIP is important in the diagnosis of inspiratory muscle weakness, which can occur in pulmonary, cardiac, and neuromuscular diseases. In addition, the measurement of MIP can aid in the differential diagnosis of dyspnea[2]; in the differential diagnosis of obstructive lung disease of unknown origin; in assessing response to cardiopulmonary physiotherapy and rehabilitation; in prescribing and monitoring respiratory muscle training[13,14]; and, in critically ill patients, in assessing the possibility and success of weaning from mechanical ventilation.[10]

Sniff nasal inspiratory pressure

The search for a method for the measurement of inspiratory muscle strength that would overcome the limitations of MIP, as well as being noninvasive (avoiding the need for an esophageal balloon), resulted in the proposal of measuring nasal inspiratory pressure during a sniff.[15] SNIP is an acronym for sniff nasal inspiratory pressure. SNIP measures the joint activity of the diaphragm and other inspiratory muscles and accurately reflects esophageal pressure (Pes), having the advantage of being noninvasive.[15,16] However, the correlation between Pes and SNIP is reduced when there is significant airway obstruction, which occurs in asthma and COPD. Electromyographic studies have shown that, during SNIP, there is selective contraction of the muscles involved in breathing, especially the inspiratory accessory muscles, which demonstrates the specificity of the test.[17]

Although SNIP has a reasonable correlation with MIP,[18] the former does not replace the latter and should be used as an additional measure in the assessment of inspiratory muscle strength, because the use of only one test can overestimate muscle weakness, whereas the use of both tests reduces the rate of false-positive results for respiratory muscle weakness by nearly 20%.[18,19]

Advantages

It uses pressure manometers, which are simple and inexpensive equipment that also measures MIP; it is easy to perform, because it is based on an intuitive maneuver, which makes the measurement more reproducible; and it has well-established normal values, in different populations (lower limit of normal of 60 cmH_2O for females and 70 cmH_2O for males; Table 1).[20-24]

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Disadvantages

It depends on patient cooperation, it cannot be used in mechanically ventilated patients, it can underestimate values in patients with marked airway obstruction, and it should be used with caution in those with nasal obstruction.

How to measure

The maneuver can be performed in any body position (the most common is sitting), because, despite minor variations, changes in body position do not result in significant changes in SNIP.[20] One nostril should be completely closed by a nose plug to prevent pressure from leaking, whereas the other nostril should be absolutely patent. After a period of quiet breathing, the maneuver begins with a fast deep inspiration from FRC and the mouth closed. A firm verbal command is needed, given that the maneuver should be short (≤ 500 ms) and explosive so that it causes the collapse of the unplugged nostril. Ten maneuvers should be performed. However, if there is a considerable increase in the values obtained in the last maneuvers, up to ten more maneuvers can be performed. Twenty maneuvers are also necessary when the values of the first ten maneuvers are below predicted values and when inspiratory muscle weakness due to exertion is suspected, such as in neuromuscular diseases.[26] The highest value recorded in this series of maneuvers is used for analysis.

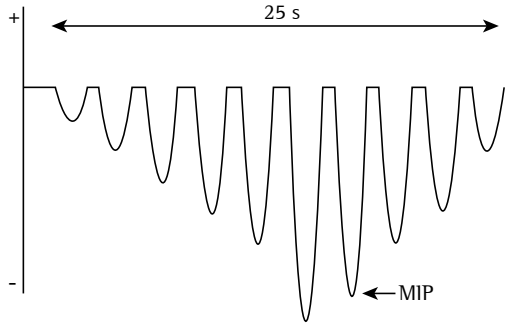

Figure 2 - Variation in inspiratory pressure during measurement of MIP with a one-way valve. The highest value usually occurs within 15 to 20 seconds.

Clinical applicability

SNIP is very useful in assessing inspiratory muscle strength and has high specificity[17] compared with MIP. In recent years, SNIP has been used for diagnosis and monitoring of muscle weakness in various pathologies in which a deficit in inspiratory muscle strength is part of the natural history of the disease, such as in neuromuscular[23] and pulmonary[25] diseases.

Inspiratory mouth pressure

Inspiratory mouth pressure (Pm) is measured with a pressure sensor attached to a mouthpiece (as in the measurement of MIP) or to a tracheal tube.[27] It is usually used in three clinical situations. First, it is used as an indirect measure of Pes during a sniff, when esophageal catheters are not available or when esophageal catheter placement is not possible. In this situation, a limitation of Pm is

Table 1 - Lower limits of normal for respiratory muscle strength tests.[a]

Method	Lower limit of normal
MIP (cmH_2O)	60 (F) / 80 (M)
MEP (cmH_2O)	120 (F) / 150 (M)
SNIP (cmH_2O)	60 (F) / 70 (M)
Sniff Pes (cmH_2O)	60 (F) / 70 (M)
Sniff Pdi (cmH_2O)	70 (F) / 80 (M)
Twitch Pes (cmH_2O)	12 (F and M)
Twitch Pdi (cmH_2O)	20 (F and M)
Twitch Pga (cmH_2O)	16 (F and M)
Cough Pga (cmH_2O)	95 (F) / 130 (M)
Twitch Pga at T10 (cmH_2O)	16 (F and M)
Diaphragm motion on US – breathing at rest (mm)	11
Diaphragm motion on US – deep breathing (mm)	47
Diaphragm thickening on US – breathing at rest (mm)	1.5
Rate of thickening during inspiration to TLC on US	20%

F: female; M: male; SNIP: sniff nasal inspiratory pressure; Pes: esophageal pressure; Pdi: transdiaphragmatic pressure; Pga; gastric pressure; and US: ultrasound. [a]Modified from Polkey & Moxham.[21].

that, for patients, its measurement is more difficult than that of SNIP.[3] Its second use is in ascertaining the correct placement of the esophageal catheter, which is discussed later. Finally, Pm is also used in the measurement of $P_{0.1}$, which is the pressure generated in the first 100 ms of an inspiratory effort against a closed airway, and it correlates better with the measurement of respiratory drive than with the measurement of MIP.

Advantages

It is a simple, noninvasive method, it can use the same instruments used in the measurement of MIP and SNIP, and it is an alternative method in patients with contraindication to esophageal catheters (esophageal varices or severe hypoxemia) or in patients in whom an esophageal catheter cannot be placed (intolerance to passage of catheters or airway anatomical changes).

Disadvantages

For patients, measurements made through the mouth are more difficult than nasal measurements, and the former provide no additional advantages over the latter. As occurs with MIP, Pm does not differentiate between which respiratory muscle is affected. In patients with severe expiratory flow limitation and parenchymal disease, the transmission of pressure along the airways may be affected, and, in such cases, Pm may not be an accurate measure of alveolar pressure.[3] As occurs with MIP, values can be affected by the type of mouthpiece used.[11]

How to measure

In the measurement of Pm, the cross-sectional area of the mouthpiece should be wide enough to prevent errors arising from the Bernoulli effect (a reduction of the cross-sectional area of a tube leads to an increase in the speed of the gas flow and a decrease in pressure). In addition, the compliance of the cheeks can distort the measurement, and, to work around this limitation, the cheeks need to be supported by both hands during the measurement. In the measurement of $P_{0.1}$, the distal end of the mouthpiece should be closed for verification of the correct positioning of the esophageal balloon.[27] Pm can be measured nonvolitionally as well, by means of phrenic nerve stimulation,[28-30] a topic that is discussed further below.

Clinical applicability

It is mainly used as an indirect measure of Pes during a sniff,[1] in order to confirm inspiratory muscle weakness[2]; and for verifying the correct positioning of the esophageal balloon (Figure 3) by using the Baydur test[27,31]—see *How to measure* in the next item.

Transdiaphragmatic pressure

Transdiaphragmatic pressure (Pdi) is the difference between gastric pressure (Pga) and Pes (Pdi = Pga – Pes; Figure 4) and translates the force generated by the diaphragm rather than by the other respiratory muscles.

Advantages

The strength of the diaphragm, which is the main inspiratory muscle, being responsible for 60 to 70% of the tidal volume in normal breathing, has well-established reference values in volunteers of different groups (lower limit of normal of 70 cmH_2O for females and 80 cmH_2O for males during a sniff),[32] as well as in patients with different respiratory diseases (Table 1).[33,34]

Disadvantages

It is an invasive method, which depends on passing catheters through the nose into the distal esophagus and stomach and which uses materials that are not readily available in most public hospitals. It depends on an experienced examiner for correct placement of the catheters.

How to measure

Pdi can be measured with air-filled latex balloon catheters, fluid-filled catheters, or microtransducer catheters.[35,36] The use of balloon catheters requires passing a catheter into the esophagus and another one into the stomach, although a catheter with two balloons, which prevents the need for a second catheter, has recently been placed on the market.[37] The microtransducer catheter makes Pes and Pga measurements with only one catheter, as well as having the advantage of being better tolerated by patients and having a fast response time, which ensures more accurate measurements in fast maneuvers,[38] such as measurements using magnetic stimulation of the phrenic nerve.

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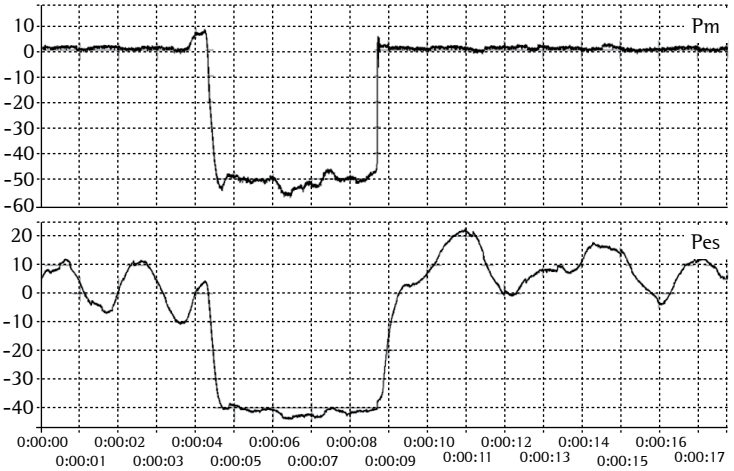

Figure 3 - Comparison between inspiratory mouth pressure (Pm) and inspiratory esophageal pressure (Pes) during mouth occlusion (Baydur maneuver), for ascertaining the correct location of the esophageal catheter. Note the good correlation between the two measurements.

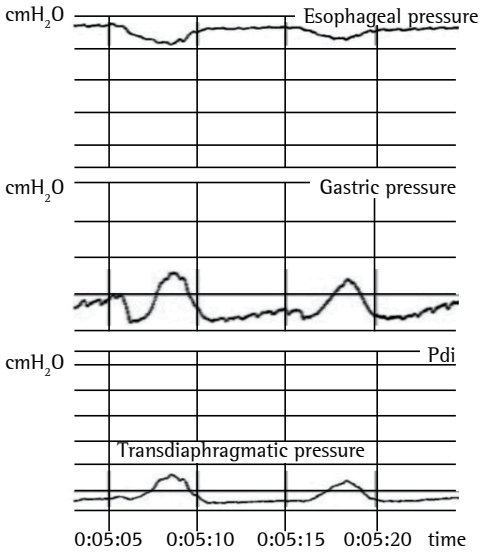

Figure 4 - Transdiaphragmatic pressure. The top curve represents esophageal pressure, the middle curve represents gastric pressure, and the bottom curve represents transdiaphragmatic pressure (Pdi). In this example, there are differences in the esophageal and gastric pressure measurement range.

When using latex balloon catheters, which are the most common ones, one catheter is placed into the distal esophagus and one is placed into the stomach. To ensure correct positioning, it is necessary to observe the Pes and Pga curves. This is easy because, during inspiration, Pes becomes negative and Pga becomes positive, in a mirror image (Figure 5). The final step to ensure that the Pes detected by the balloon catheter is correct is to compare it with the Pm measured by using the closed mouthpiece. If the esophageal positioning is correct, that is, if it reflects pleural pressure well, the variation in Pes will be at least 80% of the variation in Pm. This confirmatory test is known as the Baydur test[27] and has been validated for different lung volumes and postural positions.[31]

Pdi can be measured during normal breathing or during maximal inspiratory maneuvers, usually during a sniff. In addition, Pdi can be measured during magnetic stimulation of the phrenic nerve, which is discussed in Non-volitional tests for measuring inspiratory muscle strength (see Electrical and magnetic phrenic nerve stimulation).

Clinical applicability

Because it is an invasive method that requires complex equipment and is complex to perform, it is used almost exclusively to determine respiratory muscle strength.[35] Its main use is to enable a more representative measurement of diaphragm strength, especially in patients with airway obstruction, in whom Pes would not be accurately reflected by Pm or by SNIP.[3,18]

Non-volitional tests for measuring inspiratory muscle strength

Electrical and magnetic phrenic nerve stimulation

The use of non-volitional tests for measuring inspiratory muscle strength is recommended

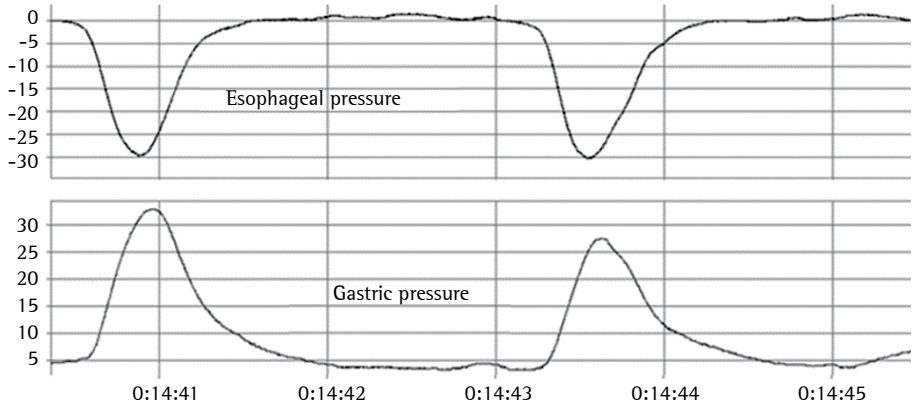

Figure 5 - Example of simultaneous recording of esophageal and gastric pressures during forced inspiration. Note that as esophageal pressure becomes more negative, gastric pressure becomes positive, creating a mirror image of the two curves.

when patients have difficulty understanding or performing the maneuvers, generating low values during the volitional maneuvers (MIP, SNIP, or Pm); or when there is considerable variation in the measurements, which is probably secondary to different levels of effort. To obtain maximal involuntary inspiratory contraction, there are two possible methods that yield similar results: electrical stimulation or magnetic (twitch) stimulation of the phrenic nerve. Both are based on stimulating the cervical phrenic nerve, which is superficial (Figure 6). Electrical stimulation is painful, and there are reports of it inducing convulsion; however, it is more specific for diaphragm stimulation than is magnetic stimulation.[39] Magnetic phrenic nerve stimulation causes minimal discomfort, which is well tolerated by most patients.[40] Its principle is to create a magnetic field in the cervical region by placing small coils over this region. Pdi values are similar with magnetic and electrical stimulation.[40] Since magnetic phrenic nerve stimulation provides greater safety and comfort, its use has surpassed that of electrical stimulation.

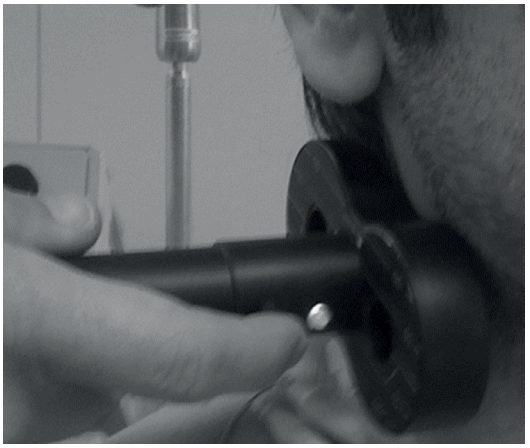

Figure 6 - Phrenic nerve magnetic stimulation coil placed on the anterior cervical area of a volunteer.

Advantages

It allows the measurement of inspiratory muscle strength, irrespective of patient cooperation or understanding. The reason for it is that the diaphragm is innervated exclusively by the phrenic nerve, and this enables overall muscle stimulation. Magnetic stimulation easily penetrates tissues and bones, preferentially activating larger neural fibers rather than smaller fibers, which are responsible for mediating pain.[41] There are well defined Pdi values after bilateral cervical magnetic stimulation (lower limit of normal of 20 cmH_2O for females and males).[40]

Disadvantages

Since the magnetic field can stimulate other cervical nerves and muscles, its use is usually less specific for the measurement of diaphragm strength than is that of electrical stimulation, although this difference does not appear to be clinically relevant.[39,40] Another disadvantage is that magnetic stimulation equipment is not readily available and is costly.

How to measure

The device consists of a base with a capacitor connected to a coil that is placed over the site to be stimulated. The type of coil has considerable

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influence on the intensity and form of the magnetic field generated. Initially, the most widely used coil was the 90-mm circular coil placed on the posterior cervical area at the level of the seventh cervical vertebra. This coil, however, created a larger magnetic field and ended up stimulating other neural fibers in the neck and upper intercostal muscles. The coil currently in use is the 45-mm figure-of-eight coil, which creates a field more focused on the phrenic nerve when it is placed over the posterior edge of the sternocleidomastoid muscle at the level of the cricoid cartilage. With one figure-of-eight coil, it is possible to measure the force generated by one hemidiaphragm alone, and with two coils activated simultaneously, it is possible to measure the force generated by both hemidiaphragms together.[3,39,40] The measurements most commonly made using magnetic phrenic nerve stimulation are those of Pdi and Pm. Although the measurement of Pm is noninvasive, it depends on the glottis remaining open after magnetic stimulation, and this may result in considerably underestimated values in patients with increased airway resistance and severe parenchymal disease. A disadvantage of measuring Pdi is the need for insertion of esophageal and gastric catheters.

Clinical applicability

It is used mainly in research and clinical settings when one wants to avoid variability related to patient cooperation or when patients cannot cooperate properly, such as mechanically ventilated patients or those who cannot understand or perform the requested maneuvers.

Diaphragm ultrasound

In recent years, there has been a great increase in interest in the use of ultrasound to assess the diaphragm.[42] The literature has demonstrated that diaphragm ultrasound is a useful tool for bedside assessment, because it is noninvasive and radiation-free, it is readily available in hospitals, and it allows repeated assessments. Diaphragm ultrasound has accuracy similar to that of fluoroscopy for assessment of diaphragm motion.[43] There have been some recent articles in different publications discussing the use of ultrasound for assessment of diaphragm function in mechanically ventilated patients, especially for predicting extubation failure,[44] and for diagnosis and monitoring of inadvertent injury occurring during surgery.[45] There have also been articles discussing the use of ultrasound for diagnosis and monitoring of diaphragm paralysis in outpatients.[46,47]

Advantages

It is a noninvasive, radiation-free method; it can be repeated several times over a short period of time; it uses a basically configured ultrasound system, which is a piece of equipment that has become common in hospitals and clinics; and the learning time is not long. Finally, normal values for diaphragm thickening and motion are well established (Table 1). For males and females, diaphragm motion during quiet breathing should be at least 11 mm, and during deep breathing, it should be at least 47 mm. For males and females, diaphragm thickening after inspiration to TLC should be at least 1.5% or 20%.[48-50]

Disadvantages

It is an operator-dependent method, and, in obese patients with abdominal distention or extensive dressings, it can be difficult to obtain good quality images. Diaphragm motion is affected by abdominal pressure and contents, and this decreases the relationship between diaphragm motion and variation in lung volume during the maneuvers, thus requiring the concomitant use of a pneumotachograph.

How to measure

The use of ultrasound allows us to measure diaphragm dome motion and diaphragm thickness in the zone of apposition to the rib cage (Figure 7A and B). Diaphragm dome motion is measured with a (cardiac or convex) low-frequency (3-5 MHz) transducer, which is held against the highest point of the diaphragm (the diaphragm dome). Depending on the method used, the transducer can be placed in the transverse[50] or longitudinal[49] direction in the subcostal region, the reference being the point between the midclavicular and anterior axillary lines. The diaphragm is visualized in B-mode, and diaphragm excursion is measured in M-mode, which reduces interobserver variability.[51] It is important to assess motion not only during normal breathing but also during fast and slow deep inspiration. Assessing motion during a sniff is useful because it enhances the detection of paradoxical motion of the

diaphragm, which may not occur during normal breathing. Motion measurement of the right and left hemidiaphragms yields equal values, but measurement on the right is easier because of the presence of the liver, which creates an acoustic window (Figure 7A).

Diaphragm thickening is measured with a high-frequency (7-10 MHz) transducer placed in the zone of apposition of the diaphragm to the midaxillary line. Diaphragm thickness is the distance between the two hyperechogenic lines representing its borders (Figure 7B). This thickness is usually measured at FRC and also at TLC after a maximal inspiration.[48] Diaphragm thickening should increase by at least 20% at TLC when compared with the value obtained at FRC.

Clinical applicability

Diaphragm ultrasound can be used at the bedside or in an outpatient setting. It allows the assessment of two useful fundamental parameters: diaphragm motion and diaphragm thickness. In addition, it can be performed in different body positions. The respiratory diseases about which there exist the largest number of studies with the use of diaphragm ultrasound are COPD and diaphragm paralysis, and there are studies with the use of diaphragm ultrasound in weaning from mechanical ventilation.[47,48]

Volitional tests for measuring expiratory muscle strength

Maximal expiratory pressure

Maximal expiratory pressure (MEP) is the most widely used measure of expiratory muscle strength in critically ill patients and in outpatients.[3]

Advantages

It is simple and rapid to perform; it uses low-cost, low-complexity equipment (the same used for measuring MIP); and it has well-established reference values (lower limit of normal of 120 cmH_2O for females and 150 cmH_2O for males; Table 1).[52]

Disadvantages

It depends on patient cooperation and on the coordination between the patient and the examiner, as well as having low accuracy for predicting cough capacity. It has a high rate of false-positive results for expiratory muscle weakness because it can overestimate the number of patients with expiratory muscle weakness, given that low values are caused by submaximal efforts or air leaks around the mouthpiece, which is common in patients with facial muscle weakness.

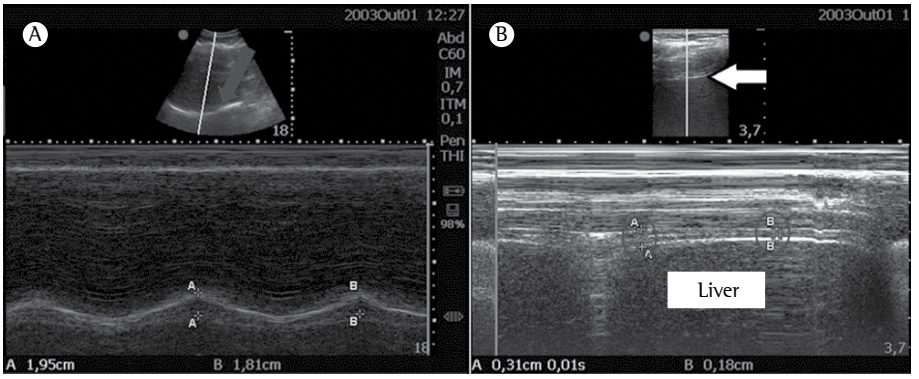

Figure 7 - Ultrasound imaging of the diaphragm. In A, an ultrasound scan for assessment of diaphragm motion. The top image is a B-mode image, and the gray arrow indicates the diaphragm, which is seen as a more echogenic line. The bottom image is the top image in M-mode and serves to measure diaphragm excursion (distances between A-A and B-B points) during breathing at rest. In A, diaphragm motion was 19.5 and 18.1 mm and was, therefore, normal. In B, an ultrasound scan for assessment of diaphragm thickening. The top image is a B-mode image, and the white arrow indicated the diaphragm, which is seen as a more echogenic line. The bottom image is the top image in M-mode and serves to measure diaphragm thickening during inspiration (A-A points) and the next expiration (B-B points). In B, diaphragm thickening was 1.3 mm and was, therefore, slightly below normal.

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How to measure

MEP is measured with a pressure manometer. Measurements are usually made with patients in a sitting position and with a nose clip, although the use of a nose clip is not necessary. MEP can be measured from TLC or from FRC. Patients perform a maximal expiratory effort and sustain it for 1 to 2 seconds. The maneuver should be repeated 3 to 8 times, and the highest value recorded is used for analysis. Since there is a direct relationship between lung volume and expiratory muscle strength,[51] measurements from TLC yield higher values than those obtained from measurements from FRC.

Clinical applicability

Its major use is in assessing cough strength, given that one of the phases of cough is explosive expiration and expiratory muscle weakness correlates with respiratory infections[53] and extubation failure.[54]

Cough gastric pressure

Measuring Pga during a cough is a useful additional test in the assessment of expiratory muscle weakness, because abdominal muscles are the primary muscles responsible for expiratory flow.

Advantages

It has well-established reference values (lower limit of normal of 95 cmH_2O for females and 130 cmH_2O for males; Table 1),[55] and its specificity is greater than that of MEP. Therefore, the negative predictive value of cough Pga is higher than that of MEP alone. A previous study showed that 42% of patients with reduced MEP actually had normal cough Pga values.[55]

Disadvantages

Its main disadvantage is that it is an invasive method that requires the insertion of a catheter with a pressure sensor into the stomach.

How to measure Pga is typically measured with a catheter, following the same recommendations as those already described for the measurement of Pdi (*see Transdiaphragmatic pressure*). Patients in a sitting position are instructed to inhale to TLC and then cough with maximum force, repeating the maneuver at 30-second intervals until the values stop increasing. Typically, up to six maneuvers are necessary.[55]

Clinical applicability

It is used to rule out expiratory muscle weakness, especially in patients suspected of having reduced cough strength due to expiratory pump impairment, such as patients with neuromuscular disease and critically ill patients immediately before or after extubation.

Non-volitional tests for measuring expiratory muscle strength

Gastric pressure after magnetic stimulation of the anterior abdominal wall muscles

In uncooperative patients, expiratory muscle strength can be assessed by measuring Pga after neural magnetic stimulation of the abdominal wall muscles.[3,56,57] Magnetic stimulation is produced by placing a circular coil over the dorsal spine, at the level of the eighth to tenth thoracic vertebra (T8 to T10).[56,58]

Advantages

Values are independent of patient cooperation.

Disadvantages

This measurement is invasive because it requires passage of a catheter into the stomach, and there exists only one study that reported reference values, in a small sample of individuals (lower limit of normal of 10 cmH_2O for females and males; Table 1).[18]

How to measure

This measurement can be made with a balloon catheter or a microtransducer catheter placed into the stomach. To ensure the correct positioning of the catheter, it is necessary to observe the pressure curve, which, during inspiration, should have positive values (Figure 4). Another means to ensure correct positioning in the stomach is to employ manual compression of the epigastrium and observe an increase in Pga. When the catheter is correctly positioned in the stomach, magnetic stimulation is performed over the dorsal spine, between T8 and T10, and the pressure variation

is recorded. Approximately 5 measurements are performed at intervals of at least 30 seconds to avoid muscle potentiation.

Clinical applicability

This measurement is used to confirm possible expiratory muscle weakness,[43,59] especially in individuals with difficulty performing volitional tests intended to assess cough strength, such as patients with neuromuscular disease and critically ill patients.

Electromyography

Electromyography is the study of muscle activity based on analysis of electromyographic signals, which are electrical manifestations generated during voluntary or stimulated contractions. It can performed with electrodes attached to the skin (surface electromyography)[59] or with fine needles inserted into the surface of the muscle that is assessed (needle electromyography).[60,61] In the case of respiratory muscles, there is a third option, which is the use of esophageal electrode catheters to perform crural diaphragm electromyography.[62,63]

Advantages

Surface electromyography is a noninvasive, easy-to-use method, being quite useful for continuous monitoring. It is extremely sensitive for detecting muscle contractions.[64] Needle electromyography is minimally invasive and mildly painful.

Disadvantages

The major problem in performing surface electromyography is interference from the activity of other muscle groups (cross-talk). Because electromyography is highly sensitive, it is often difficult to isolate the activity of only one muscle group. Another disadvantage is the limited standardization for analysis of the signal, which can be interpreted visually through its amplitude and duration components or through a numerical value obtained by squaring the signal amplitude and subsequently extracting the root square of the result (root mean square value). Diaphragm electromyography with esophageal catheters is invasive and depends on materials and skills that are highly specific and are still not readily available, although there is a mechanical ventilation apparatus available on the market that has a ventilation mode based on the acquisition of esophageal electromyography signals (the Neurally Adjusted Ventilatory Assist [NAVA] mode of ventilation of the Servo ventilators; Maquet, Sweden). In this apparatus, esophageal electromyography monitoring can be performed even with the patient off the ventilator. Finally, there are no population reference values, which makes it difficult to use this measurement as an index of diagnosis of muscle weakness.

How to measure

The received signals are amplified and filtered, and this can be adjusted and will depend on the characteristics of the acquired signal. The most commonly employed method is electromyography with electrodes over the muscle, after the region has been thoroughly cleaned to improve the transmission of the electrical signal.[59] It is also possible to use needles inserted intramuscularly, thereby obtaining a signal that is less noisy and more representative of a particular muscle activity. In obese individuals, needle electromyography of the abdominal muscles has a more significant result than that obtained with surface electrode electromyography. Often, needle insertion is ultrasound guided in order to prevent bleeding or perforation of other organs.[60,61] Finally, it is also possible to use esophageal electromyography, in which one seeks to study the activity of the crural diaphragm by positioning the electrodes 1 to 3 cm above the esophageal-gastric junction.[62,63]

Clinical applicability

Electromyography is a reliable method for continuous monitoring, especially of certain respiratory muscles, such as abdominal expiratory muscles and inspiratory accessory muscles, provided that care is taken in the technical preparation. Its major use is in monitoring the same individual continuously, because absolute values do not allow comparisons between individuals. Surface electromyography is used for qualitative assessment of recruitment of inspiratory accessory muscles and abdominal expiratory muscles. When this assessment needs to be more specific or quantitative (usually for research purposes), the method used is needle electromyography. In addition to being used for research purposes,

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diaphragm electromyography is used as a guide in the NAVA mode of ventilation.

Final considerations

Respiratory muscle impairment is present not only in respiratory diseases but also in various other diseases, and its proper assessment depends on the use of appropriate tests. Noninvasive volitional tests are still the most commonly used tests in clinical practice, because they are more widely known and because of their ease of use in different centers. However, patients highly suspected of having ventilatory muscle weakness and with difficulty understanding these tests should undergo additional assessment with more invasive, non-volitional tests, although they are not readily available and, to date, they have been mostly used in research centers.

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Comparison between objective measures of smoking and self-reported smoking status in patients with asthma or COPD: are our patients telling us the truth?*

Comparação entre medidas objetivas do tabagismo e tabagismo autodeclarado em pacientes com asma ou DPOC: será que nossos pacientes dizem a verdade?

Rafael Stelmach, Frederico Leon Arrabal Fernandes, Regina Maria Carvalho-Pinto, Rodrigo Abensur Athanazio, Samia Zahi Rached, Gustavo Faibischew Prado, Alberto Cukier

Abstract

Objective: Smoking prevalence is frequently estimated on the basis of self-reported smoking status. That can lead to an underestimation of smoking rates. The aim of this study was to evaluate the difference between self-reported smoking status and that determined through the use of objective measures of smoking at a pulmonary outpatient clinic. **Methods:** This was a cross-sectional study involving 144 individuals: 51 asthma patients, 53 COPD patients, 20 current smokers, and 20 never-smokers. Smoking status was determined on the basis of self-reports obtained in interviews, as well as through tests of exhaled carbon monoxide (eCO) and urinary cotinine. **Results:** All of the asthma patients and COPD patients declared they were not current smokers. In the COPD and asthma patients, the median urinary cotinine concentration was 167 ng/mL (range, 2-5,348 ng/mL) and 47 ng/mL (range, 5-2,735 ng/mL), respectively ($p < 0.0001$), whereas the median eCO level was 8 ppm (range, 0-31 ppm) and 5 ppm (range, 2-45 ppm), respectively ($p < 0.05$). In 40 (38%) of the patients with asthma or COPD ($n = 104$), there was disagreement between the self-reported smoking status and that determined on the basis of the urinary cotinine concentration, a concentration > 200 ng/mL being considered indicative of current smoking. In 48 (46%) of those 104 patients, the self-reported non-smoking status was refuted by an eCO level > 6 ppm, which is also considered indicative of current smoking. In 30 (29%) of the patients with asthma or COPD, the urinary cotinine concentration and the eCO level both belied the patient claims of not being current smokers. **Conclusions:** Our findings suggest that high proportions of smoking pulmonary patients with lung disease falsely declare themselves to be nonsmokers. The accurate classification of smoking status is pivotal to the treatment of lung diseases. Objective measures of smoking could be helpful in improving clinical management and counseling.

Keywords: Asthma; Pulmonary disease, chronic obstructive; Cotinine; Carbon monoxide; Smoking.

Resumo

Objetivo: O tabagismo autodeclarado é usado frequentemente para estimar a prevalência dessa condição. As taxas de tabagismo podem ser subestimadas por esse método. O objetivo deste estudo foi avaliar a diferença entre o tabagismo autodeclarado e o tabagismo determinado pelo uso de medidas objetivas em um ambulatório de doenças respiratórias. **Métodos:** Estudo transversal realizado em 144 indivíduos: 51 pacientes com asma, 53 pacientes com DPOC, 20 fumantes e 20 não fumantes. O tabagismo foi determinado por meio de autorrelato em entrevistas e medição de monóxido de carbono no ar exalado (COex) e de cotinina urinária. **Resultados:** Todos os pacientes com asma e DPOC declararam não ser fumantes. Nos pacientes com DPOC e asma, a mediana de concentração de cotinina urinária foi de 167 ng/ml (variação, 2-5.348) e de 47 ng/ml (variação, 5-2.735 ppm), respectivamente ($p < 0,0001$), enquanto . a mediana de COex foi de 8 ppm (variação, 0-31) e 5,0 ppm (variação, 2-45 ppm), respectivamente ($p < 0,05$). Em 40 (38%) dos pacientes com asma ou DPOC ($n = 104$), houve discordâncias entre o tabagismo autodeclarado e a concentração de cotinina urinária (> 200 ng/mL). Em 48 (46%) desses 104 pacientes, o não tabagismo autodeclarado foi refutado por um nível de COex > 6 ppm, considerado indicativo de fumo atual. Em 30 (29%) dos pacientes com asma ou DPOC, a concentração de cotinina urinária e o nível de COex contradisseram o autorrelato desses como não fumantes. **Conclusões:** Nossos achados sugerem que altas proporções de pacientes fumantes com doenças respiratórias declaram ser não fumantes. A classificação correta do tabagismo é fundamental no tratamento dessas doenças. Medidas objetivas do tabagismo podem ser úteis na melhora do manejo clínico e no aconselhamento.

Descritores: Asma; Doença pulmonar obstrutiva crônica; Cotinina; Monóxido de carbono; Hábito de fumar.

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Introduction

Cigarette smoking, the main risk factor for COPD,[1] can aggravate the inflammation associated with asthma, causing the symptoms to be more severe, accelerating the decline in pulmonary function, and impairing the short-term therapeutic response to corticosteroids.[2] Although self-reports of smoking status are widely used in order to estimate the prevalence of smoking in patients with asthma or COPD,[3-5] their use has been shown to underestimate smoking rates, especially because of the decreasing social acceptability of smoking.[6] Some authors have questioned the validity of self-reported smoking status in the general population and have reported significant rates of misclassification.[7]

In the city of São Paulo, Brazil, the prevalence of smoking in the adult population was reported to be 20.9% in 2008.[8] The assessment of smoking status is pivotal to the treatment of respiratory diseases. Smoking cessation is not only regarded as the most efficient intervention to slow the progression of COPD[9] but can also improve the management of and treatment response in patients with asthma.[2]

In smoking-cessation intervention studies, the use of a biochemical measure has been deemed essential, in order to validate self-reported smoking status.[10] Determining the exhaled carbon monoxide (eCO) level is a rapid, noninvasive method of assessing smoking status. Although CO has a half-life of approximately 4 h and can be detectable in the blood for up to 24 h, the contribution of environmental sources cannot be distinguished from that of cigarette smoking, potentially leading to false-positive results.[11] Several studies have shown that cut-off values between 6 and 8 ppm are appropriate to separate smokers from nonsmokers.[12] If an individual smokes only a few cigarettes per day or has not smoked a cigarette for several hours, eCO testing can yield false-negative results.[13] The major metabolite of nicotine is cotinine, and urinary cotinine is a specific marker for nicotine. Except in users of nicotine replacement therapy, elevated cotinine concentrations indicate tobacco use or exposure to environmental tobacco smoke.[14] Cotinine concentrations are less dependent on the time elapsed since the last cigarette smoked than are eCO levels, because the half-life of cotinine in urine is approximately 16 h.[15] However, the urinary cotinine concentration is highly dependent on the assay method and on the laboratory performing the analysis, making it difficult to identify a universal cut-off concentration for classifying an individual as a smoker or nonsmoker.[16]

The purpose of this study was to draw comparisons between self-reports of smoking status and the results of objective measures of smoking (urinary cotinine assays and eCO testing) in patients with stable asthma or COPD.

Methods

Study design

This was a cross-sectional study involving asthma patients and COPD patients recruited from among those under regular treatment at the Pulmonary Outpatient Clinic of the Heart Institute at the University of São Paulo School of Medicine *Hospital das Clínicas*, in the city of São Paulo, Brazil. Information about smoking habits, symptoms, lifestyle, exposure, and medication usage were collected by an interviewer. All interviewers were trained to avoid pressuring or judging the patients. All subjects were assured that the results were confidential, in order to encourage accurate reporting of smoking habits. The Research Ethics Committee of the *Hospital das Clínicas* approved the study protocol, and all participants gave written informed consent.

Subjects

The diagnoses of COPD and asthma were based on the definitions provided in the guidelines established by the Global Initiative for Chronic Obstructive Lung Disease[1] and the Global Initiative for Asthma,[17] respectively. Patients with asthma or COPD were recruited in person by members of the research team or interviewers after regular visits to the outpatient clinic. Inclusion criteria were having been in outpatient treatment for at least 12 months at recruitment and having had no changes in treatment regimen within the last 4 weeks. Patients using nicotine replacement therapy were excluded, as were those with any cognitive disorder that would have impaired their ability to complete a questionnaire, those with renal failure requiring dialysis, and those with facial deformities that would have impeded the use of spirometry or measurement of the eCO level. To ensure that the urinary cotinine and eCO results were reliable, we also recruited

normal subjects without asthma, COPD, or other identifiable respiratory problems: 20 current smokers (positive control group) and 20 never-smokers (negative control group). The control subjects were recruited from among university students and employees, through the use of posters displayed in the hospital and university. We employed the following definitions of smoking status: a current smoker was defined as a subject who reported current, regular use of cigarettes; a never-smoker was defined as a subject who reported never having smoked cigarettes; and a former smoker was defined as a subject who reported a lifetime smoking history of ≥ 100 cigarettes and smoking abstinence for at least the last 12 months before inclusion in the study.

Determination of self-reported smoking status

Immediately after recruitment, we conducted face-to-face interviews to collect data related to health history and demographic characteristics. Participants were asked "Do you smoke?"; "Are you smoking now?"; "When did you quit?"; "How many cigarettes do you smoke per day?"; and "How many smokers live in your household?" Responses to these questions were recorded on a flowchart as either nominal (yes/no) or interval data.

Pulmonary function tests

For all subjects, we determined FEV_1 and FVC using a spirometer (KoKo; nSpire Health Inc., Longmount, CO, USA). All spirometry procedures were performed in accordance with the recommendations made jointly by the American Thoracic Society and European Respiratory Society.[18] All pulmonary function tests were performed between 8:00 and 12:00 a.m.

Determination of urinary cotinine concentration

To determine urinary cotinine concentrations, morning urine samples were collected from patients at the time of an appointment at the outpatient clinic. Urine samples were collected in sterile bottles. Aliquots of those samples were stored at −80°C for later batched laboratory analysis.

The quantitative analysis of cotinine in urine samples was performed with a modified HPLC method. A cotinine concentration > 200 ng/mL is considered indicative of active use of nicotine-containing products.[19,20]

Determination of eCO level

The levels of eCO were measured in an exhaled breath sample with a CO tester (Micro CO; Micro Medical Ltd., Rochester, UK). The subjects were given a detailed explanation of the breath analysis test and were given the opportunity to practice. Although the test has good reproducibility,[21] it was performed in duplicate to ensure consistency. The eCO values are expressed in ppm, 0-6 ppm indicating no smoking and > 6 ppm being suggestive of smoking.[13,22] Before each test, we recorded ambient levels of CO, using the CO tester calibrated against room air with a calibration syringe. The eCO tests were performed between 8:00 and 12:00 a.m.

Sample size calculation

The sample size was calculated with the aim of selecting a sample that would be sufficient to detect a 10% difference between self-reported smoking status and that detected by objective measurement. We thus determined that a sample of approximately 140 subjects was needed in order to achieve a power of 80% with a two-tailed significance of 0.05.

Statistical analysis

Continuous variables are presented as mean ± standard error; nonparametric data are presented as median (interquartile range); and categorical variables are presented as absolute and relative frequencies. Chi-square tests were used in order to evaluate any discordance between self-reported smoking status and that determined through objective measures. To compare patient characteristics by smoking status, eCO level, and urinary cotinine concentration, we used Student's t-tests, the Mann-Whitney test, and one-way ANOVA. To assess the strength of associations between continuous variables related to patient characteristics, we calculated Pearson's correlation coefficient. Finally, we used stepwise logistic regression analysis to compare misclassified patients with patients who provided reliable information about their smoking status, with the objective of identifying predictors of such misclassification. The characteristics included in those analyses were age, level of education, and pulmonary

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function. The minimum level of significance adopted was 0.05. All statistical analyses were performed with SigmaStat software, version 3.5 (Systat Software Inc., San Jose, CA, USA).

Results

The recruitment flowchart is presented in Figure 1. Of the 213 eligible subjects, 69 were excluded from the analysis (for not meeting the study criteria, for not providing consent, for not complying with the protocol, or for other reasons). Therefore, the final study sample comprised a total of 144 participants (70 men and 74 women): 53 COPD patients (37 men and 16 women); 51 asthma patients (16 men and 35 women); 20 current smokers (9 men and 11 women); and 20 never-smokers (8 men and 12 women). None of the subjects enrolled in the study were using nicotine replacement therapy during the evaluation. All of the asthma patients and COPD patients declared they were not current smokers. There were 51 COPD patients and 12 asthma patients who described themselves as former smokers, stating that they had quit the habit 1-17 years prior. There were 28 COPD patients and 15 asthma patients who reported that they shared a household with one or more smokers (median, one smoker in each of the two groups). Asthma patients and COPD patients both presented with impaired pulmonary function, the mean FEV_1 being 57% and 36% of the predicted value, respectively. This indicates that the patient portion of our study sample was composed of patients with the severe forms of their respective conditions. Clinical and functional data are presented in Table 1.

As can be seen in Figure 2, the median eCO levels of the never-smokers and current smokers were 3.0 ppm (range, 1-4 ppm) and 18 ppm (range, 10-45 ppm), respectively ($p < 0.05$), whereas they were 8.0 ppm (range, 0-31 ppm) and 5.0 ppm (range, 2-45 ppm), respectively, for the COPD patients and asthma patients ($p < 0.05$). Ambient air concentrations of CO were at 0-2 ppm during the measurements.

Figure 3 shows the urinary cotinine concentrations. The median urinary cotinine concentration was 70 ng/mL (range, 19-179 ng/mL) in the never-smokers and 2,036 ng/mL (range, 459-3,736 ng/mL) in the current smokers, respectively ($p < 0.05$). In the COPD patients, the median urinary cotinine concentration was 167 ng/mL (range, 2-5,348 ng/mL), compared with 47 ng/mL (range, 5-2,735 ng/mL) for the asthma patients ($p < 0.05$).

All 20 of the current smokers in the positive control group tested positive for smoking, showing urinary cotinine concentrations > 200 ng/mL and eCO levels > 6 ppm. Conversely, all 20 of the never-smokers in the negative control group tested negative for smoking, by both methods.

Urinary cotinine concentrations were > 200 ng/mL in 15 asthma patients (29%) and 25 COPD patients (47%). In addition, eCO levels > 6 ppm were recorded for 16 asthma patients (31%) and 32 COPD patients (60%). Therefore, the results of the urinary cotinine assays and eCO tests, respectively, suggested that 40 (38%) and 48 (46%) of the 104 patients were misclassified as nonsmokers on the basis of their self-reports. The combination of an eCO level > 6 ppm and a urinary cotinine concentration > 200 ng/mL was identified in 7 asthma patients (14%) and 23 COPD patients (43%), collectively corresponding to 29% of the patient portion of the sample.

As can be seen in Figure 4, the univariate analysis showed that eCO level correlated with urinary cotinine concentration: overall ($r = 0.43$, $p = 0.05$); in asthma patients ($r = 0.57$, $p < 0.0001$); and in COPD patients ($r = 0.69$, $p < 0.0001$). When we analyzed only the patients who were identified as smokers (Figure 5), we found that an eCO level > 6 ppm correlated significantly with a urinary cotinine concentration > 200 ng/mL in the COPD patients ($r = 0.68$, $p < 0.0003$), although not in the asthma patients ($r = 0.62$, $p = 0.13$). Analyzing the identified-as-smoking

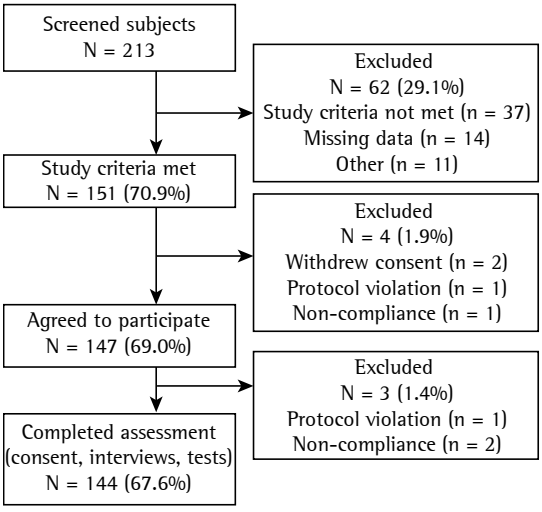

Figure 1 - Flowchart of the sample selection process.

Table 1 - Clinical and functional characteristics of COPD patients, asthma patients, smokers, and never-smokers.

Variable	Patients		Controls	
	COPD	Asthma	Smokers	Never-Smokers
	n = 53	n = 51	n = 20	n = 20
Gender				
Male, n (%)	37 (69.8)	16 (31.4)	9 (45.0)	8 (40.0)
Female, n (%)	16 (30.2)	35 (68.6)	11 (55.0)	12 (60.0)
Age (years), mean ± SE	64 ± 1.5*,†,‡	43 ± 2.0	45 ± 4.4	32 ± 3.2
FVC (% predicted), mean ± SE	86 ± 2.8	87 ± 2.6	81 ± 4.0	88 ± 2.2
FEV_1 (% predicted), mean ± SE	36 ± 2.0*,†,‡	57 ± 3.2‡	73 ± 3.5	84 ± 1.1
FEV_1/FVC (% predicted), median (IQR)	73 (24-92)†,‡	75 (24-95)†,‡	84 (79-88)	84 (81-87)
eCO (ppm), median (IQR)	8.0 (0-31)†, ‡	5.0 (2-45)†,‡	18 (10-45)‡	3.0 (1-4)
Urinary cotinine (ng/mL), median (IQR)	167 (2-5,348)*,†,‡	47 (5-2,735)†,‡	2,036 (459-3,736)*,‡	70 (19-179)

eCO: exhaled carbon monoxide; and IQR: interquartile range. ANOVA or Kruskal-Wallis test: *p < 0.05 vs. asthma patients; †p < 0.05 vs. smokers; ‡p < 0.05 vs. never-smokers.

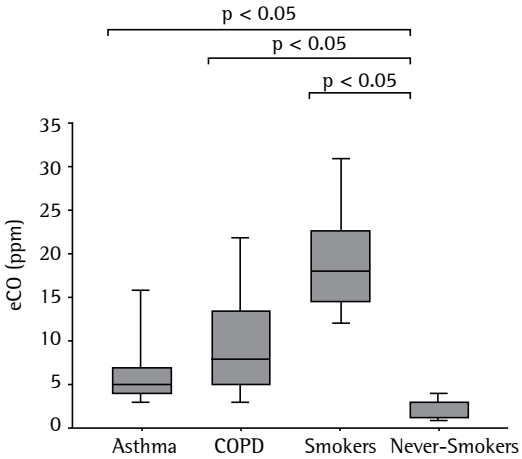

Figure 2 - Medians and confidence intervals for exhaled carbon monoxide (eCO) in asthma patients, COPD patients, smokers, and never-smokers.

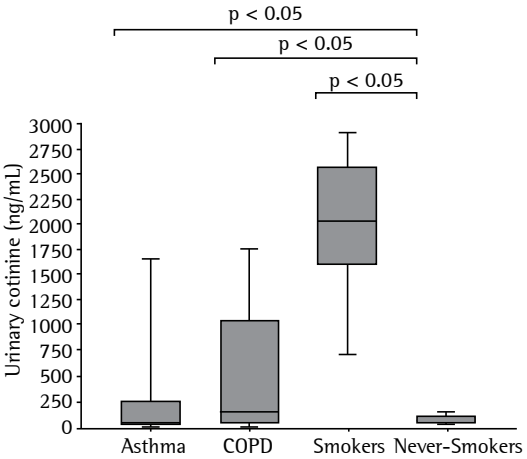

Figure 3 - Medians and confidence intervals for urinary cotinine in asthma patients, COPD patients, smokers, and never-smokers.

asthma and COPD patients collectively (Figure 5), we found that there was still a strong correlation between an eCO level > 6 ppm and a urinary cotinine concentration > 200 ng/mL (r = 0.63, p < 0.0001). The stepwise logistic regression, adjusted for patient characteristics such as age, level of education, exposure to passive smoking, and pulmonary function, identified no predictors of smoking status misclassification.

Discussion

The results of the present study suggest that patients with asthma or COPD commonly provide misinformation regarding their smoking status. Although that behavior was more prominent among COPD patients, asthma patients also underreported the smoking habit. We have also shown that measuring eCO identifies most smokers, and that eCO correlates significantly with urinary cotinine. It is noteworthy that the correlation between eCO and urinary cotinine was not statistically significant among the asthma patients (p = 0.13). This might be due to a lack of power (type II error), given that few asthma patients tested positive for urinary cotinine. When the COPD and asthma patients were evaluated as a group, that correlation was significant. Few previous studies exploring the association between obstructive lung diseases and smoking behavior have used the highly sensitive and specific methods of measuring urinary cotinine and eCO for biochemical validation.

Considering the critical aspect of smoking status for the clinical management of COPD and asthma, we find it surprising that there is such

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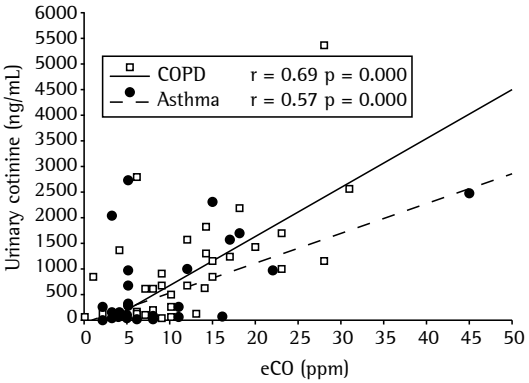

Figure 4 - Exhaled carbon monoxide (eCO) plotted against urinary cotinine in asthma patients and COPD patients.

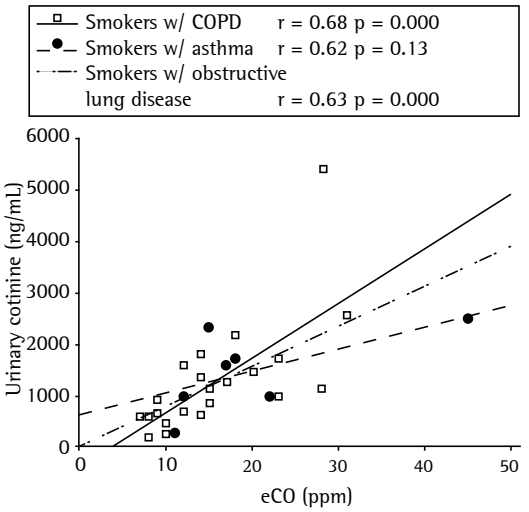

Figure 5 - Correlation between exhaled carbon monoxide (eCO) > 6 ppm and urinary cotinine > 200 ng/mL in COPD patients (smokers w/ COPD), asthma patients (smokers w/ asthma), and both (smokers w/ obstructive lung disease).

a paucity of studies on the invalidity of self-reported nonsmoking by "true" smokers among patients with obstructive lung diseases. In the present study, we found that, although all of the patients described themselves as nonsmokers, 38% (47% of the COPD patients and 29% of the asthma patients) showed urinary cotinine concentrations > 200 ng/mL, a value strongly associated with current smoking.[20]

A study conducted in Spain showed that 17% of all patients seen at a respiratory medicine clinic continued to smoke while denying doing so; a higher proportion (34%) was observed in the patients with COPD.[23] In another study, conducted in France, the measurement of cotinine in patients being treated with home oxygen therapy allowed the authors to identify 43 smokers (17% of the sample as a whole) who had theretofore described themselves as nonsmokers.[24] In contrast, a study conducted in Japan showed that, of 351 patients with COPD or asthma, only 11 (2 with asthma and 9 with COPD) claimed to be nonsmokers and had a serum cotinine level > 50 ng/mL, which is suggestive of current smoking.[25] These results suggest that cultural differences play a role in the proportion of patients who attempt to hide their smoking habits from health care practitioners.

The inclusion of positive and negative control groups in our study was of great importance for discussing cut-off points in the population under study. In our positive (smoker) control group, the lowest urinary cotinine concentration was 458 ng/mL, and none of the subjects had an eCO level < 10 ppm. Conversely, most of the subjects in the negative (never-smoker) control group had a cotinine concentration < 100 ng/mL, and none had an eCO level > 6 ppm. False-positive eCO results were obtained in 6 COPD patients and in only 1 asthma patient. All false-positive results were within the 7-10 ppm range, which is usually observed in light smokers. All patients with false-positive results shared a household with a smoker. Therefore, these results could be explained by environmental exposure to tobacco smoke. Exposure to pollution and underlying inflammatory lung diseases are also potential reasons for false-positive eCO testing results.

In a previous survey conducted at our institution, an eCO level ≥ 6 ppm was shown to have the greatest sensitivity and specificity for differentiating between smokers and nonsmokers.[13] However, when trying to identify misreporting of smoking status by patients with obstructive lung diseases, these clear-cut differences disappear, and there is a boundary where overlapping occurs. If we used the highest eCO cut-off points suggested in the literature (11 ppm for COPD and 10 ppm for asthma), 32% of our COPD patients and 40% of our asthma patients would be falsely classified as nonsmokers, despite having urinary cotinine concentrations > 200 ng/mL. However, a high proportion of our patients with urinary cotinine concentrations < 100 ng/mL had eCO levels between 6 ppm and 8 ppm, which underscores the difficulty in establishing an appropriate cut-off point for eCO. This suggests that the cut-off level should vary among populations, and that

borderline results should be evaluated with care in clinical practice, especially because the level of environmental exposure to tobacco smoke is likely to be high among asthma patients.[26]

The accurate determination of smoking status is pivotal to the treatment of asthma and COPD. A "real-life" study on the effectiveness of smoking cessation therapy in Brazil showed that respiratory comorbidities were not associated with treatment failure.[27] Counseling and pharmacologic treatment can change patient smoking status and improve the course of the lung disease.

The present study has certain limitations. We did not obtain patient histories regarding passive smoking outside the home, the last cigarette smoked, or smoking patterns. Those factors can influence eCO levels and could decrease the sensitivity and specificity of eCO monitoring. In addition, we did not collect demographic data related to ethnic or racial characteristics. Ethnic or racial differences in the metabolism and clearance of nicotine could constitute an alternative explanation for our findings. There have been reports that race can influence cotinine concentrations, serum cotinine levels being higher among black smokers than among white smokers, due to differences in the metabolism of nicotine.[28] If the Brazilian population metabolizes nicotine more slowly, our results would be partly accounted for without underreporting. Another explanation is that airway obstruction might influence levels of eCO. Therefore, eCO measurements could be inaccurate in patients with severe airway obstruction.[29] Nevertheless, although the patients in our sample had moderate-to-severe airway obstruction, we found no significant correlation between eCO and FEV_1. Another potential limitation of our study is that we used a convenience sample of consecutive participants, rather than a random sample of subjects.

The results of our study confirm that patient-offered smoking history is unreliable, because we did not find that patient-reported smoking status correlated with urinary cotinine concentration or eCO level. Our findings also indicate that eCO is sufficient to discriminate between smokers and nonsmokers. If our findings can be generalized to other populations and diseases, then there is cause for concern about the use of questionnaires as the only sources of data on smoking in epidemiological studies and surveys involving respiratory patients.

In summary, the present study further substantiates the idea that self-reported smoking status is unreliable in the population of patients with obstructive lung diseases, given that a considerable proportion of our patients lied to their physicians. Objective measurement of smoking status could be helpful in allowing better clinical management and patient counseling in COPD and asthma.

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Assessment of quality of life in patients with advanced non-small cell lung carcinoma treated with a combination of carboplatin and paclitaxel*

Avaliação da qualidade de vida de pacientes com carcinoma pulmonar de células não pequenas em estágio avançado, tratados com carboplatina associada a paclitaxel

Camila Uanne Resende Avelino, Rafael Marques Cardoso, Suzana Sales de Aguiar, Mário Jorge Sobreira da Silva

Abstract

Objective: Non-small cell lung carcinoma (NSCLC) is the most common type of lung cancer. Most patients are diagnosed at an advanced stage, palliative chemotherapy therefore being the only treatment option. This study was aimed at evaluating the health-related quality of life (HRQoL) of advanced-stage NSCLC patients receiving palliative chemotherapy with carboplatin and paclitaxel. **Methods:** This was a multiple case study of advanced-stage NSCLC outpatients receiving chemotherapy at a public hospital in Rio de Janeiro, Brazil. The European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire was used in conjunction with its supplemental lung cancer-specific module in order to assess HRQoL. **Results:** Physical and cognitive functioning scale scores differed significantly among chemotherapy cycles, indicating improved and worsened HRQoL, respectively. The differences regarding the scores for pain, loss of appetite, chest pain, and arm/shoulder pain indicated improved HRQoL. **Conclusions:** Chemotherapy was found to improve certain aspects of HRQoL in patients with advanced-stage NSCLC.

Keywords: Carcinoma, non-small-cell lung; Quality of life; Palliative care; Carboplatin; Paclitaxel.

Resumo

Objetivo: O carcinoma pulmonar de células não pequenas (CPCNP) é tipo mais comum de câncer de pulmão. Como a maioria dos pacientes é diagnosticada em estágio avançado, a quimioterapia paliativa é a única opção de tratamento. Este estudo avaliou a qualidade de vida relacionada à saúde (QVRS) de pacientes com CPCNP avançado no decorrer da quimioterapia paliativa com carboplatina e paclitaxel. **Métodos:** Trata-se de um estudo de casos múltiplos de pacientes ambulatoriais com CPCNP em estágio avançado recebendo quimioterapia em um hospital público no Rio de Janeiro (RJ). Para a avaliação da QVRS, foram usados o *European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire* e seu módulo específico para câncer de pulmão. **Resultados:** Houve diferenças significativas na pontuação nas escalas de capacidade física e cognitiva durante a quimioterapia, indicando melhora e piora da QVRS, respectivamente. As diferenças na pontuação nos itens dor, perda de apetite, dor no tórax e dor no braço ou ombro indicaram melhora da QVRS. **Conclusões:** Observou-se que a quimioterapia melhora alguns aspectos da QVRS de pacientes com CPCNP avançado.

Descritores: Carcinoma pulmonar de células não pequenas; Qualidade de vida; Cuidados paliativos; Carboplatina; Paclitaxel.

Introduction

For 2015, the estimated incidence of tracheal, lung, and bronchial cancer in the Brazilian population is 27,330 cases.[1] Lung neoplasms are the most common cancers in the world, accounting for nearly 15% of all cancers; the death rate is high, and the 5-year survival rate is less than 15%.[2]

Non-small cell lung carcinoma (NSCLC) has the highest incidence of all lung neoplasms, accounting for 80-85% of all cases of lung

*Study carried out at the José Alencar Gomes da Silva National Cancer Institute, Rio de Janeiro, Brazil.

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cancer.[2] The biology of NSCLC and delayed diagnosis are the main reasons why NSCLC is the leading cause of cancer death worldwide.[3]

It is believed that 70% of patients present with advanced disease at diagnosis,[4] and palliative chemotherapy is often indicated.[5] Its goal is to control the signs and symptoms of advanced disease, which can affect the performance status, quality of life, and survival of patients.[4,6,7]

Currently, the palliative treatment of advanced-stage (stage IIIB and stage IV) NSCLC frequently involves the use of platinum coordination compounds such as carboplatin in combination with other antineoplastics, such as paclitaxel.[2] Nevertheless, the scientific literature is inconclusive regarding the impact of these drugs on the quality of life of patients with advanced-stage NSCLC,[6,8] which is an underexplored topic in clinical practice.

Health-related quality of life (HRQoL) can be described as the perception of patients of their own physical well-being, daily activities, psychological well-being, social relations, and disease symptoms.[9,10] Assessment of patients with lung cancer is of great importance because of the increased morbidity and mortality associated with NSCLC.[11-13]

Studies have indicated that quality of life assessment is the main predictor of survival, describing it as a relevant outcome in the context of palliative chemotherapy.[4,13] The use of questionnaires and periodic review of HRQoL facilitate communication between the health care team and the patients, optimizing the treatment.[13]

The objectives of the present study were to evaluate the HRQoL of advanced-stage NSCLC patients receiving palliative chemotherapy with carboplatin-paclitaxel and to promote a scientific discussion of this issue, which is currently underexplored, particularly in Brazil.

Methods

This was a multiple case study with a prospective descriptive analytical design. The study was conducted between May and July of 2013 at the adult chemotherapy outpatient clinic of a public cancer hospital located in the city of Rio de Janeiro, Brazil. The study included advanced-stage lung cancer patients receiving chemotherapy with carboplatin (area under the curve = 4-6) and paclitaxel (175 mg/m^2), with a 21-day interval between cycles. Patients with IIIB or IV stage NSCLC were sequentially enrolled in the study. Patients under 18 years of age were excluded, as were those who had undergone chemotherapy less than 5 years prior to the study, those who were diagnosed with a second primary malignancy, those who were unable to answer the questions clearly, and those who were already participating in another research protocol.

For the evaluation of quality of life, the instruments used were the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30) and its supplemental lung cancer-specific module (QLQ-LC13),[14] both of which had previously been translated into Portuguese and validated for use in Brazil.[12] The EORTC QLQ-C30 consists of five functional scales evaluating physical, role, emotional, cognitive, and social functioning; global health status/QoL; three scales measuring symptoms (nausea/vomiting, fatigue, and pain); and 6 items assessing the occurrence and severity of symptoms related to cancer and its treatment.[4,11,12] The QLQ-LC13 consists of 13 questions regarding the symptoms associated with lung cancer and the most common reactions to the medical treatment of lung cancer.

All HRQoL scores were calculated in accordance with the rules established by the EORTC.[9] Higher scores on the functional and quality of life scales translated to better HRQoL, whereas higher scores on the symptom scales translated to worse HRQoL. For a better understanding of the results, the symptom scales and items were inverted so that higher scores translated to fewer reports of symptoms and better quality of life.[15]

In each chemotherapy cycle, all HRQoL evaluations were used as a unit of analysis. The questionnaires were completed by the patients themselves before the 1st, 2nd, and 4th cycles of chemotherapy in order to compare pre-chemotherapy HRQoL, HRQoL during chemotherapy, and post-chemotherapy HRQoL. When asked to, the interviewer read the questions out to patients.

We collected data on the following sociodemographic and clinical variables: age; gender; self-reported race; marital status; number of years of schooling (0-7 years or ≥ 8 years); occupation; histological type; clinical stage; performance status; comorbidities; number of

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drugs used (≤ 4, 5-7, or 8-10); self-reported allergies; family history of cancer; smoking; daily cigarette consumption (< 20 cigarettes/day, low or medium consumption; ≥ 20 cigarettes/day, high consumption); and alcoholism.

For statistical analysis of the data, we used the IBM SPSS Statistics software package, version 20.0 (IBM Corporation, Armonk, NY, USA). Descriptive statistics included measures of central tendency and dispersion for continuous variables and absolute and relative frequencies for categorical variables.

In order to assess HRQoL during chemotherapy, we subtracted the mean functional and symptom scale scores for the 2nd chemotherapy cycle from those for the 1st cycle; those for the 4th cycle from those for the 2nd cycle; and those for the 4th cycle from those for the 1st cycle. In order to evaluate the changes in mean scores between cycles, we used the Wilcoxon signed-rank test, the level of significance being set at $p < 0.05$. In order to interpret the changes in mean HRQoL scores between chemotherapy cycles, we used the criteria proposed by Osoba et al.,[16] changes of 5-10 points in the mean scores being considered small, changes of 10-20 points being considered moderate, and changes of more than 20 points being considered large.

All ethical principles for research involving human subjects were followed. The study was approved by the Research Ethics Committee of the José Alencar Gomes da Silva National Cancer Institute (Protocol no. CAEE 14472813.9.0000.5274).

Results

A total of 18 patients completed the EORTC QLQ-C30 and the QLQ-LC13 for the evaluation of HRQoL before the 1st cycle of chemotherapy. Of those 18 patients, 2 were excluded during the study (1 because of a change in the chemotherapy protocol and 1 because of outpatient treatment discontinuation during the 2nd cycle of chemotherapy), 16 patients remaining in the study. Because of clinical worsening, 3 patients did not receive the 4th cycle of chemotherapy and therefore did not complete the EORTC QLQ-C30 or the QLQ-LC13 for the evaluation of HRQoL.

The median age of the participants was 63.7 years (mean age, 66 ± 11.1 years), and 56.3% were male. Table 1 shows the sociodemographic and clinical characteristics of the study population.

Table 1 - Sociodemographic and clinical characteristics of the study participants.

Patient characteristic	n	%
Age, years		
< 65	6	37.5
≥ 65	10	62.5
Gender		
Male	9	56.3
Female	7	43.8
Race		
White	9	56.3
Black	3	18.8
Others	4	25.0
Histological type of NSCLC		
Adenocarcinoma	9	56.3
Others	7	43.8
Stage at diagnosis		
IIIB	6	37.5
IV	10	62.5
Performance status		
1	12	75.0
2	4	25.0
Comorbidities		
Yes	9	56.3
No	7	43.8
Number of drugs used		
< 4	1	6.3
5-7	9	56.3
8-10	6	37.5
Family history of cancer		
Yes	8	50.0
No	8	50.0
History of smoking		
Yes	13	81.3
No	3	18.8
History of alcoholism		
Yes	8	50.0
No	8	50.0

NSCLC: non-small cell lung carcinoma.

Adenocarcinoma was the most prevalent type of NSCLC in the study population, being found in 56.3% of the participants. In addition, 62.5% had stage IV NSCLC.

Most (75%) of the participants were found to have a performance status of 1 before the 1st cycle of chemotherapy. In addition, nearly 56% had previously diagnosed chronic diseases and were on polypharmacy (≥ 5 different types of drugs).

Of the 16 participants, 13 (81.3%) declared themselves to be smokers or former smokers and 7 (53.9%) reported smoking at least 20 cigarettes

per day. In addition, 50% reported consuming or having consumed alcoholic beverages.

The mean scores on the EORTC QLQ-C30 functional and quality of life scales were ≥ 59.8. This indicates that the study participants had lower HRQoL scores in the 1st cycle of chemotherapy (Table 2).

Figure 1 shows a comparison of the mean EORTC QLQ-C30 functional scale scores in each treatment cycle. There were no significant differences among the scores, the exception being the physical functioning scale scores in the 1st and 2nd cycles (p = 0.002; Figure 1A), showing improved HRQoL in the 2nd cycle of chemotherapy, and in the 1st and 4th cycles (p = 0.028; Figure 1C), showing improved HRQoL in the 4th cycle of chemotherapy.

Taking into consideration the criteria proposed by Osoba et al.[16] for interpreting the significance of changes in HRQoL scores and the different numbers of patients at each assessment time point, we found a moderate change (of 11.7 points) in the role functioning score between the 1st and 4th cycles of chemotherapy (Figure 1C), a finding that shows a trend toward an improvement in HRQoL.

There were no changes in the global quality of life/QoL scores between the 2nd and 4th cycles of chemotherapy. However, there was a small change (of 6.3 points) in the global quality of life/QoL scores between the 1st and 2nd cycles of chemotherapy (Figure 1A).

The symptom scale scores and the scores on the items assessing the occurrence and severity

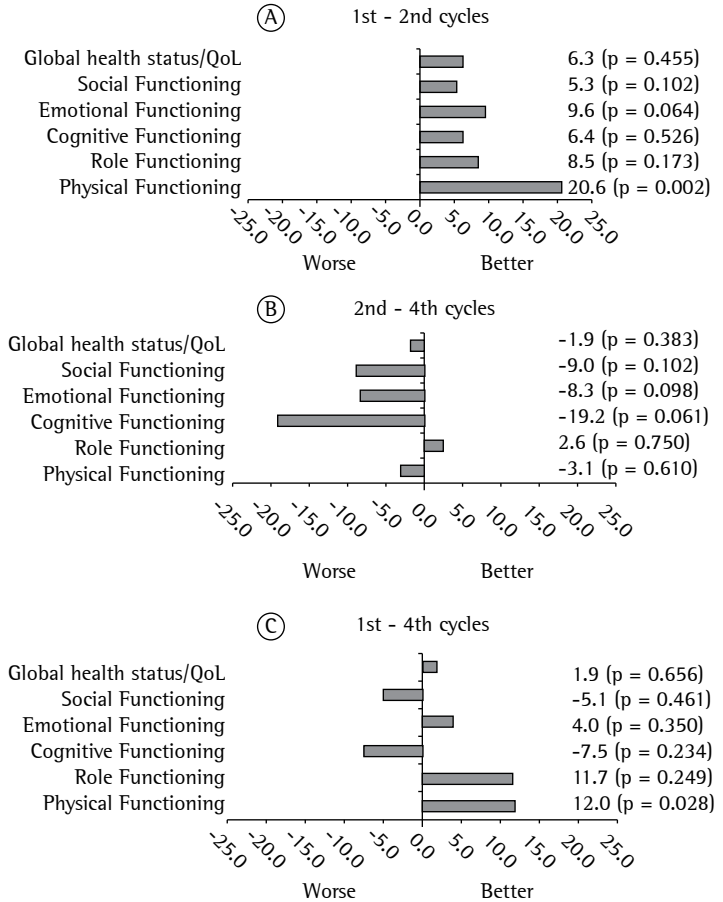

Figure 1 - Changes in mean European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30) functional scale scores. In A, differences in mean EORTC QLQ-C30 scores between the 1st and 2nd cycles of chemotherapy (n = 16); in B, differences in mean EORTC QLQ-C30 scores between the 2nd and 4th cycles of chemotherapy (n = 13); and in C, differences in mean EORTC QLQ-C30 scores between the 1st and 4th cycles of chemotherapy (n = 13). QoL: quality of life.

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Table 2 - Mean European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire and European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire supplemental lung cancer-specific module scores during chemotherapy.

Questionnaire	1st cycle (n = 16)		2nd cycle (n = 16)		4th cycle (n = 13)	
Module/Item	Mean ± SD	Median	Mean ± SD	Median	Mean ± SD	Median
EORTC QLQ-C30						
Functional scale						
Global health status/QoL	67.2 ± 28.0	62.5	73.4 ± 21.6	79.2	77.6 ± 21.9	83.3
Physical functioning	59.8 ± 27.7	60.0	80.4 ± 18.6	83.3	81.5 ± 20.9	93.3
Role functioning	70.7 ± 39.7	91.5	79.2 ± 34.2	100.0	91.0 ± 22.2	100.0
Cognitive functioning	79.0 ± 35.9	100.0	85.4 ± 24.2	100.0	73.1 ± 30.1	83.3
Emotional functioning	63.9 ± 28.6	75.0	73.4 ± 25.5	75.0	66.0 ± 32.2	83.3
Social functioning	91.6 ± 16.3	100.0	96.9 ± 12.5	100.0	91.0 ± 18.8	100.0
Symptom scale						
Fatigue	55.6 ± 36.7	66.7	69.5 ± 27.4	66.7	77.8 ± 20.8	88.9
Pain	60.4 ± 35.4	58.4	80.2 ± 28.0	81.7	78.2 ± 23.9	83.3
Dyspnea	62.5 ± 40.1	66.7	75.0 ± 35.5	100.0	74.4 ± 38.9	100.0
Insomnia	77.1 ± 35.9	100.0	72.9 ± 38.9	100.0	71.8 ± 38.1	100.0
Appetite loss	41.7 ± 46.4	16.5	79.2 ± 40.1	100.0	79.5 ± 39.8	100.0
Nausea/vomiting	91.7 ± 16.1	100.0	89.6 ± 21.0	100.0	92.3 ± 18.8	100.0
Constipation	47.9 ± 50.1	33.4	64.6 ± 44.7	100.0	76.9 ± 43.9	100.0
Diarrhea	100.0 ± 0.0	100.0	91.7 ± 25.8	100.0	92.3 ± 27.7	100.0
Financial difficulties	70.8 ± 41.9	100.0	83.3 ± 32.2	100.0	87.2 ± 25.6	100.0
QLQ-LC13						
Dyspnea	68.8 ± 37.0	83.4	75.7 ± 32.5	88.9	86.3 ± 25.3	100.0
Cough	47.9 ± 40.3	50.0	58.3 ± 35.5	66.7	48.7 ± 44.3	66.7
Hemoptysis	93.8 ± 13.4	100.0	87.5 ± 24.0	100.0	94.9 ± 18.5	100.0
Sore mouth	89.6 ± 29.1	100.0	97.9 ± 8.3	100.0	94.9 ± 12.5	100.0
Dysphagia	87.5 ± 24.0	100.0	93.8 ± 18.1	100.0	82.3 ± 27.7	100.0
Peripheral neuropathy	83.3 ± 29.8	100.0	77.1 ± 39.8	100.0	76.9 ± 39.4	100.0
Alopecia	97.9 ± 8.3	100.0	22.9 ± 33.8	0.0	53.8 ± 51.9	100.0
Chest pain	58.3 ± 46.4	83.4	85.4 ± 27.1	100.0	82.1 ± 37.6	100.0
Arm/shoulder pain	60.4 ± 45.9	83.4	81.3 ± 29.7	100.0	84.6 ± 29.2	100.0
Pain in other body parts	58.3 ± 49.4	100.0	77.1 ± 35.9	100.0	71.8 ± 42.7	100.0

of cancer-related symptoms were higher at the first assessment of quality of life, the exception being the scores for diarrhea. This indicates that the HRQoL of the study participants was worse at that time (Table 2).

Figure 2 shows a comparison of the mean EORTC QLQ-C30 symptom scores in each cycle of chemotherapy. There was little or no change in the scores during chemotherapy. There were significant differences in pain scores between the 1st and 2nd cycles of chemotherapy ($p = 0.027$; Figure 2A), as well as in the scores for loss of appetite between the 1st and 2nd cycles ($p = 0.037$; Figure 2A) and between the 1st and 4th cycles ($p = 0.026$; Figure 2C). There was a large change in the scores for constipation between the 1st and 4th cycles of chemotherapy (Figure 2C). There were moderate changes in the scores for fatigue, insomnia, and financial difficulties between the 1st and 4th cycles of chemotherapy. These changes suggest an improvement in all of the aforementioned HRQoL aspects except insomnia, which was reported more frequently in the 4th cycle of chemotherapy.

The QLQ-LC13 scores for dyspnea, cough, sore mouth, chest pain, arm/shoulder pain, and body pain were lower at the first assessment of HRQoL (i.e., in the 1st cycle of chemotherapy). Hemoptysis and alopecia were found to be more common and more severe at the second assessment of HRQoL, whereas dysphagia and peripheral neuropathy were found to be worse in the 4th cycle of chemotherapy.

Figure 3 shows a comparison of the mean QLQ-LC13 scores in each chemotherapy cycle. There was a significant improvement in chest

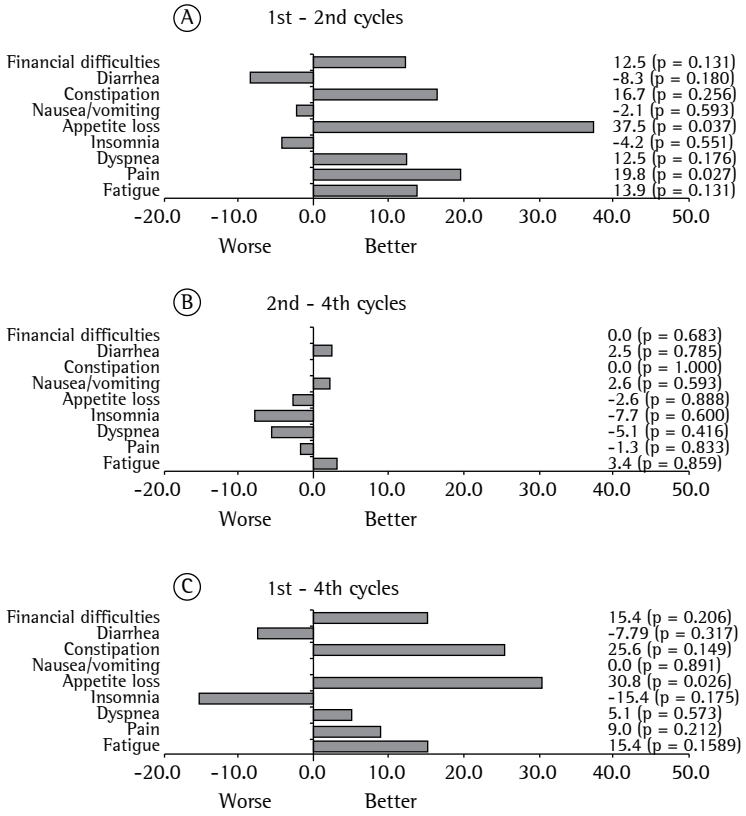

Figure 2 - Changes in mean European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30) symptom scores. In A, differences in mean EORTC QLQ-C30 scores between the 1st and 2nd cycles of chemotherapy (n = 16); in B, differences in mean EORTC QLQ-C30 scores between the 2nd and 4th cycles of chemotherapy (n = 13); and in C, differences in mean EORTC QLQ-C30 scores between the 1st and 4th cycles of chemotherapy (n = 13).

pain between the 1st and 2nd cycles (p =0.016; Figure 3A). There were significant differences in the scores for alopecia between the 1st and 2nd cycles, as well as between the 1st and 4th cycles. There were moderate changes (of 10.4 and 18.8 points, respectively) in the scores for cough and pain in other body parts between the 1st and 2nd cycles of chemotherapy. These changes indicate an improvement in the aforementioned aspects of HRQoL (Figure 3A).

Discussion

In the study population, there was a predominance of White, married, male smokers or former smokers, with stage IV adenocarcinoma. The median age was 63.7 years. Although the logistics and operational aspects of data collection represented a limitation to the selection of study participants, the clinical and sociodemographic characteristics of the participants were consistent with those reported in the literature,[2,17-21] ensuring the external validity of the study.

The use of structured methods for collecting data and the interpretation of the data brought internal validity to our conclusions, as did the use of multiple sources of evidence and the consistency between such evidence and the results of the study. The possibility of reproducing the present study and the use of statistical analysis brought greater reliability to the study, allowing us to make inferences. Therefore, the present study presents relevant data for the evaluation of clinical oncology patients and raises new hypotheses regarding the possible connections of clinical and sociodemographic variables with the quality of life of patients with advanced-stage NSCLC.

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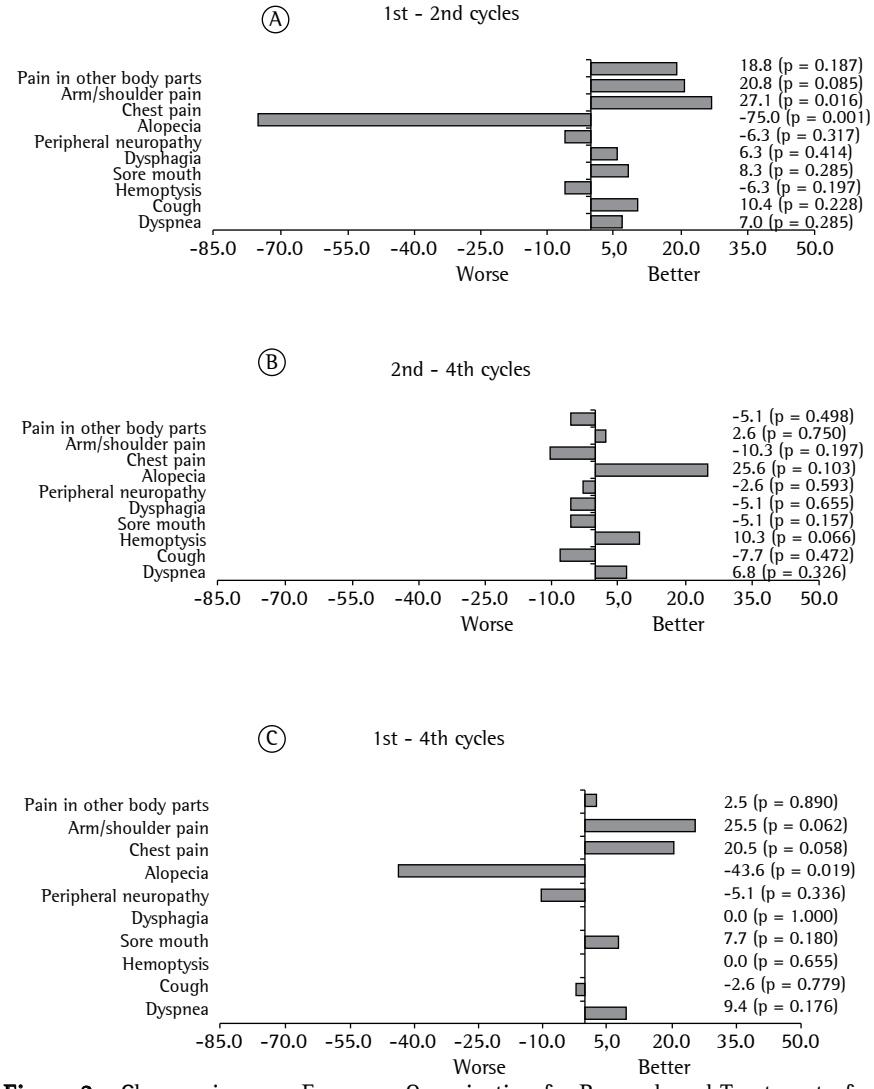

Figure 3 - Changes in mean European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire supplemental lung cancer-specific module (EORTC QLQ-LC13) scores. In A, differences in mean EORTC QLQ-LC13 scores between the 1st and 2nd cycles of chemotherapy (n = 16); in B, differences in mean EORTC QLQ-LC13 scores between the 2nd and 4th cycles of chemotherapy (n = 13); and in C, differences in mean EORTC QLQ-LC13 scores between the 1st and 4th cycles of chemotherapy (n = 13).

With regard to the EORTC QLQ-C30 functional scale scores, we noted a trend toward stability at all assessment time points. Wintner et al.[22] stated that chemotherapy alone, regardless of the number of cycles, had no impact on the quality of life of patients with lung cancer. The authors found that the HRQoL scores remained unchanged throughout the treatment period, a finding that is consistent with ours.

Despite the demonstrated trend toward stability, a significant difference was observed regarding physical function improvement and cognitive function worsening. Braun et al.[23] demonstrated that improvement in physical function was a predictor of survival in patients with lung cancer, confirming that every 10-point increase in physical function is associated with a 10% increase in survival time. However, the changes in the aforementioned aspects might have been influenced by factors such as the use of antineoplastic drugs and drugs for the management of symptoms, as well as by variables such as age,

gender, performance status, histological type, stage of the disease, and preexisting comorbidities.

Grønberg et al.[24] reported that, among NSCLC patients receiving platinum-based chemotherapy, clinical complications appear to be more common in those with severe comorbidities than in those without. Larsson et al.[25] demonstrated significant associations of HRQoL with performance status, age, gender, and disease stage, as well as with EORTC QLQ-C30 and QLQ-LC13 symptom scales and items. Quinten et al.[26] found a correlation between patient-reported physical function and performance status, raising questions regarding the association between self-reported quality of life and the prediction of survival. However, further studies are needed in order to confirm these hypotheses.

In the present study we found moderate changes in the mean global health status/QoL scores between chemotherapy cycles, with a trend toward improved quality of life, when we used the criteria of Osoba et al.[16] These findings differ from those of Braun et al.,[23] who demonstrated that HRQoL is worse in previously treated patients than in newly diagnosed patients, suggesting that chemotherapy has a negative impact on HRQoL.

With regard to the most common signs and symptoms experienced by the NSCLC patients investigated in the present study, the results showed an improvement in fatigue, pain, and appetite during chemotherapy, indicating low HRQoL at the first evaluation. Park et al.[19] evaluated the HRQoL of NSCLC patients treated with chemotherapy after a surgical intervention and found no significant changes in fatigue or pain. However, appetite improved during treatment, a result that is similar to ours. Increased loss of appetite has been reported to be associated with shorter survival.[23] Maric et al.[17] reported that although chemotherapy had beneficial effects on fatigue, dyspnea, insomnia, and appetite loss, NSCLC patients undergoing chemotherapy had higher pain scores than did newly diagnosed NSCLC patients. Lin et al.[27] demonstrated that concomitant occurrence and increased severity of the aforementioned symptoms have a negative impact on HRQoL.

We found no significant changes in the scores for nausea/vomiting and diarrhea when we compared the scores obtained at the first HRQoL assessment with those obtained subsequently. This might be due to the pharmacological characteristics of the drugs in the chemotherapy protocol. Literature data show a low incidence of the aforementioned symptoms when platinum coordination compounds are used in combination with paclitaxel, a factor that should be considered in the choice of drug therapy because it affects the quality of life of patients.[28]

Alopecia is a very common side effect of antineoplastic drugs. The study participants reported increased occurrence of alopecia after the 1st chemotherapy cycle, a result that indicates low HRQoL. According to Bonassa and Molina,[29] hair loss is the most devastating effect and can directly affect social and emotional aspects of the quality of life of patients undergoing chemotherapy.

Our finding of a moderate improvement in cough during chemotherapy is consistent with those of Rolke et al.[30] and Park et al.,[19] who reported that cough tends to improve during chemotherapy. Given that cough negatively influences HRQoL, there is a need for therapeutic interventions for the management of this symptom.[31]

Rapid detection of the emergence or worsening of a sign or symptom through periodic assessment of HRQoL allows therapeutic interventions to be performed in a more immediate way, optimizing the treatment of cancer patients and, consequently, impacting their survival.[10,13] However, the assessment of quality of life in daily clinical practice is little discussed in the literature, despite its recognized importance for monitoring the disease and improving communication between the health care team and the patient.[10,23,32]

The present study explored self-reported quality of life in advanced NSCLC patients receiving chemotherapy, with the objective of gaining a better understanding of how chemotherapy with carboplatin and paclitaxel influences HRQoL. The importance of patient perception of their own health is highlighted within the context of the complexity of cancer, which is a disease that affects every dimension of life and the way in which individuals perceive the environment, the diagnosis, and the therapy.[10] Therefore, the combination of periodic quality of life assessments and clinical practice should be more extensively discussed in the scientific literature in order to improve the understanding of aspects that define patient health and the benefits arising from it. Although the changes in HRQoL scores between chemotherapy cycles were small, chemotherapy

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was found to improve the HRQoL of the study participants, having a greater impact on physical and cognitive functioning and on cancer-related symptoms such as pain and loss of appetite.

With regard to the state of the art, the present study can be considered innovative because it provides elements that are essential to the assessment of quality of life in clinical practice. Further studies should be conducted in order to evaluate the association of sociodemographic and clinical variables such as polypharmacy and comorbidities with aspects of the quality of life of patients undergoing chemotherapy. Because of their extensive knowledge of drugs and their toxicity profile, pharmacists should be involved in studies of quality of life assessment, analyzing the connection between drug therapy and the severity of signs and self-reported symptoms, given their impact on certain aspects of HRQoL.

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Variability of the perception of dyspnea in healthy subjects assessed through inspiratory resistive loading*

Variabilidade da percepção da dispneia medida através de um sistema de cargas resistivas inspiratórias em indivíduos saudáveis

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Abstract

Objective: Few studies have evaluated the variability of the perception of dyspnea in healthy subjects. The objective of this study was to evaluate the variability of the perception of dyspnea in healthy subjects during breathing against increasing inspiratory resistive loads, as well as to assess the association between the level of perception of dyspnea and the level of physical activity. **Methods:** This was a cross-sectional study involving healthy individuals 16 years of age or older. Subjects underwent inspiratory resistive loading testing, in which the level of perception of dyspnea was quantified with the modified Borg scale. We also determined body mass indices (BMIs), assessed maximal respiratory pressures, performed pulmonary function tests, applied the international physical activity questionnaire (IPAQ)-long form, and conducted six-minute walk tests (6MWTs). The level of perception of dyspnea was classified as low (Borg score < 2), intermediate (Borg score, 2-5), or high (Borg score > 5). **Results:** We included 48 healthy subjects in the study. Forty-two subjects completed the test up to a load of 46.7 $cmH_2O/L/s$. The level of perception of dyspnea was classified as low, intermediate, and high in 13, 19, and 10 subjects, respectively. The level of perception of dyspnea was not significantly associated with age, gender, BMI, IPAQ-long form score, maximal respiratory pressures, or pulmonary function test results. **Conclusions:** The scores for perceived dyspnea induced by inspiratory resistive loading in healthy subjects presented wide variability. The perception of dyspnea was classified as low in 31% of the subjects, intermediate in 45%, and high in 24%. There was no association between the level of perception of dyspnea and the level of physical activity (IPAQ or six-minute walk distance).

Keywords: Dyspnea; Respiratory function tests; Exercise test.

Resumo

Objetivo: Poucos estudos avaliaram a variabilidade da percepção da dispneia em indivíduos saudáveis. O objetivo deste estudo foi avaliar a variabilidade da percepção da dispneia em indivíduos saudáveis através do uso de cargas resistivas inspiratórias crescentes, assim como avaliar a associação entre o nível de percepção da dispneia e o nível de atividade física. **Métodos:** Estudo transversal realizado em indivíduos saudáveis com idade ≥ 16 anos. Os indivíduos foram submetidos ao teste de cargas resistivas inspiratórias, no qual o nível de percepção da dispneia foi quantificado pela escala de Borg modificada. Foram também determinados os índices de massa corpórea (IMC), pressões respiratórias máximas, testes de função pulmonar, *international physical activity questionnaire* (IPAQ)-*long form*, e testes de caminhada de seis minutos (TC6). Os indivíduos foram classificados em percepção baixa (Borg < 2), intermediária (Borg, 2-5) e alta (Borg > 5). **Resultados:** Foram incluídos no estudo 48 indivíduos saudáveis. Desses, 42 completaram o teste até a carga de 46,7 $cmH_2O/l/s$. O nível de percepção da dispneia foi classificado como baixo, intermediário e alto em 13, 19 e 10 indivíduos, respectivamente. Não houve associações significativas do nível de percepção da dispneia com idade, sexo, IMC, IPAQ e testes de função pulmonar. **Conclusões:** Os escores da percepção da dispneia induzida por cargas resistivas inspiratórias em indivíduos saudáveis apresentaram uma ampla variabilidade. A percepção da dispneia foi classificada como baixa, intermediária e alta em 31%, 45% e 24%, respectivamente. Não houve associações entre o nível de percepção da dispneia e o nível de atividade física (IPAQ ou distância no TC6).

Descritores: Dispneia; Testes de função respiratória; Teste de esforço.

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Introduction

Breathlessness, or dyspnea, is the subjective experience of respiratory discomfort and consists of qualitatively distinct sensations that vary in intensity. This symptom has multidimensional aspects, involving physiological, psychological, social, and environmental factors that result in a behavioral response.[1] In patients with pulmonary impairment, dyspnea is often accompanied by physical inactivity, decreased exercise capacity, and impaired quality of life.[2-5]

Dyspnea is a common problem that is seen in up to half of all acute cases admitted to tertiary care hospitals.[1] Assessment of the multidimensional aspects of dyspnea has become more important in recent years. Dyspnea is an important warning symptom and is considered a predictor of hospitalization and mortality in patients with chronic lung disease, mainly in a subgroup of patients with a blunted perception of dyspnea.[6,7]

Healthy subjects can experience dyspnea in different situations—at high altitudes, after breath-holding, during stressful situations that cause anxiety or panic, and (most commonly) during strenuous exercise.[8] Dyspnea occurs in a highly variable way in comparison with the levels of pathophysiology. However, little is known about the variability of the perception of dyspnea in healthy subjects.[7]

Various studies have used inspiratory resistive loading in order to evaluate the perception of dyspnea and to investigate factors associated with increased or decreased sensitivity to dyspnea.[9-15] Testing with inspiratory resistive loading involves the use of a circuit within which loads of increasing magnitudes can be created, thus inducing the sensation of dyspnea by increasing inspiratory effort and the overall work of breathing. Subjects quantify the severity of dyspnea using instruments such as the Borg scale.[11,12,14]

The objective of this study was to evaluate the variability of the perception of dyspnea in healthy subjects during inspiratory resistive loading. A secondary objective was to investigate the association between the perceived severity of dyspnea and the level of physical activity.

Methods

Study design

We conducted a prospective cross-sectional study designed to evaluate the perception of dyspnea in healthy subjects. For each subject, over the course of a single day, we quantified the perceived severity of dyspnea during inspiratory resistive loading, determined maximal respiratory pressures, performed pulmonary function tests, and conducted a nutritional evaluation, as well as applying the long form of the International Physical Activity Questionnaire (IPAQ-long form) and the six-minute walk test (6MWT). The study was approved by the Research Ethics Committee of the *Hospital de Clínicas de Porto Alegre* (HCPA, Porto Alegre *Hospital de Clínicas*), in the city of Porto Alegre, Brazil (Protocol no. 08-063). All participants (or their parents or legal guardians) gave written informed consent.

Population

Using notices posted in the HCPA and online announcements, we recruited 48 healthy subjects. We excluded subjects who were < 16 years of age, as well as those who were pregnant, had acute conditions affecting the respiratory tract, were current or former smokers, or had any chronic medical condition, such as asthma, chronic pain, heart disease, musculoskeletal disorders, and traumatic injury. Otherwise, all subjects who volunteered during the period of the study were consecutively enrolled.

Measurements and procedures

Healthy subjects underwent perception of dyspnea testing involving inspiratory resistive loading.[16] Before the tests, subjects were familiarized with the apparatus and measurement procedures. After receiving standardized instructions, subjects were seated in a comfortable chair and acclimatized to the setting. Wearing a nose clip, subjects breathed through a mouthpiece in a system composed of a two-way non-rebreathing valve (Hans Rudolph, Shawnee, KS, USA). A circular plastic mouthpiece (with eight different orifices) was employed in order to generate inspiratory resistive loads of increasing magnitude (0.6, 7.0, 15.0, 25.0, 46.7, 67.0, and 78.0 $cmH_2O/L/s$, calculated according to a constant flow of 300 mL/s). The sensation of dyspnea was assessed during the inspiratory resistive loading. After breathing at each level of resistance for 2 min, the subjects were questioned about the feeling of shortness of breath (dyspnea), as quantified with the modified Borg scale,[17]

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ranging from 0 (no dyspnea) to 10 (maximum severity of dyspnea). To monitor the effects of dyspnea induction, we monitored inspiratory pressure, inspiratory time and respiratory rate continuously at the mouthpiece using computer software developed by the HCPA Department of Engineering. Exhalation was not loaded. Subjects were free to choose their respiratory rate, volume, and flow, in order to have as natural a breathing pattern as possible.

The functional capacity of subjects was measured with the 6MWT, which was conducted in accordance with the guidelines established by the American Thoracic Society and the Brazilian Thoracic Association.[18,19] Following a standardized protocol, subjects walked along a flat 30-m track established in a corridor. The subjects were instructed to walk as far as possible for 6 min under the supervision of a physiotherapist. The physiotherapist encouraged subjects with the standardized statements "you are doing well" or "keep up the good work", but was asked not to use other phrases. The total six-minute walk distance (6MWD) was recorded. The pre- and post-6MWT SpO_2 were measured with a pulse oximeter (NPB-40; Nellcor Puritan Bennett, Pleasanton, CA, USA). We also recorded pre- and post-6MWT scores on the modified Borg scale.[17]

Pulmonary function tests were performed with a computerized spirometer (MasterScreen, v 4.31; Jaeger, Würtzburg, Germany). We recorded FVC, FEV_1, and the FEV_1/FVC ratio, in triplicate, and the best of the three was selected for analysis. All parameters are expressed as percentages of the values predicted for age, stature, and gender.[20] Nutritional status was classified on the basis of the body mass index (BMI), determined by dividing weight (in kg) by height (in m^2).

Maximal respiratory pressures were used as indexes of respiratory muscle strength. Pressure measurements were made in the seated position with a digital manometer (Microhard MVD300, version 1.0; Globalmed, Porto Alegre, Brazil). All subjects wore nose clips and were instructed to press their lips tightly against the mouthpiece to prevent air leakage during the pressure measurements.

We measured MIP at RV and MEP at TLC. The pressures measured were maintained for at least 1 s. Five determinations were made, with a suitable rest interval between each determination, until a plateau value had been reached and no further learning effect was seen. Once the operator was satisfied, the maximum values of two maneuvers that varied by less than 10% were recorded. The MIP and MEP were expressed in cmH_2O and as percentages of the predicted values. We obtained the predicted values for adolescents and adults from Wilson et al. and Neder et al., respectively.[21,22] On the basis of the scores on the IPAQ-long form,[23] the level of physical activity was categorized as low, moderate, or high.

Statistical analysis

Data are expressed as number (percentage), mean ± standard deviation, or median (interquartile range). We divided the subjects into three groups, by the level of perception of dyspnea, according to the tertiles of Borg scores generated at an inspiratory resistive load of 46.7 cmH_2O/L/s: low perception group (Borg score < 2; n = 13), intermediate perception group (Borg score 2-5; n = 19), and high perception group (Borg score > 5; n = 13). The inspiratory resistive load of 46.7 cmH_2O/L/s was selected because it generated high dyspnea scores with little drop-off.

Categorical comparisons were performed with the chi-square test for proportions. Continuous variables with normal distribution were compared with one-way ANOVA for quantitative variables. Ordinal variables were compared with the Kruskal-Wallis H test. Kaplan-Meier curves were used in order to profile the subjects during the perception of dyspnea test at the different inspiratory resistive loads. To compare males and females in terms of the dyspnea scores during the inspiratory resistive loading, we used a generalized linear model. Correlations were determined using Spearman's rank correlation coefficient.

Data analysis was performed with the IBM SPSS Statistics software package, version 18.0 (IBM Corporation, Armonk, NY, USA). The level of statistical significance was set at $p < 0.05$. All statistical tests were two-tailed ($\alpha = 0.05$ and $1-\beta = 90\%$).

Results

From February 2010 to November 2012, we screened 54 subjects. We excluded 6 subjects: 2 presented abnormal spirometry values; 1 dropped out because of anxiety at the outset of the testing; and 3 failed to complete all required examinations. Therefore, 48 healthy subjects

(19 males and 29 females) were included in the study. All of the subjects were White, the mean age was 31.2 ± 12.1 years (range, 16-61 years), and the mean BMI was 23.5 ± 3.4 kg/m^2. Spirometry values (in % of predicted) were as follows: FEV_1, 96 ± 12%; FVC, 95.1 ± 11.2%; and FEV_1/FVC ratio, 100.6 ± 8.3%. The 6MWD was 579.2 ± 72 m.

Figure 1 shows the modified Borg dyspnea score and inspiratory pressure at the various inspiratory resistive loads ($p < 0.001$). Figure 2 presents the Kaplan-Meier analysis of interruption of the perception of dyspnea test at increasing inspiratory resistive loads. Thirty-eight subjects (79.2%) completed the entire test (all inspiratory resistive loads), and 10 (20.8%) did not, because of the following symptoms: dyspnea (n = 3); respiratory fatigue (n = 3); headache (n = 2); drooling (n = 1); and dry throat (n = 1).

Figure 3 shows the perception of dyspnea groups, by tertiles of the scores on the modified Borg dyspnea scale scores generated at an inspiratory resistive load of 46.7 $cmH_2O/L/s$. Forty-two subjects continued the test up to that load. The perception of dyspnea was classified as low (Borg score < 2), intermediate (Borg score, 2-5), and high (Borg score > 5) in 13, 19, and 10 subjects, respectively.

To compare males and females in terms of the dyspnea scores during the inspiratory resistive load testing, we used a generalized linear model. Although there was a statistically significant difference among the various inspiratory resistive loads ($p < 0.001$), there was no significant difference for gender ($p = 0.590$) or for the interaction between increasing inspiratory resistive loads and gender ($p = 0.253$).

Table 1 presents the characteristics of the subjects according to the level of perception of dyspnea. We found that the level of perception of dyspnea was not significantly associated with age, gender, BMI, IPAQ-long form score, maximal respiratory pressures, or pulmonary function test results. In addition, the inspiratory pressure at the various inspiratory resistive loads did not differ among the groups.

Spearman's correlation coefficient between the inspiratory pressure and MIP generated at inspiratory resistive loads of 0.6, 7.0, 15.0, 25.0, 46.7, 67.0, 78.0, and 0.6 $cmH_2O/L/s$ was 0.04, 0.05, 0.08, 0.11, 0.12, 0.13, 0.15 and 0.05, respectively. Spearman's correlation between Borg scores and inspiratory pressure/MIP was not significant ($p > 0.05$).

Discussion

The main finding of this cross-sectional study was that the scores for the perception of dyspnea induced by inspiratory resistive loads presented wide variability in healthy subjects. Among the 42 subjects who completed the test up to a load of 46.7 $cmH_2O/L/s$, the perception of dyspnea was classified as low (or blunted) in 13 (31%), intermediate in 19 (45%), and high in 10 (24%). In addition, the level of perception of dyspnea was not found to be associated with age, gender, BMI, IPAQ-long form score, maximal respiratory pressures, or pulmonary function test results.

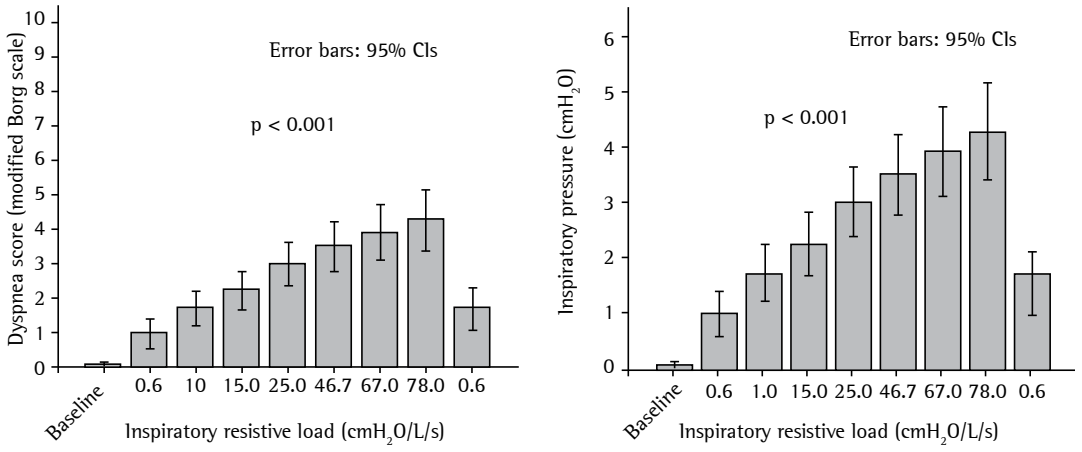

Figure 1 - Dyspnea scores on the modified Borg scale, together with inspiratory pressures, at increasing inspiratory resistive loads in healthy subjects.

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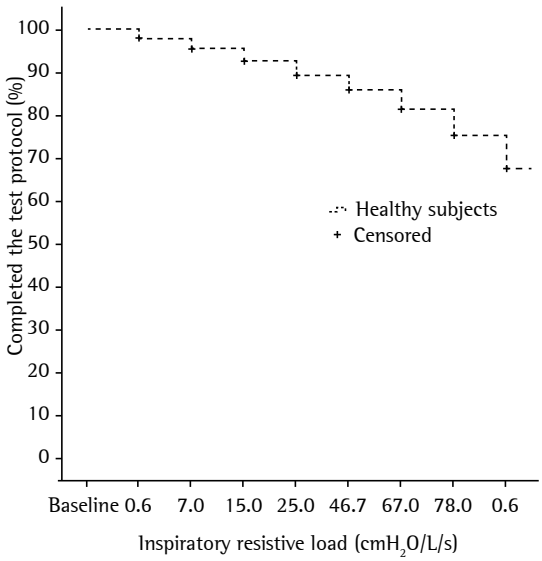

Figure 2 - Kaplan-Meier analysis for interruption of the perception of dyspnea test at increasing inspiratory resistive loads in healthy subjects.

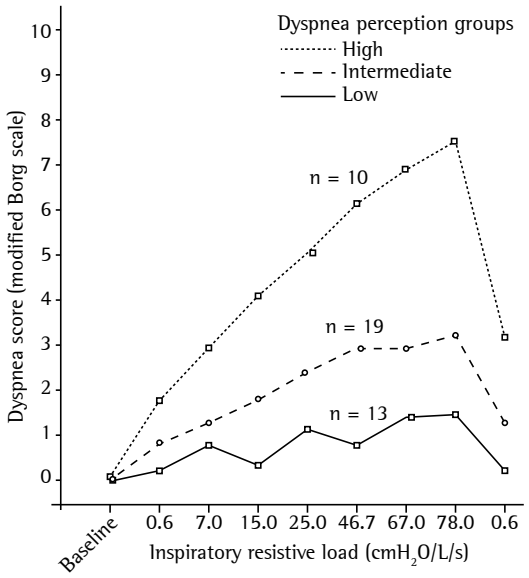

Figure 3 - Patients stratified by the level of the perception of dyspnea (tertiles of scores on the modified Borg scale), with a focus on the differences at an inspiratory resistive load of 46.7 $cmH_2O/L/s$. Dyspnea perception groups (modified Borg scale scores): low (< 2), intermediate (2-5), and high (> 5).

In the present study, dyspnea was successfully induced in healthy subjects through the application of inspiratory resistive loads of increasing magnitude, which significantly increased inspiratory pressure. These findings correspond with the reported typical effects of inspiratory resistive loads, which increase inspiratory effort and the overall work of breathing.[15] We used a protocol with seven different inspiratory resistive loads, ranging from 0.6 to 78.0 $cmH_2O/L/s$. The fact that we performed the test without pauses could explain why many subjects failed to complete all of its phases. When the inspiratory resistive load returned to 0.6 $cmH_2O/L/s$ at the end of the test, dyspnea scores decreased in all subjects but remained higher in the high perception group than in the other groups. This could be explained by the multidimensional aspects of dyspnea, as well as by the differences between the sensory and emotional aspects of its perception.[15]

It is worth noting that our approach differed from those taken in previous studies[13,14,16,24] in that we did not apply a randomized sequence of inspiratory resistive loads. In the present study, we used inspiratory resistive loads of progressive magnitude in order to simulate the character of naturally occurring dyspnea. However, randomized presentations of different inspiratory resistive loads might be an alternative method that would avoid subject perception of the progressive magnitude of the loads.

Simon et al.[25] investigated whether dyspnea induced in healthy subjects by different stimuli represents one or more than one sensation. The authors studied 30 subjects in whom dyspnea was induced by eight different stimuli. One of the stimuli used was breathing with an inspiratory resistive load. Subjects breathed for 2 min through a device used in inspiratory muscle training with an inspiratory resistive load of 260-280 $cmH_2O/L/s$, at flow rates ranging from 0.3 L/s to 0.5 L/s. The mean intensity rating of dyspnea on the modified Borg scale associated with breathing against inspiratory resistance was 6.5 ± 2.5 points.

Kikuchi et al.[6] examined whether dyspnea and chemosensitivity to hypoxia and hypercapnia were factors in fatal asthma. Those authors studied 22 asthma patients (11 who had had near-fatal asthma attacks and 11 who had not) and 16 healthy subjects, scoring the level of perception of dyspnea on the Borg scale during breathing against inspiratory resistance ranging from 0 $cmH_2O/L/s$ to 30.9 $cmH_2O/L/s$. During breathing against a resistance of 20.0 $cmH_2O/L/s$, the Borg scale scores of the healthy subjects ranged from 1 to 6.

Table 1 - Characteristics of healthy subjects, according to the level of perception of dyspnea.[a]

Variable	All	Perception of dyspnea			p[b]
		Low	Intermediate	High	
	(n = 42)	(n = 13)	(n = 19)	(n = 10)	
Age (years)	31.5 ± 11.5	34 ± 11.2	28.6 ± 11.3	33.8 ± 12.4	0.345
Gender (male/female), n/n	15/27	5/8	7/12	3/7	0.907
BMI (kg/m²)	23.3 ± 3.2	24.7 ± 2.8	22.7 ± 3.4	22.6 ± 2.8	0.150
Level of physical activity[c]					
Low, n (%)	7 (16.7)	3 (7.1)	3 (7.1)	1 (2.4)	
Moderate, n (%)	14 (33.3)	5 (11.9)	6 (14.3)	3 (7.1)	
High, n (%)	21 (50.0)	5 (11.9)	10 (23.8)	6 (14.3)	
MIP (cmH_2O)	100.3 ± 36.6	105.2 ± 28.3	99.2 ± 39.4	95.1 ± 44.7	0.820
MEP (cmH_2O)	109.8 ± 29.1	114.7 ± 18.4	111.8 ± 32.8	96.8 ± 33.4	0.364
PEF (% of predicted)	93.3 ± 15.4	97.5 ± 10.7	87.9 ± 18	97.9 ± 13.2	0.126
FEV_1 (% of predicted)	96.2 ± 11.9	99.2 ± 12.5	94.6 ± 13.2	94.8 ± 8.4	0.560
FVC (% of predicted)	95.2 ± 10.6	98.2 ± 11	94.4 ± 11.2	92.6 ± 8.4	0.423
FEV_1/FVC ratio (% of predicted)	101.1 ± 6.9	100.8 ± 5.7	100.8 ± 7.9	100.2 ± 6.8	0.859
Total 6MWD (m)	577 ± 70.9	548.6 ± 79.8	601 ± 67.2	568.3 ± 53.9	0.109
Pre-6MWT (at-rest) SpO_2 (%)	98.2 ± 1.2	98.1 ± 1	98.3 ± 1.1	98 ± 1.2	0.753
Post-6MWT SpO_2 (%)	97.7 ± 1.6	97.9 ± 2.0	97.9 ± 1.2	97.2 ± 1.6	0.504
Post-6MWT oxygen desaturation (%)	0.4 ± 1.8	0.2 ± 1.9	0.4 ± 1.5	0.8 ± 2.2	0.692
IP (cmH_2O) at an IRL of 0.6 cmH_2O/L/s	3.2 ± 2.4	3.4 ± 1.6	3.3 ± 3.1	2.9 ± 1.8	0.852
IP (cmH_2O) at an IRL of 7.0 cmH_2O/L/s	4.6 ± 2.4	5.5 ± 2.9	4.4 ± 2.3	3.7 ± 1.9	0.219
IP (cmH_2O) at an IRL of 15.0 cmH_2O/L/s	7 ± 4.2	7.8 ± 3.9	7.1 ± 4.7	6 ± 3.6	0.581
IP (cmH_2O) at an IRL of 25.0 cmH_2O/L/s	10.2 ± 6.7	12 ± 5.9	10.2 ± 8.1	8 ± 4	0.368
IP (cmH_2O) at an IRL of 46.7 cmH_2O/L/s	11.9 ± 7.7	13.4 ± 6.8	12 ± 9.6	9.7 ± 4.4	0.531
IP (cmH_2O) at an IRL of 67.0 cmH_2O/L/s	13.5 ± 9.3	14.3 ± 8.7	13.9 ± 11.5	11.6 ± 5.6	0.773
IP (cmH_2O) at an IRL of 78.0 cmH_2O/L/s	14.6 ± 8.9	16.5 ± 10	14.1 ± 9.5	13.1 ± 6.2	0.637
IP (cmH_2O) at an IRL of 0.6 cmH_2O/L/s	4.5 ± 2.6	4.6 ± 2.1	5.1 ± 3.3	3.4 ± 1.1	0.255

BMI: body mass index; 6MWD: six-minute walk distance; 6MWT: six-minute walk test; IP: inspiratory pressure; and IRL: inspiratory resistive load. [a]Values expressed as mean ± SD, except where otherwise indicated. [b]Pearson's chi-square test for proportions; one-way ANOVA for quantitative variables; and Kruskal-Wallis H test for ordinal variables. [c]Determined on the basis of the score on the International Physical Activity Questionnaire-long form.

Paulus et al.[26] examined the hypothesis that elite athletes, in comparison with control subjects, show attenuated insular cortex activation during an aversive interoceptive challenge. Those authors studied 10 elite adventure racers and 11 healthy subjects. The subjects breathed through an inspiratory resistive load of 40 cmH_2O/L/s. The authors asked the subjects to rate their experience, using a 10-cm visual analog scale. The mean perceived intensity of dyspnea among the healthy subjects, as rated on the visual analog scale, was 5.1 ± 0.9 points.

Ebihara et al.[7] quantified the sensation of dyspnea during breathing through inspiratory resistive loads of 10, 20, and 30 cmH_2O/L/s in 479 Japanese community-dwelling elderly people with normal lung function. Patients were divided into tertiles according to the perception of dyspnea, which was classified as low in 153 subjects, intermediate in 160, and high in 166. The authors found that, among community-dwelling elderly people, a blunted perception of dyspnea was associated with hospitalization, high medical costs, and all-cause mortality.

The present study has some limitations. First, the cross-sectional study design precluded the examination of temporal relationships between the perception of dyspnea and clinical outcomes. Second, our sample was small, and further investigations, involving larger cohorts, are therefore needed in order to elucidate the mechanisms related to a blunted perception of dyspnea in healthy subjects.

In the present study, the finding with the greatest clinical implications was that nearly one third of the subjects failed to discriminate the perception of dyspnea. The significance of this finding, in terms of its effect on clinical

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outcomes and the factors involved, remains unknown. Screening for the perception of dyspnea in asymptomatic and healthy subjects might be a means of identifying the need for more careful medical follow-up in order to avoid greater health care costs and higher mortality.

In conclusion, the scores for the perception of dyspnea induced by inspiratory resistive loads in healthy subjects presented wide variability. The level of perception of dyspnea was classified as low in 31% of the subjects, as intermediate in 45%, and as high in 24%. In addition, the level of perception of dyspnea was not found to be associated with the IPAQ-long form score or with the 6MWD.

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Lung-dominant connective tissue disease among patients with interstitial lung disease: prevalence, functional stability, and common extrathoracic features*

Colagenose pulmão dominante em pacientes com doença pulmonar intersticial: prevalência, estabilidade funcional e manifestações extratorácicas comuns

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Abstract

Objective: To describe the characteristics of a cohort of patients with lung-dominant connective tissue disease (LD-CTD). **Methods:** This was a retrospective study of patients with interstitial lung disease (ILD), positive antinuclear antibody (ANA) results (≥ 1/320), with or without specific autoantibodies, and at least one clinical feature suggestive of connective tissue disease (CTD). **Results:** Of the 1,998 patients screened, 52 initially met the criteria for a diagnosis of LD-CTD: 37% were male; the mean age at diagnosis was 56 years; and the median follow-up period was 48 months. During follow-up, 8 patients met the criteria for a definitive diagnosis of a CTD. The remaining 44 patients comprised the LD-CTD group, in which the most prevalent extrathoracic features were arthralgia, gastroesophageal reflux disease, and Raynaud's phenomenon. The most prevalent autoantibodies in this group were ANA (89%) and anti-SSA (anti-Ro, 27%). The mean baseline and final FVC was 69.5% and 74.0% of the predicted values, respectively ($p > 0.05$). Nonspecific interstitial pneumonia and usual interstitial pneumonia patterns were found in 45% and 9% of HRCT scans, respectively; 36% of the scans were unclassifiable. A similar prevalence was noted in histological samples. Diffuse esophageal dilatation was identified in 52% of HRCT scans. Nailfold capillaroscopy was performed in 22 patients; 17 showed a scleroderma pattern. **Conclusions:** In our LD-CTD group, there was predominance of females and the patients showed mild spirometric abnormalities at diagnosis, with differing underlying ILD patterns that were mostly unclassifiable on HRCT and by histology. We found functional stability on follow-up. Esophageal dilatation on HRCT and scleroderma pattern on nailfold capillaroscopy were frequent findings and might come to serve as diagnostic criteria.

Keywords: Idiopathic interstitial pneumonias; Autoantibodies; Connective tissue diseases; Autoimmunity.

Resumo

Objetivo: Descrever as características de uma coorte de pacientes com colagenose pulmão dominante (CPD). **Métodos:** Estudo retrospectivo de pacientes com doença pulmonar intersticial (DPI), anticorpo antinuclear (ANA) positivo (≥ 1/320), com ou sem autoanticorpos específicos, e com a presença de ao menos uma manifestação clínica sugestiva de doença do tecido conjuntivo (DTC). **Resultados:** Dos 1.998 avaliados, 52 preencheram inicialmente os critérios para o diagnóstico de CPD: 37% eram homens; a média de idade ao diagnóstico era de 56 anos e a mediana do tempo de seguimento era de 48 meses. Durante o seguimento, 8 pacientes preencheram os critérios para um diagnóstico definitivo de DTC. Os 44 pacientes restantes formaram o grupo CPD, no qual as manifestações extratorácicas mais prevalentes foram artralgia, doença do refluxo gastroesofágico e fenômeno de Raynaud. Os autoanticorpos mais prevalentes nesse grupo foram ANA (89%) e anti-SSA (anti-Ro, 27%). A média de CVF no início e na última avaliação foi de 69,5% e 74,0% do predito, respectivamente ($p > 0,05$). Pneumonia intersticial não específica e pneumonia intersticial usual foram identificadas em 45% e 9% das TCARs, respectivamente; 36% das TCARs eram não classificáveis. Uma prevalência semelhante foi identificada na histologia. Dilatação esofágica difusa foi identificada em 52% das TCARs. Capilaroscopia subungueal foi realizada em 22 pacientes; 17 apresentavam um padrão de esclerodermia. **Conclusões:** No grupo CPD, houve predominância feminina, e os pacientes apresentaram alterações espirométricas leves ao diagnóstico, com diferentes padrões de DPI, em sua maioria não classificáveis, tanto em TCAR como na histologia. Estabilidade funcional foi identificada no seguimento. A dilatação esofágica em TCAR e o padrão de esclerodermia na capilaroscopia subungueal foram achados frequentes que poderiam servir como critérios diagnósticos.

Descritores: Pneumonias intersticiais idiopáticas; Autoanticorpos; Doenças do tecido conjuntivo; Autoimunidade.

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Introduction

There is a dilemma surrounding the classification of patients with interstitial lung diseases (ILDs) and clinical features that are suggestive of *formes frustes* (limited forms) of connective tissue disease (CTD), because such patients do not meet the accepted rheumatological criteria for a definitive diagnosis of CTD.[1-3] Since the first recognition of the nonspecific interstitial pneumonia (NSIP) pattern as a possible independent disease, it has been strongly associated with CTD.[4] Previous studies have shown different characteristics regarding the prognosis and natural history of idiopathic interstitial pneumonia (IIP) with a "rheumatological flavor" but without a definitive diagnosis of CTD.[5-7] The majority of such studies have departed from the NSIP histology to scrutinize the clinical, physiological, and tomographic features of patients. However, it remains unclear whether other ILD patterns are associated with this subgroup, and only a few studies have considered patterns that are either exclusively usual interstitial pneumonia (UIP)[8,9] or mixed.[6,10] Although patients with CTD and ILD have better survival, regardless of their histology,[11-13] uncertainties remain regarding how isolated autoantibody positivity in IIP affects the natural course of the disease and the response to treatment.[7,14]

Fischer et al.[4] recently proposed "lung-dominant" CTD, or LD-CTD, as a new classification and the term best suited to describing the association between ILD and undifferentiated CTD, theretofore referred to by myriad terms. The authors proposed comprehensive and restrictive provisional criteria that recognize any classical ILD pattern as a possible association with LD-CTD. Positivity for autoantibodies that are more specific, with special attention to their titers, and histological features that are strongly associated with collagen vascular diseases were also included in the definition of LD-CTD proposed by the authors.[4]

We hypothesized that comprehensive and restrictive criteria would be needed in order to define LD-CTD appropriately. We further hypothesized that the definition would be more accurate if ILDs were accompanied not only by autoantibody positivity but also by any extrathoracic feature of CTD. The main objective of this study was to characterize a retrospective cohort of patients in Brazil who met the clinical, functional, serological, tomographic, and histological criteria for a diagnosis of LD-CTD, including the presence of extrathoracic manifestations. We also evaluated how the pulmonary physiology behaves throughout follow-up in patients with LD-CTD.

Methods

Patients

This was a retrospective study of patients with ILD seen at the outpatient clinic of a tertiary university hospital in Brazil over the previous 16 years (1996-2012). From among the 1,998 cases in the ILD patient database, we selected 75 in which the patients met the LD-CTD criteria proposed by Fischer et al.,[4] as detailed in Chart 1, at the time of their first clinical evaluation. After the records had been evaluated by a multidisciplinary team composed of radiologists, pathologists, and pulmonologists with expertise in the diagnosis of ILD, we excluded patients with classifiable forms of CTD or ILDs with known etiologies, such as hypersensitivity pneumonitis, smoking, and idiopathic pulmonary fibrosis (IPF). In addition, we excluded cases in which basic initial complementary tests were not performed. A rheumatologist also evaluated every case included in the analysis.

Data collection

On the basis of our review of the patient charts, we selected ILD patients with a high antinuclear antibody (ANA) titer (≥ 1:320), with or without positivity for specific autoantibodies, and at least one clinical extrathoracic feature suggestive of CTD. We collected data related to demographic characteristics; comorbidities; clinical features of CTD (including clinical extrathoracic features at diagnosis and over the course of the disease); imaging findings (HRCT scans of the chest and nailfold capillaroscopy); pulmonary function tests (PFTs) at the initial visit and last available evaluation; biological parameters (including the results of a broad autoantibody panel and routine blood tests); histological features; and details of the medical treatment.

Within the data collected at the initial evaluation, we searched for extrathoracic features suggestive of CTD, including arthritis; arthralgia; morning stiffness; photosensitivity; cutaneous

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Chart 1 - Proposed provisional diagnostic criteria for lung-dominant connective tissue disease.

1. NSIP, UIP, LIP, OP, and DAD (or DIP if no smoking history), as determined by surgical lung biopsy specimen or suggested by [HRCT] *and*

2. Insufficient extrathoracic features of a definite CTD to allow a specific CTD designation *and*

3. No identifiable alternative etiology for IP *and*

4. Any *one* of the following autoantibodies or *at least two* of the [following] histopathology features:

Autoantibodies	Histopathology features
a. High-titer ANA (> 1:320) or RF (> 60 IU/mL)	(a) Lymphoid aggregates with germinal centers
b. Nucleolar ANA	
c. Anti-CCP	
d. Anti-Scl-70	(b) Extensive pleuritis
e. Anti-Ro	
f. Anti-La	
g. Anti-dsDNA	(c) Prominent plasmacytic infiltration
h. Anti-Sm	
i. Anti-RNP	
j. Anti-tRNA synthetase (e.g., Jo-1, PL-7, [and] PL-12)	(d) Dense perivascular collagen
k. Anti-PM-Scl	
l. Anticentromere	

Reproduced, with permission, from Fischer et al.[4] and adapted for use in the Brazilian Journal of Pulmonology. NSIP: nonspecific interstitial pneumonia; UIP: usual interstitial pneumonia; LIP: lymphocytic interstitial pneumonia; OP: organizing pneumonia; DAD: diffuse alveolar damage; DIP: desquamative interstitial pneumonia; CTD: connective tissue disease; IP: interstitial pneumonia; ANA: antinuclear antibody; CCP: cyclic citrullinated peptide; Scl: scleroderma; RF: rheumatoid factor; Sm: Smith; RNP: ribonucleoprotein; and PM: polymyositis.

lesions, such as "mechanic's hands" (hyperkeratosis of the hands or fingers), Gottron's papules, and heliotrope rash; Raynaud's phenomenon; sicca syndrome (dry mouth, dry eyes, or a positive Schirmer's test result); and refractory gastrointestinal symptoms, such as heartburn, acid regurgitation, and dysphagia.

We collected initial and last-registered FVC and FEV_1 values. We used standard spirometry techniques, and the predicted spirometric values were derived from the data reported for the Brazilian population.[15] The chest HRCT scan patterns were retrieved from radiology reports made by radiologists experienced in evaluating ILD and were based on international consensus criteria.[16-18] To standardize the HRCT criteria for esophageal dilatation on HRCT images, two experienced pulmonologists blindly evaluated HRCT scans for the presence of esophageal dilatation, occurring below the aortic arch with a large (> 10-mm) collection of intraluminal air in the coronal plane on four or more consecutive axial images.[19] The esophagus was also considered dilated when it was filled with fluid or showed an air-fluid level.[20] The autoantibody panel consisted of the following tests: ANA (titer and pattern), rheumatoid factor (RF), anti-cyclic citrullinated peptide (anti-CCP), anti-Ro, anti-La, anti-ribonucleoprotein (anti-RNP), anti-topoisomerase 1 (anti-Scl-70), anticentromere, anti-Jo-1, anti-DNA, and anti-Smith (anti-Sm). Histological patterns were also retrieved from anatomopathological reports made by experienced lung pathologists and based on international consensus statements.[16,17]

Statistical analysis

Descriptive statistics were obtained with the statistical software STATA, version 12.1 (StataCorp LP, College Station, TX, USA). Categorical variables are expressed as proportions, and continuous variables are expressed as median (interquartile range [IQR]) or mean ± standard deviation. Statistical measurements were performed with the Student's t-test, or Wilcoxon rank sum (Mann-Whitney U) test, for continuous variables, and with Fisher's exact test for categorical variables. To evaluate the associations between two continuous variables, we used multiple linear regression, adjusting for covariates according to model-building strategies. Multiple test correction (Bonferroni correction) was performed for

parametric tests. We managed missing data (all missing completely at random) using complete case analysis. The level of statistical significance was set at $p < 0.05$.

Results

Of the 75 patients selected, 23 were excluded from the analysis because the spirometric data were incomplete. Therefore, there were 52 patients who met the LD-CTD criteria at baseline (Table 1). Approximately half (28 patients) had a history of smoking, and 21 reported relevant environmental exposure, mainly to mold (13 patients), which was, however, not consistent enough to yield a diagnosis of hypersensitivity pneumonitis. By the end of follow-up—after a median of 61 months (IQR, 48.5-78.0 months)—only 8 patients met the criteria for a definitive diagnosis of a CTD (definite-CTD group): antisynthetase syndrome (n = 3); systemic sclerosis (n = 2); Sjögren's syndrome (n = 2); and rheumatoid arthritis (n = 1). Compared with those who did not meet the criteria for another definitive diagnosis (i.e., the LD-CTD patients), the patients in the definite-CTD group had longer follow-up periods and worse PFT results at the initial evaluation, although the differences were of only marginal statistical significance (Tables 1 and 2). Among the definite-CTD group patients, the histology samples showed only unclassifiable patterns. However, four of those patients underwent transbronchial biopsy. The definite-CTD and LD-CTD groups did not differ statistically in terms of any other characteristics, whether related to the autoantibody profiles or to the extrathoracic features of CTD.

In the LD-CTD group (n = 44), there was a predominance of females and the median follow-up period was 30 months (IQR, 16-68 months), as shown in Table 1. The shortest follow-up period was 6 months and the longest was 120 months. As can also be seen in Table 1, the most prevalent extrathoracic features were arthralgia and symptoms of gastroesophageal reflux disease (GERD), both in approximately two-thirds of the group, followed by Raynaud's phenomenon, in 14 patients (32%); cutaneous lesions, in 13 patients (30%); and proximal muscle weakness, in 11 patients (25%).

We found that, in the LD-CTD group, the most prevalent autoantibody was ANA, which was identified in 39 patients, with a median titer of 1:320 (IQR, 1:160-1:640), followed by anti-Ro, in 12 patients, and RF, in 10 (Table 1). However, we did not classify these patients as having LD-CTD solely on the basis of ANA positivity. A diagnosis of LD-CTD can be made on the basis of a high titer for any autoantibody. Therefore, some patients were included in the LD-CTD group because they had a high titer for a specific autoantibody despite showing a low ANA titer. A high ANA titer ($\geq$ 1:320) was identified in 22 of the 39 ANA-positive patients, and the remaining 17 ANA-positive patients were included in the LD-CTD group on the basis of high titers for anti-Ro (5 patients), RF (4 patients), anti-Sm (3 patients), anti-Jo-1 (2 patients), anti-La (2 patients), or anti-DNA (1 patient).

Nailfold capillaroscopy was initially performed in 22 patients, two of whom later received a definitive diagnosis of a CTD. Both had a scleroderma pattern of capillary changes and eventually met the criteria for systemic sclerosis. In the LD-CTD group, capillaroscopic abnormalities were identified in 15 patients, a scleroderma pattern being seen in 11 (Table 1).

At diagnosis, the PFT results for the LD-CTD group patients showed mild restriction, as evidenced by low mean FVC—as a percentage of the predicted value (FVC%, 69.5% ± 21.0%) or as an absolute value (2.18 ± 0.76 L)—with no obstructive pattern (Table 2). After a median follow-up period of 30 months (IQR, 15-57 months), there were no clinically or statistically significant changes in the mean FVC (74% ± 22%; 2.19 ± 0.77 L). As can be seen in Figure 1, multiple linear regression analysis comparing the initial and final FVC% revealed that, even after adjustments for age, gender, treatment, interval between measures, and ANA titer, the initial values were the main predictors of final values ($r2 = 0.75$; $p < 0.001$). Subjects who met the criteria for a definitive diagnosis of CTD tended to have worse physiology at initial evaluation, although the difference was of only marginal statistical significance (Table 2).

First-evaluation HRCT scans of the chest were available for 42 patients. As depicted in Figure 2, the predominant patterns were ground-glass opacities (in 90%), reticulation (in 90%), and traction bronchiectasis (in 78%). Twenty-two patients showed diffuse esophageal dilatation. Peribronchovascular distribution was reported in 11 patients, even among those with deemed-definite

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Table 1 - Baseline characteristics and relevant test results for 52 patients selected from among 1,998 patients with interstitial lung disease seen over a 16-year period.

Variable	Total	LD-CTD	Definite-CTD	p-value
	(n = 52)	(n = 44)	(n = 8)	
Age (years), mean ± SD	56 ± 12	57 ± 12.5	51.5 ± 8.4	NS
Female, n (%)	33 (63)	27 (61)	6 (75)	NS
Follow-up (months), median (IQR)	48 (19-69.5)	30 (16-68)	61 (48.5-78)	0.052
Smoking history, n (%)	28 (53)	25 (56)	3 (37)	NS
Extrathoracic features				
Arthralgia	34 (65%)	29 (66%)	5 (62%)	NS
GERD symptoms	33 (63%)	30 (68%)	3 (37%)	NS
Raynaud's phenomenon	17 (32%)	14 (32%)	3 (37%)	NS
Skin lesions	16 (30%)	13 (30%)	3 (37%)	NS
Sicca symptoms	12 (23%)	8 (18%)	4 (50%)	0.07
Muscle weakness	13 (25%)	11 (25%)	2 (25%)	NS
Morning stiffness	6 (11%)	5 (11%)	1 (12.5%)	NS
Autoantibody positivity/titer				
ANA, n (%)	44 (84)	39 (89)	5 (62)	0.09
Titer, median (IQR)	1:320 (1:160-1:640)	1:320 (1:160-1:640)	1:320 (1:160-1:320)	NS
High titer (≥ 1:320), n (%)	25 (58)	22 (57)	3 (60)	NS
RF, n (%)	12 (23)	10 (23)	2 (25)	NS
Titer, mean ± SD		1:327 ± 224.5	1:293 ±151	NS
Anti-Ro, n (%)	15 (29)	12 (27)	3 (37)	NS
Anti-La, n (%)	6 (11)	5 (11)	1 (12.5)	NS
Anti-RNP, n (%)	5 (9)	4 (9)	1 (12.5)	NS
Anti-Jo-1, n (%)	6 (11)	4 (9)	2 (25)	NS
Anti-Sm, n (%)	5 (9)	4 (9)	1 (12.5)	NS
Anti-DNA, n (%)	2 (4)	2 (5)	-	NS
Anti-Scl-70, n (%)	1 (2)	1 (3)	-	NS
Anti-CCP, n (%)	2 (4)	1 (3)	1 (12.5)	0.07
Abnormal capillaroscopy, n (%)	17 (32)	15 (34)	2 (25)	NS
Scleroderma pattern, n (%)	13 (25)	11 (25)	2 (25)	NS
HRCT scan pattern	(n = 50)	(n = 42)	(n = 8)	
NSIP, n (%)	22 (44)	19 (45)	3 (37)	NS
UIP, n (%)	6 (12)	4 (9)	2 (25)	NS
Unclassifiable, n (%)	18 (36)	16 (38)	2 (25)	NS
Other, n (%)	4 (8)	3 (7)	1 (12.5)	NS
Esophageal involvement, n (%)	26 (52)	22 (52)	4 (50)	NS
HRCT scan evolution	(n = 40)	(n = 33)	(n = 7)	
Stable, n (%)	22 (55)	19 (57)	3 (42)	NS
Improvement, n (%)	7 (17)	4 (12)	3 (42)	NS
Worsening, n (%)	11 (28)	10 (30)	1 (15)	NS
Histology pattern	(n = 31)	(n = 26)	(n = 5)	
NSIP, n (%)	7 (22)	7 (27)	-	NS
UIP, n (%)	4 (13)	4 (15)	-	NS
Other, n (%)	5 (16)	5 (19)	-	NS
Unclassifiable, n (%)	15 (48)	10 (38)	5 (100)	0.01
Treatment	(n = 52)	(n = 44)	(n = 8)	
None, n (%)	8 (15)	7 (16)	1 (12.5)	NS
Prednisone, n (%)	44 (84)	37 (84)	7 (87)	NS
Prednisone and azathioprine, n (%)	34 (65)	29 (66)	5 (62)	NS

LD-CTD: (patients classified as having) lung-dominant connective tissue disease; Definite-CTD: (patients meeting the criteria for) a definitive diagnosis of a CTD; NS: not significant; IQR: interquartile range; GERD: gastroesophageal reflux disease; ANA: antinuclear antibody; RF: rheumatoid factor; RNP: ribonucleoprotein; Sm: Smith; Scl: scleroderma; CCP: cyclic citrullinated peptide; NSIP: nonspecific interstitial pneumonia; and UIP: usual interstitial pneumonia.

Table 2 - Pulmonary function test results at the initial and final evaluations of 52 patients with interstitial lung disease.

Parameter	Total (n = 52)	LD-CTD (n = 44)	Definite-CTD (n = 8)	p-value
Initial evaluation				
FVC (L), mean ± SD	2.10 ± 0.77	2.18 ± 0.76	1.66 ± 0.75	0.09
FVC (% of predicted), mean ± SD	67.5 ± 21.9	69.5 ± 21.5	56.6 ± 22.8	0.08
FEV_1 (L), mean ± SD	1.79 ± 0.64	1.86 ± 0.63	1.38 ± 0.63	0.08
FEV_1 (% of predicted), mean ± SD	71.9 ± 23.0	74.0 ± 22.3	58.0 ± 24.4	0.08
Final evaluation				
FVC (L), mean ± SD	2.14 ± 0.77	2.19 ± 0.77	1.88 ± 0.68	0.24
FVC (% of predicted), mean ± SD	71.8 ± 22.3	74.0 ± 22.0	61.2 ± 22.2	0.14
FEV_1 (L), mean ± SD	1.74 ± 0.56	1.78 ± 0.56	1.49 ± 0.57	0.28
FEV_1 (% of predicted), mean ± SD	72.9 ± 22.0	75.3 ± 21.9	60.0 ± 24.4	0.07

LD-CTD: (patients classified as having) lung-dominant connective tissue disease; and Definite-CTD: (patients meeting the criteria for) a definitive diagnosis of a CTD.

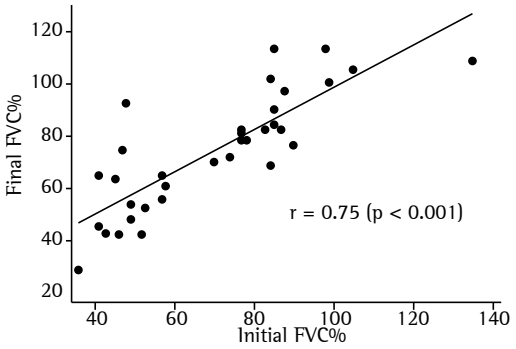

Figure 1 - Multiple linear regression analysis between initial and final FVC as a percentage of the predicted value (FVC%) in patients with lung-dominant connective tissue disease (n = 32), showing a strong correlation between initial and final values after adjustment for covariates (time between measures, age, gender, treatment, and antinuclear antibody titer).

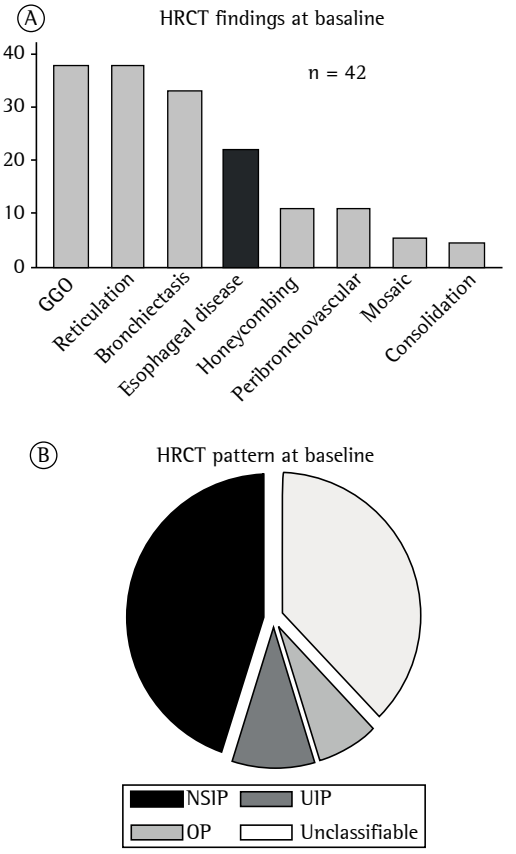

Figure 2 - First-evaluation chest HRCT scan findings in patients with lung-dominant connective tissue disease. (A) Bar chart of the total count of HRCT findings in 42 patients. Although ground-glass opacity (GGO), reticulation, and traction bronchiectasis predominated, roughly half of the scans met the published criteria for esophageal disease.[20] (B) Pie chart of the patterns assigned by an experienced radiologist. NSIP: nonspecific interstitial pneumonia; UIP: usual interstitial pneumonia; and OP: organizing pneumonia.

classical HRCT patterns. The HRCT pattern was classifiable in 26 patients, NSIP and UIP patterns being noted in 19 and 4 patients, respectively. Most importantly, 36% of the initial HRCT scans were considered unclassifiable after evaluation by an experienced thoracic radiologist. Follow-up HRCT scans were available for only 33 patients, and the findings remained unchanged in 57%.

Histological data were available for 26 of the LD-CTD group patients. There were 18 surgical samples and 8 transbronchial samples, evaluation of the latter being conclusive in only one patient with organizing pneumonia. An unclassifiable pattern, mainly transbronchial, was seen in 38% of the samples. The predominant pattern in the surgical samples was NSIP (in 27%), followed by UIP (in 15%) and organizing pneumonia (in

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16%). Immunosuppressant therapy had been started in 44 of the LD-CTD group patients, and all of them received prednisone. The treatment regimen comprised the azathioprine/prednisone combination in 66% of the cases.

Discussion

We have reported the findings of a retrospective evaluation of a group of LD-CTD patients characterized by a predominance of young female patients who complained mainly of arthralgia and GERD symptoms, showed mild restriction on PFTs, were physiologically stable on follow-up, and predominantly had an NSIP pattern (tomographically and histologically). The most relevant autoantibodies in our sample were ANA, anti-Ro, and RF. A scleroderma pattern of capillary changes was observed in 75% of the patients who underwent nailfold capillaroscopy, and diffuse esophageal dilatation was seen on half of the HRCT scans of the chest. Both findings support the relevance of the "rheumatological flavor" in such cases. From a large population of patients diagnosed with ILD, only approximately 2.6% initially met the criteria for an LD-CTD etiology. To date, there has been no estimate of the prevalence of LD-CTD in such a population. It is of note that, after a reasonable follow-up period, 15% of those patients prospectively met the criteria for a definitive diagnosis of a CTD.

There is growing recognition that ILD might be the first or an isolated manifestation of a CTD.[21] In 1995, Homma et al.,[22] having followed, for up to 11 years, 68 patients in whom the initial evaluation showed no clinical or serological evidence of CTD,[1] showed that it is possible for ILD to be the sole presentation of occult CTD. Homma et al.[22] showed that the incidence of definite CTD during long-term follow-up was 19%, similar to the rate observed in the present study, and also found no difference between patients who have definite CTD and LD-CTD patients from a clinical or serological standpoint. The authors concluded that there are no clinical markers that are useful in predicting which patients will develop a definite CTD.

Since Homma et al.[22] first suggested that ILD could be the pulmonary manifestation of an undefined systemic autoimmune disease, the body of literature on the subject has grown considerably. Kinder et al.[5] sought to determine whether idiopathic NSIP is actually the pulmonary manifestation of a systemic autoimmune disease and, consequently, the respiratory counterpart of what rheumatologists know as undifferentiated CTD (UCTD).[23] By applying a broader set of UCTD criteria, the authors compared UCTD patients with IIP patients (specifically IPF patients) and concluded that such criteria could be used in predicting NSIP.[5] These preliminary results were followed by those from several retrospective cohort studies employing different diagnostic criteria and terminology to refer to ILD patients with equivocal CTD features. Corte et al.[7] called into question the specificity of UCTD criteria in predicting NSIP and suggested that only specific features such as Raynaud's phenomenon and a compatible demographic profile (female < 50 years of age) could predict an NSIP pattern in such patients. Therefore, the authors of some studies have applied inclusion criteria that are more stringent. One such study was conducted by Vij et al.,[6] who thus defined an entity referred to as autoimmune-featured ILD. The authors described a UIP-predominant group of patients, in which UIP was identified on the basis of CT scans in 62% and histology in 81%, with characteristics similar to those of patients with IPF (older and male) and, as in the present study, relevant prevalence of GERD symptoms. However, their findings contrast with ours regarding ILD pattern prevalence, because we recognize the relevance of the unclassifiable pattern to this population. Patients with unclassifiable IIP have only recently come to be considered a possible distinct subgroup of ILD patients. When a patient cannot be satisfactorily classified, a diagnosis of unclassifiable IIP is suggested, which is an acknowledgment that a final diagnosis might not be achieved after a multidisciplinary discussion.[17,24] Another retrospective study predicted a 10% prevalence of unclassifiable cases in a large ILD cohort that was characteristically heterogeneous in terms of several clinical variables.[24] It is noteworthy that 70% of our final pathological unclassifiable patterns were observed in transbronchial biopsy samples, which is in accordance with the findings of Ryerson et al.,[24] who reported that 69% of the unclassifiable cases identified in their study were attributable to biopsy samples being either insufficient or unavailable. Our results embody recognition of the updated (2013) American Thoracic Society/European Respiratory Society joint statement on multidisciplinary classification

of ILD, which states that unclassifiable interstitial pneumonia often proves to be related to CTD, especially when there is an overlap of histological patterns within the same sample.[17] Even though transbronchial biopsy plays an unequivocal role in the histological classification of ILD, the limitations of transbronchial biopsy samples should be acknowledged.[25]

When we excluded the patients who had definite CTD, we found a strong correlation between initial and final FVC%, suggesting that the main contributor to the final value is the initial measurement itself (Figure 1). After adjusting for several covariates, we found that PFTs remained stable throughout follow-up. Despite the inconclusive role played by histological patterns and the possibility of multiple patterns in LD-CTD patients, the stability of lung function indicates that the disease was milder in our sample than in historical samples of patients with IPF.[11] Such stability was also noted on HRCT scans of the chest: at the last evaluation, 55% of available scans showed stable interstitial abnormalities. In contrast with our finding of stable PFT results, Kinder et al.[26] reported significantly greater improvement in FVC% during follow-up in patients with UCTD than in those with IPF. However, the authors defined improvement at a low cutoff (an absolute increase ≥ 5%), lung function remained stable in a third of their sample, and the diagnostic criteria employed in their study differed from those applied in our study.

Nailfold capillaroscopy is an easily implemented, noninvasive methodology for evaluating the microvascular abnormalities commonly found in several types of CTDs, especially systemic sclerosis, polymyositis/dermatomyositis, and mixed CTD.[27] In our sample, 22 patients were submitted to nailfold capillaroscopy, of whom 17 were found to have at least one significant microvascular abnormality, substantiating the suspicion of CTD. The sensitivity and specificity of nailfold capillaroscopy have yet to be evaluated. However, in the recent American College of Rheumatology/New European League Against Rheumatism revised classification criteria for systemic sclerosis, capillaroscopy is given only minor weight in a probability score—notably, the same weight given to interstitial lung abnormalities.[28] Therefore, microvascular alterations are still under scrutiny as predictors of definite CTD.[27] We strongly recommend that, in association with close physical examination of the hands, nailfold capillaroscopy be included in the armamentarium for the initial evaluation of ILD patients, mainly in those under high suspicion of having CTD, with specific autoantibody positivity, and presenting with overt lesions of the skin or joints of the hands. Another easily identifiable characteristic suggestive of associated systemic autoimmunity is esophageal dilatation on HRCT scans, recognizable by a large collection of intraluminal air that is fluid-filled or has an air-fluid level.[20] In the present study, we observed a 50% prevalence of esophageal impairment, including hiatal hernia and esophageal dilatation, corroborating our high frequency of GERD symptoms and suggesting that it is important to screen for esophageal dysmotility when a CTD etiology is suspected.

Our study has certain limitations, in particular the retrospective design, which accounted for a considerable amount of missing data—an obstacle that we overcame by performing a complete case-analysis. In addition, the evaluation time points varied widely among patients, reducing the external validity of our results and possibly contributing to an overestimation of physiological stability and an underestimation of the odds of developing a definite CTD. Follow-up was longer in the definite-CTD group patients than in the LD-CTD group patients, and the difference was statistically significant, albeit only marginally so ($p = 0.052$). Furthermore, in the majority of patients in our sample, diffusion of carbon dioxide was not measured. However, it can be argued that, despite the ongoing debate on the appropriateness of FVC as a surrogate marker for disease evolution, it is a physiological measure that is frequently used as such.[26,29] Although evidence of esophageal impairment was common in our sample, that should be interpreted with caution, because our findings (which were based on imaging and symptoms) were only suggestive of esophageal involvement (specific tests to identify unequivocal esophageal disease were not conducted). Nevertheless, this retrospective study was the first of its kind to include patients from Brazil, where economic status might play a role in delaying diagnosis and healthcare access. Moreover, we used a more stringent criterion as a starting point for cohort definition,[4] allowing many different classical ILD patterns to be included in the study. To our knowledge, ours is the first study assessing the

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importance of evaluating nailfold capillaries for the diagnosis of LD-CTD.

In summary, a fair number of patients with ILD might present with one or more features of a CTD without meeting the established diagnostic criteria for such. Among such patients, lung disease seems to be characteristically mild, functional stability being the main feature. Attention to the standard extrathoracic features of CTD should be accompanied by attention to less straightforward GERD symptoms, diffuse esophageal dilatation on HRCT scans, and specific capillaroscopy findings. Although much, if not all, of the current evidence related to LD-CTD relies on retrospective designs, the importance of prospective studies involving LD-CTD patients cannot be overstated. In addition, the relevance of subgrouping patients with ILD into idiopathic, definite-CTD, and LD-CTD groups should be evaluated more comprehensively, specifically regarding prognosis and treatment response. Otherwise, this classification will lack translational use in real-life situations.

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Diffuse aspiration bronchiolitis: analysis of 20 consecutive patients*

Bronquiolite aspirativa difusa: análise de 20 pacientes consecutivos

Xiaowen Hu, Eunhee Suh Yi, Jay Hoon Ryu

Abstract

Objective: Aspiration can cause a variety of pulmonary syndromes, some of which are not well recognized. The objective of this study was to assess the demographic, clinical, radiological, and histopathological correlates of diffuse aspiration bronchiolitis (DAB), a bronchiolocentric disorder caused by recurrent aspiration. **Methods:** This was a retrospective study of 20 consecutive patients with DAB seen at the Mayo Clinic in Rochester, Minnesota, between January 1, 1998 and June 30, 2014. **Results:** The median age of the patients was 56.5 years (range, 22-76 years), and the male/female ratio was 2.3:1.0. In 18 patients, the diagnosis of DAB was based on the results of a lung biopsy; in the 2 remaining patients, it was based on clinical and radiological features, together with documented aspiration observed in a videofluoroscopic swallow study. In 19 patients (95%), we identified predisposing factors for aspiration, including gastroesophageal reflux disease (GERD), drug abuse, and dysphagia. Common presenting features included cough, sputum production, dyspnea, and fever. Twelve patients (60%) had a history of recurrent pneumonia. In all of the patients, chest CT revealed bilateral pulmonary infiltrates consisting of micronodules and tree-in-bud opacities. In the majority of patients, interventions aimed at preventing recurrent aspiration (e.g., anti-GERD therapies) led to improvement in the symptoms of DAB. **Conclusions:** Young to middle-aged subjects with recognizable predisposing factors for aspiration and who report a history of recurrent pneumonia are at increased risk for DAB. Although DAB is not well recognized, certain chest CT features are characteristic of the disorder.

Keywords: Pneumonia, aspiration; Bronchiolitis; Gastroesophageal reflux; Lung diseases, interstitial.

Resumo

Objetivo: A aspiração pode causar diferentes síndromes pulmonares, algumas das quais não são bem reconhecidas. O objetivo deste estudo foi avaliar as correlações demográficas, clínicas, radiológicas e histopatológicas da bronquiolite aspirativa difusa (BAD), um distúrbio bronquiolocêntrico causado por aspiração recorrente. **Métodos:** Estudo retrospectivo de 20 pacientes consecutivos com BAD atendidos na Clínica Mayo, em Rochester, Minnesota, entre 1 de janeiro de 1998 e 30 de junho de 2014. **Resultados:** A mediana de idade dos pacientes foi de 56,5 anos (variação, 22-76 anos), e a relação homem/mulher foi de 2,3:1,0. Em 18 pacientes, o diagnóstico de BAD foi baseado nos resultados de biópsia do pulmão; nos 2 casos restantes, ele foi baseado em características clínicas e radiológicas, em conjunto com aspiração documentada observada em um estudo de deglutição videofluoroscópico. Em 19 pacientes (95%), foram identificados fatores predisponentes para a aspiração, incluindo doença do refluxo gastroesofágico (DRGE), abuso de drogas e disfagia. Características de apresentação comuns incluíam tosse, produção de escarro, dispneia e febre. Doze pacientes (60%) tinham uma história de pneumonias de repetição. Em todos os pacientes, a TC de tórax revelou infiltrado pulmonar bilateral com micronódulos e opacidades do tipo árvore em brotamento. Na maioria dos pacientes, as intervenções destinadas a impedir a aspiração recorrente (por exemplo, terapias anti-DRGE) levaram a uma melhoria nos sintomas de BAD. **Conclusões:** Indivíduos jovens até os de meia-idade com fatores predisponentes reconhecíveis para aspiração e que relatam uma história de pneumonias de repetição apresentam um risco aumentado para BAD. Embora BAD não seja bem reconhecida, certos aspectos na TC de tórax são característicos da doença.

Descritores: Pneumonia aspirativa; Bronquiolite; Refluxo gastroesofágico; Doenças pulmonares intersticiais.

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Introduction

Bronchiolitis, characterized by inflammation and fibrosis of the small airways, is associated with a variety of causes.[1] In 1996, Matsue et al.[2] described "diffuse aspiration bronchiolitis" (DAB) as a disorder characterized by chronic inflammation of the bronchioles due to recurrent aspiration. In that study, the diagnosis was made at autopsy in a cohort of mostly elderly bedridden subjects with neurological disorders and at obvious risk for aspiration. More recently, Barnes et al.[3] reported the cases of four relatively young, healthy patients (41-59 years of age) with persistent bilateral pulmonary infiltrates, who were diagnosed with diffuse bronchiolar disease due to recurrent occult aspiration, the diagnosis being based on the evaluation of surgical lung biopsy specimens. Because of its atypical clinical and radiological presentation, DAB is not well recognized in clinical practice and often goes undiagnosed. The objective of the current study was to analyze patients with DAB treated at a tertiary referral center, in order to provide a more detailed description of the demographic, clinical, and radiological features, as well as the clinical course, of the disorder.

Methods

Study subjects

Using a computer-assisted search of medical records, we identified 20 patients who were diagnosed with DAB at the Mayo Clinic in Rochester, Minnesota, between January 1, 1998 and June 30, 2014 (a period of more than 16 years). The current study was approved by the Mayo Clinic Institutional Review Board.

Clinical data

Medical records were reviewed in detail, and data related to the following aspects were retrieved: age, gender, clinical presentation, comorbidities, predisposing factors for aspiration, radiological findings, histopathological features, diagnosis, treatment, and follow-up. The diagnosis of DAB was made by excluding other potential causes of pulmonary infiltrates and by applying the following diagnostic criteria[2]: respiratory symptoms (cough or dyspnea); features characteristic of bronchiolitis (i.e., micronodules and tree-in-bud opacities) seen on chest CT scans; and histopathological (lung biopsy) evidence of foreign material or foreign-body giant cell reaction, associated with chronic, bronchiolocentric inflammation, or aspiration definitively demonstrated in a videofluoroscopic swallow study. Patients who were diagnosed with exogenous lipoid pneumonia were excluded. The predisposing factors and the diagnosis of aspiration-related pulmonary disease were assigned by consensus based on a review of all available medical records.

Statistical analyses

Continuous variables are presented as median and range (minimum, maximum), when appropriate, whereas categorical variables are presented as frequency and percentage.

Results

A total of 20 patients with DAB were identified; 14 (70%) were male (Table 1). The median age at diagnosis was 56.5 years (range, 22-76 years). The review of the medical records identified one or more predisposing factors for aspiration in 19 patients (95%), including gastroesophageal reflux disease (GERD) in seven (35%); a history of drug abuse in six (30%); dysphagia in five (25%); and GERD plus a history of drug abuse in one (5%). Six of the seven patients with a history of drug abuse had chronic opioid dependency. The median age was 45 years (range, 27-56 years) among the seven patients with GERD and 56.5 years (range, 22-76 years) among the six patients with a history of drug abuse, compared with 64 years (range, 57-69 years) in the five patients with dysphagia (p = 0.14). Four of the eight

Table 1 - Demographic and clinical characteristics of patients with diffuse aspiration bronchiolitis.

Characteristic	N = 20
Gender, n (%)	
Male	14 (70)
Female	6 (30)
Age (years), median (range)	56.5 (22-76)
BMI* (kg/m^2), median (range)	27.4 (17.3-51.8)
Main presentations, n (%)	
Cough	19 (95)
Sputum	16 (80)
Fever	16 (80)
Dyspnea	15 (75)
Hemoptysis	4 (20)
Recurrent pneumonia	12 (60)

BMI: body mass index. *Data missing for one patient.

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patients with GERD (including one of the patients with a history of chronic drug abuse) presented with active symptoms of GERD (i.e., heartburn and regurgitation). The four remaining patients with GERD were diagnosed with esophagitis by esophagogastroduodenoscopy. In one of those patients, there was spontaneous gastroesophageal reflux of barium into the cervical esophagus during an esophagram. Three of those four patients also underwent an esophageal motility study, and the lower esophageal sphincter pressure was found to be below normal in all three. Other comorbidities at the time of DAB diagnosis included malignancy, in three patients (esophageal cancer, thymoma, and chronic lymphocytic leukemia, respectively); depression, in two; chronic rhinosinusitis, in two; asthma, in two; chronic obstructive pulmonary disease, in one; obstructive sleep apnea, in one; cystic fibrosis, in one; and coronary artery disease, in one.

The most common presenting symptoms were cough (seen in 95% of the patients), sputum production (seen in 80%), fever (seen in 80%), and dyspnea (seen in 75%). One patient did not have active symptoms but was referred for evaluation of recurrent pneumonia. Twelve patients (60%) had a history of recurrent pneumonia. Among those 20 patients evaluated, choking episodes were reported by five (25%), although aspiration was suspected to be the cause of the lung disease in only three (15%). Overall, aspiration was unsuspected in 15 (75%) of the patients prior to the eventual diagnosis of DAB.

In our study sample, the median body mass index (BMI) was 27.4 kg/m^2 (range, 17.3-51.8 kg/m^2); six patients (30%) were obese (BMI $\geq$ 30 kg/m^2). Sixteen patients (80%) had a history of smoking. On examination, crackles were noted on lung auscultation in 14 patients (70%) and wheezing was heard in 2 (10%); digital clubbing was not observed. Pulmonary function test results were available for 11 patients, indicating an obstructive pattern in six (55%), a nonspecific pattern in one (9%), and normal function in the remaining four (36%). The DLCO was below normal in six of the 10 patients in whom it was measured. Arterial blood gas results were available for eight patients, one of whom was hypoxemic (PaO_2 < 60 mmHg).

All of the patients underwent chest imaging studies, 17 undergoing chest X-ray plus CT of the chest and three undergoing chest CT only. Among the 17 patients for whom chest X-rays were available, bilateral involvement was observed in 15; the pattern was predominantly interstitial with patchy or diffuse distribution but was more micronodular in three patients. On the CT scans of the chest, bilateral distribution of parenchymal abnormalities was seen in 19 patients (95%) and posterior-dominant distribution of infiltrates was seen in only three (15%). One patient with unilateral lung involvement reported always sleeping on the ipsilateral side. Micronodules and tree-in-bud opacities consistent with bronchiolitis were seen on CT scans of the chest in all 20 patients (Figure 1); bronchiectasis was seen in seven patients (35%).

Among the 20 patients evaluated, the diagnosis of DAB was based on examination of the surgical lung biopsy specimen in 13 (65%); on examination of the transbronchial lung biopsy specimen in five (25%); and on the CT findings, together with gross aspiration demonstrated in a videofluoroscopic swallow study, in two (10%). Of the 13 patients diagnosed on the basis of the results of the examination of the surgical lung biopsy specimen (Figure 2), nine had previously undergone transbronchial lung biopsy that proved to be nondiagnostic. In eight of those nine, the biopsy specimens had been submitted to microbial culture; positive cultures were obtained in five patients—four testing positive for *Candida* spp., one testing positive for *Pseudomonas aeruginosa*, and one testing positive for *Staphylococcus aureus*. The five patients in whom the diagnosis of DAB was based on examination of the transbronchial lung biopsy specimen were among a total of 16 patients who had undergone transbronchial lung biopsy.

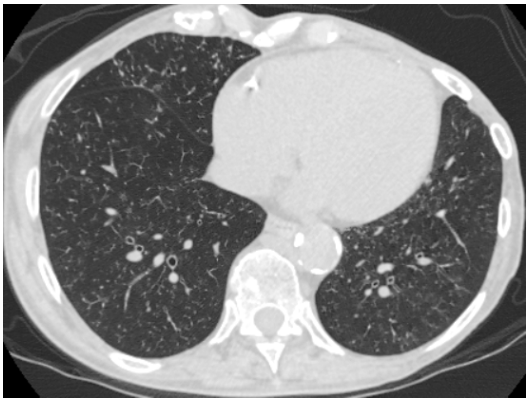

Figure 1 - HRCT scan of the chest, showing diffuse micronodules and tree-in-bud opacities.

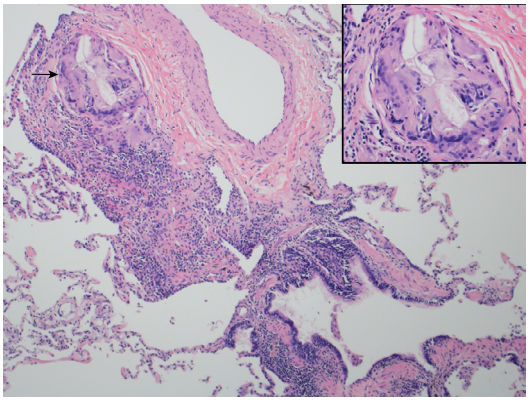

Figure 2 - Photomicrograph of bronchiolar wall thickening (H&E staining; original magnification, ×100), showing chronic inflammation and a giant cell containing vegetable matter (arrow; inset magnification, ×400).

Two remaining patients (10%) were diagnosed based on characteristic CT features and gross aspiration demonstrated on video swallow study. In 15 patients (75%), aspiration was not suspected prior to the establishment of histopathological evidence of DAB in transbronchial or surgical lung biopsy specimens (Figure 2).

Seventeen patients were under pharmacological treatment for GERD, which included proton-pump inhibitors in 12, histamine type 2 receptor blockers in two, and a combination of the two therapies, together with lifestyle changes, in three. Of those 17 patients, 14 had been under pharmacological treatment for GERD before being diagnosed with DAB. In addition, empirical treatment included the use of prednisone in eight patients and bronchodilators in nine. There was no clear evidence that those medications provided any clinical benefit. Abstinence from drug abuse was achieved in six patients, leading to improvement in five.

Three patients underwent surgical interventions to prevent recurrent aspiration: Nissen fundoplication in two; and Roux-en-Y gastric bypass in one. None of those three patients subsequently experienced recurrence of the aspiration.

Of the 15 patients for whom follow-up information was available, 12 showed partial improvement or complete resolution of the symptoms and radiological abnormalities over a median follow-up period of 8 months (range, 1-74 months). Among the 20 patients evaluated, there were four deaths: two patients died of progressive cancer 5 and 8 months, respectively, after being diagnosed with DAB; one patient died of advanced cystic fibrosis; and one patient with opioid drug dependency died at home of unknown causes.

Discussion

Since 1996, when Matsuse et al.[2] proposed DAB as a new disease entity based on their autopsy study, there have been only a limited number of studies describing the clinical, radiological, and histopathological features associated with this disorder.[3-7] The present study involved the largest sample of patients with DAB evaluated to date.

Our results demonstrate that DAB is most commonly encountered in young to middle-aged subjects with identifiable predisposing factors and presenting with bilateral pulmonary infiltrates manifesting radiological features of bronchiolitis. It appears likely that many cases of DAB go undiagnosed, because the clinical and radiological features of DAB have not typically been associated with aspiration. Our data also show that GERD, a prevalent condition in the general population, was the most common predisposing factor for DAB, followed by drug abuse and dysphagia. Among our DAB patients, the median age was lower among those presenting with GERD or drug abuse than among those presenting with dysphagia. Dysphagia has been shown to be a common risk factor for aspiration-related pulmonary syndromes in prior studies, particularly among individuals with neurological disorders.[8,9] In their study of elderly patients with DAB, Matsuse et al.[2] found that half of those patients had oropharyngeal dysphagia. Similar to Barnes et al.,[3] we identified GERD in nearly 40% of our DAB patients, suggesting that the risk for chronic occult aspiration is not limited to the elderly.

The prevalence of GERD has been reported to be high in lung transplant recipients, and aspiration has been implicated as a contributor to the development of bronchiolitis obliterans syndrome in such patients.[10,11] One recent study reported a reduced rate of decline in lung function after laparoscopic fundoplication in lung transplant recipients with GERD.[12] In patients with idiopathic pulmonary fibrosis, GERD is highly prevalent and the use of acid-suppressive therapy has been associated with a

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longer survival, as well as with a slower rate of decline in pulmonary function.[13] Because GERD is quite common, additional exploration of occult aspiration-related pulmonary syndromes such as DAB seems warranted.

Drug abuse has been considered a common predisposing factor for aspiration pneumonitis.[14,15] Similarly to GERD, chronic drug abuse, which affects relatively young subjects, likely predisposes to aspiration, possibly resulting in DAB.[16] It is noteworthy that all of our patients with a history of drug abuse presented with chronic drug abuse, which has been associated with delayed gastric emptying.[17]

Cough, sputum production, dyspnea, and fever were the most common symptoms observed in our patients with DAB. A history of recurrent pneumonia was common in our patient sample (in 60% of patients) and could serve as a clue to the diagnosis of aspiration-related lung diseases. Recurrent pneumonia with persistent pulmonary symptoms that do not respond to antimicrobial therapy should alert clinicians to the possibility of recurrent aspiration.[2,7,18]

Although aspiration-related lung diseases are common, some forms are not well recognized.[19,20] Only 25% of our DAB patients were clinically suspected to have aspiration as the underlying cause of their lung disease. Bilateral lung involvement was noted on chest imaging studies for most of our patients with DAB. Although classic aspiration pneumonia has been associated with posterior-dominant distribution of infiltrates,[21] only 15% of our DAB patients exhibited that feature. That might be explained by the small volume and recurrent nature of aspiration, which occurs mainly during sleep. Frequent changes in position during the night might lead to the diffuse distribution of aspirated material. In our patients with DAB, the chest CT findings (micronodules and tree-in-bud opacities) were characteristic of bronchiolitis, reflecting chronic bronchiolocentric inflammation caused by recurrent aspiration. Recognition of these radiological features could also serve as an important clue to the diagnosis of DAB.[3]

Management of patients with DAB focuses on prevention of recurrent aspiration by addressing the underlying risk factors, such as GERD and drug abuse. Our data demonstrate that this strategy led to improvement for the majority of DAB patients. Although these patients are unlikely to benefit from antimicrobial or corticosteroid therapy, there are virtually no data on the issue. Prior to being diagnosed with DAB (by surgical lung biopsy), one of our patients was treated with a 12-week course of prednisone for suspected hypersensitivity pneumonitis, and that treatment provided no clinical or radiological improvement. Optimal management strategies for patients with DAB have yet to be fully defined.

The present study has certain limitations. The major limitation is the retrospective design, which limited the analysis to clinical data available in medical records. Given the aforementioned impediments to the diagnosis of this disorder, it is likely that there were other patients with DAB who went undiagnosed at our institution and were not included in the study sample.

We conclude that DAB is an under-recognized lung disease, that it is related to recurrent aspiration, and that it can be clinically occult. It is generally encountered in young to middle-aged adults with identifiable risk factors for aspiration, most commonly GERD. Radiological features consistent with bronchiolitis and a history of recurrent pneumonia are important clues to the diagnosis of DAB.

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Uncoupling protein-2 mRNA expression in mice subjected to intermittent hypoxia*

Expressão do mRNA da *uncoupling protein-2* em camundongos submetidos à hipóxia intermitente

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Abstract

Objective: To investigate the effect of intermittent hypoxia—a model of obstructive sleep apnea (OSA)—on pancreatic expression of uncoupling protein-2 (UCP2), as well as on glycemic and lipid profiles, in C57BL mice. **Methods:** For 8 h/day over a 35-day period, male C57BL mice were exposed to intermittent hypoxia (hypoxia group) or to a sham procedure (normoxia group). The intermittent hypoxia condition involved exposing mice to an atmosphere of 92% N and 8% CO_2 for 30 s, progressively reducing the fraction of inspired oxygen to 8 ± 1%, after which they were exposed to room air for 30 s and the cycle was repeated (480 cycles over the 8-h experimental period). Pancreases were dissected to isolate the islets. Real-time PCR was performed with TaqMan assays. **Results:** Expression of UCP2 mRNA in pancreatic islets was 20% higher in the normoxia group than in the hypoxia group ($p = 0.11$). Fasting serum insulin was higher in the hypoxia group than in the normoxia group ($p = 0.01$). The homeostasis model assessment of insulin resistance indicated that, in comparison with the control mice, the mice exposed to intermittent hypoxia showed 15% lower insulin resistance ($p = 0.09$) and 21% higher pancreatic β-cell function ($p = 0.01$). Immunohistochemical staining of the islets showed no significant differences between the two groups in terms of the area or intensity of α- and β-cell staining for insulin and glucagon. **Conclusions:** To our knowledge, this is the first report of the effect of intermittent hypoxia on UCP2 expression. Our findings suggest that UCP2 regulates insulin production in OSA. Further study of the role that UCP2 plays in the glycemic control of OSA patients is warranted.

Keywords: Blood glucose; Sleep apnea syndromes; Pancreas; Glucagon-secreting cells.

Resumo

Objetivo: Investigar o efeito da hipóxia intermitente com um modelo de apneia obstrutiva do sono (AOS) sobre a expressão de *uncoupling protein-2* (UCP2), assim como sobre perfis glicêmicos e lipídicos, em camundongos C57BL. **Métodos:** Camundongos C57BL machos foram expostos a hipóxia intermitente ou hipóxia simulada (grupo controle) 8 h/dia durante 35 dias. A condição de hipóxia intermitente envolveu a exposição dos camundongos a uma atmosfera de 92% de N e 8% de CO_2 por 30 s, com redução progressiva de fração de O_2 inspirado até 8 ± 1%, seguida por exposição a ar ambiente por 30 s e repetições do ciclo (480 ciclos no período experimental de 8 h). Os pâncreas foram dissecados para isolar as ilhotas. Foi realizada PCR em tempo real utilizando o método TaqMan. **Resultados:** A expressão do mRNA da UCP2 nas ilhotas pancreáticas foi 20% maior no grupo controle que no grupo hipóxia ($p = 0,11$). A insulina sérica de jejum foi maior no grupo hipóxia do que no grupo controle ($p = 0,01$). O modelo de avaliação da homeostase de resistência à insulina indicou que, em comparação com os camundongos controle, aqueles expostos à hipóxia intermitente apresentaram 15% menor resistência à insulina ($p = 0,09$) e 21% maior função das células beta ($p = 0,01$). A coloração das ilhotas pancreáticas por imuno-histoquímica não mostrou diferenças significativas entre os grupos em termos da área ou da intensidade das células alfa e beta, marcadas por insulina e glucagon. **Conclusões:** Segundo nosso conhecimento, esta é a primeira descrição do efeito da hipóxia intermitente sobre a expressão da UCP2. Nossos achados sugerem que UCP2 regula a produção de insulina na AOS. Futuras investigações sobre o papel da UCP2 no controle glicêmico em pacientes com AOS são justificadas.

Descritores: Glicemia; Síndromes da apneia do sono; Pâncreas; Células secretoras de glucagon.

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Introduction

Obstructive sleep apnea (OSA) is characterized by recurrent collapse of the pharynx during sleep. Each apneic event results in oxygen desaturation and, occasionally, arousal, causing intermittent hypoxia, oxidative stress, and sleep fragmentation.[1] Up to 32% of the adult population is affected by OSA.[2]

Various cardiovascular and metabolic outcomes have been attributed to OSA.[3] Metabolic syndrome shares several features with OSA, including obesity, hyperlipidemia, hypertension, and insulin resistance, which might be implicated in an increased risk of cardiovascular disease.[4-6] In patients with OSA, metabolic syndrome can be improved by treatment with continuous positive airway pressure,[7-9] indicating a causal relationship between the two conditions.

Experimental models that subject animals to intermittent hypoxia are used in order to study the consequences of OSA. Insulin resistance and metabolic changes have been reported after exposure to such models.[10,11] The mechanisms underlying the changes in glucose metabolism induced by intermittent hypoxia have yet to be fully explored.

Uncoupling protein-2 (UCP2) is a negative regulator of pancreatic β-cell insulin secretion.[12-14] The UCPs, located in the mitochondrial inner membrane, translocate protons from the intermembrane space to the mitochondrial matrix. The protons that leak through a UCP can no longer be used to drive the rotation of ATP synthase, such proton leakage thus decreasing the generation of ATP. By abating ATP synthesis, UCP2 regulates glucose-stimulated insulin secretion.[15] Free radicals generated during hypoxia-reoxygenation in sleep apnea may play a regulatory role in the pancreatic β-cells.[16] This is the rationale for investigating a possible apnea-UCP2 relationship.

Because of the epidemic proportions that diabetes and OSA are assuming, there is interest in understanding the interplay between these two conditions. In an extensive search of the literature, we found no reference to the molecular regulation of insulin secretion in OSA. We hypothesized that intermittent hypoxia would change the expression of UCP2. Therefore, we investigated the effect of intermittent hypoxia on pancreatic UCP2 expression in C57BL mice.

Methods

Animals and intermittent hypoxia

We evaluated 36 male C57BL mice, in two groups: exposed to intermittent hypoxia (hypoxia group, n = 18); and subjected to a control (sham) procedure (normoxia group, n = 18). All of the mice were 8-9 weeks of age at the start of the study. All procedures were conducted in accordance with the Guide for the Care and Use of Laboratory Animals,[17] and the study protocol was approved by the Research Ethics Committee of the Porto Alegre *Hospital de Clínicas*, in the city of Porto Alegre, Brazil (Protocol no. 09-300).

Groups of 6 mice were housed under temperature-controlled conditions (22.5-24.5°C), on a 12/12-h light/dark cycle (lights on at 7:00 a.m.), and provided with standard mouse chow and water *ad libitum*. Using a precision balance with a resolution of 0.01 g (AS 5500C; Marte Científica, São Paulo, Brazil), we weighed the mice at baseline and every 3 days thereafter, until the end of the experiment. The food pellets in each cage were weighed daily, in order to quantify food intake.

Over a period of 35 days, for 8 h a day during the lights-on period (from 9:00 a.m. to 5:00 p.m.), the mice were placed in the intermittent hypoxia system. In the intermittent hypoxia condition, a gas mixture consisting of 92% nitrogen and 8% CO_2 was released into the hypoxia chamber for 30 s, progressively reducing the fraction of inspired oxygen (FiO_2) from 21% to a nadir of 8 ± 1%. Next, a fan moved room air into the chamber for 30 s, restoring the FiO_2 to 21% within 5 s. Therefore, each hypoxia/normoxia cycle lasted for 60 s (60 cycles/h), for a total of 480 hypoxia cycles over the 8-h period. In the control (normoxia) condition (sham procedure), the mice were housed in an adjacent cage and were exposed to the same fan-off/fan-on cycles, although no gas mixture was released into the chamber at any point.

At the end of the experimental period, the animals were fasted for 6-10 h, after which they were anesthetized by intraperitoneal injection of ketamine (100 mg/kg) and xylazine (10 mg/kg). After anesthesia was confirmed, blood samples were collected from the retro-orbital sinus. The mice were exsanguinated during the procedure. Blood samples were centrifuged at 10,000 rpm for 10 min at 4°C to obtain serum

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samples. The pancreases of 12 mice per group were dissected, extracted, soaked for 24 h in five volumes of tissue storage reagent (RNAlater®; Applied Biosystems/Ambion, Austin, TX, USA), and stored at 4°C overnight, after which they were frozen at −80°C until analysis. The pancreases of 6 mice per group were fixed in 10% formalin for 24 h and embedded in paraffin for future processing.

Real-time PCR for UCP2, islet immunohistochemistry, and biochemical assays

The pancreases were unfrozen, dissected to isolate the islets, and homogenized in optimized phenol/guanidine-based lysis solution. Total RNA was isolated using TRI reagent solution (Applied Biosystems/Ambion). We quantified RNA and tested its quality by photometric measurement on a spectrophotometer (ND-1000; NanoDrop Technologies, Wilmington, DE, USA). Using a High Capacity cDNA Reverse Transcription Kit (Applied Biosystems, Foster City, CA, USA), we synthesized cDNA from 2 µg of highly purified RNA (A260/A280>1.95). The cDNA was stored at −20°C and diluted in DNase-free water (1:100) before relative quantification by real-time PCR. Gene expression analysis was performed using TaqMan Gene Expression Assays for the UCP2 gene (Mm00627598_m1; Applied Biosystems), using the following primer sequences: forward, 5′-ACAAGACCATTGCACGAGAG-3′ and reverse, 5′-ATGAGGTTGGCTTTCAGGAG-3′. The results were normalized to glyceraldehyde-3-phosphate dehydrogenase (GAPDH) expression. Thermal cycling was performed in a real-time PCR system (StepOne™; Applied Biosystems).

Gene expression was quantified using the 2-ΔΔCt (threshold cycle) method.[18] Each sample was analyzed in duplicate, and the ΔCt value was obtained by subtracting the GAPDH Ct value from the Ct value of the UCP2 gene. To calculate the difference between groups, the mean ΔCt value obtained for the control group was used to calculate the ΔΔCt of the gene (2-ΔΔCt).

The paraffin-embedded pancreases were sectioned into 5-µm slices. Sections were mounted on glass slides, coated with 3-aminopropyltriethoxysilane, deparaffinized with xylene (two changes, 5 min each), and rehydrated in a graded ethanol series (four successive washes), after which they were immersed in distilled water and PBS. For antigen retrieval, the slides were immersed in 10 mM sodium citrate buffer, pH 6.0, heated in a microwave oven for 21 min and cooled to room temperature. To inhibit endogenous peroxidase activity, the slides were twice immersed in 5% hydrogen peroxide for 15 min. Nonspecific antibody-binding sites were blocked with 5% nonfat dry milk diluted in PBS for 20 min. Immunohistochemistry staining for β- and α-cells was performed using polyclonal guinea pig anti-insulin (A0564, 1:200 dilution; Dako, Carpinteria, CA, USA) and rabbit polyclonal antibody to glucagon (GA 1181, 1:4,000; Enzo Life Sciences, Farmingdale, NY, USA), respectively. After three washes, in running water, distilled water, and PBS, respectively, the slides were incubated for 1 h in a humidity chamber at room temperature. They were then washed once with distilled water and three times with PBS, after which they were incubated with a secondary antibody (Picture-MAX Polymer Kit; Invitrogen, Camarillo, CA, USA) for 30 min in the humidity chamber. We developed the slides using 3,3'-diaminobenzidine as chromogen, according to manufacturer instructions. The slides were then counterstained with Harris's hematoxylin for 20 s, washed in running water, and rinsed with ammonium hydroxide to obtain a light blue color. They were subsequently washed once with water, twice with ethanol, and three times with xylene. All sections were analyzed under light microscopy (magnification, ×400), digitized, and assessed with a computer image analysis system (Image-Pro Plus, version 6.0; Media Cybernetics, Bethesda, MD, USA). The area of β-cells in the islets was determined by the insulin-positive cell area, which was calculated as the ratio of intra-islet insulin-positive area to total islet area. The relative area of glucagon, which represented the amount of α-cells in each islet, was evaluated by the same method. The insulin positive- and glucagon positive-cell indices for each group were calculated as the average of at least 24 sections. Nuclei were not taken into account for quantitative analysis of islet cell composition.

Fasting serum glucose, total cholesterol, HDL cholesterol, and triglycerides were measured by enzymatic colorimetric methods using commercially available kits (Labtest Diagnostics, Belo Horizonte, Brazil). We estimated LDL cholesterol levels by the Friedewald formula[19]:

LDL cholesterol = (*total cholesterol* – *HDL cholesterol* – *triglycerides)*/ 5

Fasting serum insulin was determined using a mouse insulin ELISA kit (ALPCO Diagnostics, Salem, NH, USA). Fasting serum glucagon was quantified with a glucagon enzyme immunoassay (EIA) kit (Phoenix Pharmaceuticals, Burlingame, CA). To evaluate the degree of insulin resistance, we calculated the homeostasis model assessment of insulin resistance (HOMA-IR) value, using the following formula[20]:

HOMA-IR = *fasting serum insulin* (μU/mL) × *fasting blood glucose* (mmol/L) / 22.5

In addition, we calculated the HOMA of pancreatic β-cell function (HOMA-β), as follows:

HOMA-β = [*fasting serum insulin level* (μU/mL) × 20] / [*fasting blood glucose level* (mmol/L) – 3.5]

Statistical analysis

Data were tabulated and expressed as medians and interquartile ranges and in box plots showing 10th, 25th, 50th, 75th, and 90th percentiles, as well as outliers. The Mann-Whitney U test was used for between-group comparison of median UCP2 mRNA, insulin/glucagon-positive cell area, and biochemical assay values. Body weight in each group was adjusted for food intake using the generalized estimating equations (GEE) method, followed by pairwise comparisons with sequential Bonferroni correction. All statistical analyses were performed with the Statistical Package for the Social Sciences, version 17.0 for Windows (SPSS Inc., Chicago, IL, USA). Statistical significance was assumed if the probability of alpha error was < 0.05.

Results

Data showing the expression of UCP2 in both groups are displayed in Figure 1A. The relative expression of UCP2 was 16% lower in the hypoxia group than in the normoxia group, (0.82 [0.71-0.94] vs. 0.98 [0.78-1.19]), although the difference between the two groups was not significant (p = 0.11).

Fasting serum glucose levels (Figure 1B) were 12% lower in the hypoxia group than in the normoxia group (144 [115-156] vs. 163 [133-184] mg/dL; p = 0.025). Fasting serum insulin levels (Figure 1C) were 5% higher in the hypoxia group as compared with the normoxia group (0.44 [0.42-0.46] vs. 0.42 [0.40-0.44] ng/mL; p = 0.01). Fasting serum glucagon levels (Figure 1D) were 37% lower in the hypoxia group than in the normoxia group (6.84 [3.64-9.90] vs. 10.87 [7.43-14.21] ng/mL; p = 0.023).

After exposure to intermittent hypoxia, the mean HOMA-IR value (Figure 1E) was 15% lower in the hypoxia group than in the normoxia group, although the difference was not significant (3.45 [3.00-4.17] vs. 4.06 [3.35-4.55]; p = 0.095). The mean HOMA-β value (Figure 1F) was 21% higher in the hypoxia group than in the normoxia group (46.6 [42-74] vs. 36.6 [29-52]; p = 0.014).

As shown in Figure 2, the relative area of insulin-positive cells in the hypoxia group was non-significantly higher than in the normoxia group: 0.62 [0.56-0.67] vs. 0.56 [0.51-0.59] respectively (p = 0.14). The area of glucagon-positive cells was 0.10 [0.06-0.15] in the hypoxia group and 0.09 [0.08-0.17] in the normoxia group (p = 0.67).

Lipid profile parameters were compared between groups. Mice exposed to intermittent hypoxia did not differ significantly from the control mice in terms of fasting serum triglycerides or the levels of HDL, LDL, and total cholesterol.

Body weights remained relatively stable over the 35-day study period: 23.7 ± 0.3 g at day 1 versus 25.1 ± 0.3 g at day 35 in the normoxia group; and 24.6 ± 0.5 g at day 1 versus 24.8 ± 0.3 g at day 35 in the hypoxia group. Body weight entered as a dependent variable in the GEE model showed no effect of group allocation or of food intake. Time had a significant effect, and there was a significant interaction between time and group (p < 0.001 for both).

Discussion

To our knowledge, this was the first study to analyze the effect of an intermittent hypoxia-based model of OSA on the expression of UCP2 mRNA in the pancreas. In this model, exposure to 480 cycles per day of intermittent hypoxia with an 8% FiO_2 nadir for 35 days resulted in levels of UCP2 mRNA expression lower than those observed for the control condition, although the difference was not statistically significant. These preliminary results supplement the current knowledge of the mechanisms underlying the metabolic consequences of OSA, generating various

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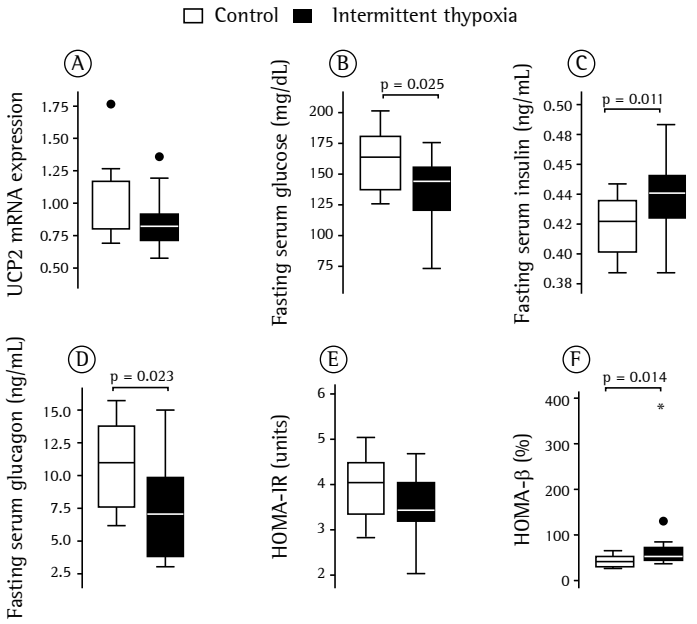

Figure 1 - Box plots of glucose metabolism variables showing 10th, 25th, 50th, 75th, and 90th percentiles; outliers (filled circles); and extreme outliers (asterisk). UCP2: uncoupling protein-2; HOMA-IR: homeostasis model assessment of insulin resistance; and HOMA-β; homeostasis model assessment of pancreatic β-cell function. Values of p were calculated by the Mann-Whitney U test.

hypotheses. The lack of a significant reduction in UCP2 expression in the hypoxia group might indicate that intermittent hypoxia has no effect on the expression of UCP2 or that it downregulates that expression to a degree below the threshold of the statistical power conveyed by the small number of animals evaluated.

The results of the present study add to the debate on the metabolic changes induced by OSA. Our data show that mice exposed to intermittent hypoxia had lower fasting serum glucose and glucagon levels than did the control mice. Previous studies have demonstrated that mice exposed to intermittent hypoxia show glucose levels that are either elevated[10,21] or lowered.[11] Our findings agree with those of the latter study, which involved lean and obese C57BL/6J mice exposed to chronic intermittent hypoxia for 5 days.[11] In the lean mice, glucose levels and insulin resistance decreased after hypoxia. In the obese (leptin-deficient) mice, glucose levels also decreased, although insulin resistance increased.[11] In the present study, only lean mice were employed, and our results might therefore represent a true response of lean mice exposed to intermittent hypoxia as evidenced by the increased insulin levels and decreased levels of glucagon.

Our finding that fasting serum insulin levels and β-cell function were higher in the hypoxia group than in the normoxia group is consistent with the lower glucose and glucagon levels previously reported as a response to hypoxia. In previous studies, obese mice exposed to intermittent hypoxia showed higher insulin levels than did control mice,[11,21,22] although the FiO_2 and exposure period differed from those employed in the present study. Another study showed that insulin levels were lower in lean mice exposed to intermittent hypoxia than in control mice.[23]

In the present study, insulin levels were higher in mice exposed to intermittent hypoxia than in the control mice. The significantly lower levels of glucagon found in the hypoxia group might indicate that compensatory mechanisms are activated to maintain glucose homeostasis. A review of the literature found no comparable studies reporting the response of glucagon to intermittent hypoxia.

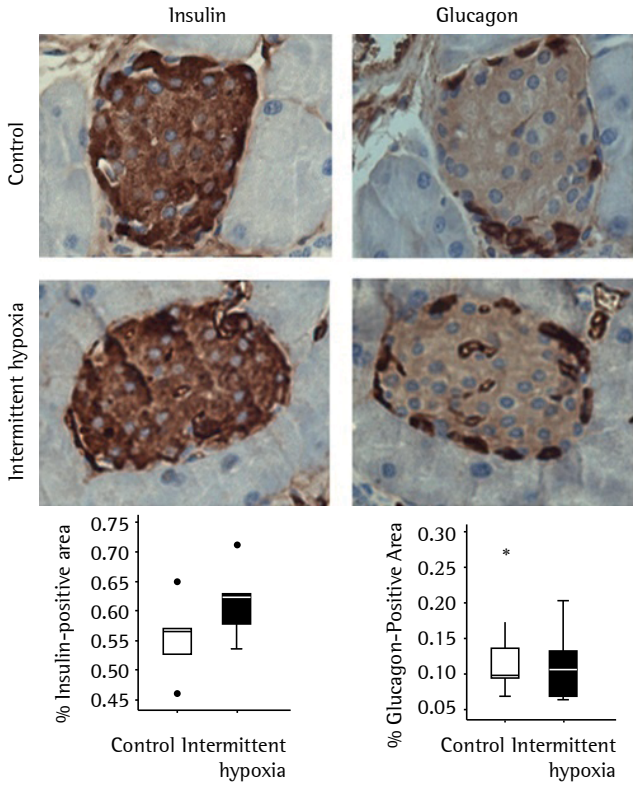

Figure 2 - Immunohistochemical staining for insulin and glucagon (magnification, ×400) with box plots of the relative area of the islet occupied by β-cells and α-cells. Box plots show 10th, 25th, 50th, 75th, and 90th percentiles; outliers (filled circles); and extreme outliers (asterisk).

No differences in insulin resistance were detected by HOMA-IR in the mice subjected to intermittent hypoxia, their glucose levels being lower than were those of controls. The HOMA-β value was higher in the former group, suggesting that some mechanism—perhaps a lowering of UCP2 levels—was activated in order to increase insulin production. The HOMA-IR and HOMA-β have not been validated for use in rodents, the formula for the latter representing a measure of β-cell function in humans.[24] However, the difference in the insulin to glucose ratio suggests that the mice might become insulin resistant, as previously reported.[11]

To date, there have been few reports in the literature addressing pancreatic β-cell function and sleep. In the experiment reported here, the HOMA-β values were significantly elevated in the animals exposed to intermittent hypoxia for 35 days, being 10% higher in the hypoxia group than in the normoxia group. The increase in the HOMA-β value implies that OSA causes an excessive increase in the functional demand on pancreatic β-cells, which leads to worsening of insulin secretion as the disease progresses.

Our findings should be interpreted with caution. The data related to glucose levels might be unreliable, because even the normoxia group mice had high glucose levels, despite fasting. One possible explanation for this, other than an error in measurement, is that, although the food pellets were removed from the cages, a significant ration could have remained inside the cage. However, the error might have been systematic, the lower glucose level in the hypoxia group being an effect of the higher insulin level. Although the result is negative, further exploration of the effect of intermittent hypoxia on UCP2 could be useful. Models employing UCP2 knockout mice could clarify the actual reaction of this protein to intermittent hypoxia. An oral glucose challenge would confirm insulin resistance, and a

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curve would be more informative than are single measurements. Although difficult in mice, this has been done previously.[6] The low triglycerides suggest that the hypoxia group mice were not eating as much as were the normoxia group mice. This could be a potential confounder of the findings.

Hyperlipidemia is common in persons with sleep apnea. Experiments evaluating the effect of intermittent hypoxia on lipid profile have reported discordant findings due to inconsistency in methods among studies. Examples of parameters that vary from study to study and could account for discrepant findings are differences in the duration of exposure (in days and in hours per day), in the duration of each hypoxia cycle (in seconds), in the FiO_2 nadirs, and in mouse strains. The magnitude of the metabolic disorder induced by intermittent hypoxia depends on the nadir of FiO_2. Experiments using 10% FiO_2 as the nadir of the hypoxia cycle did not induce metabolic changes after 28 days. Conversely, using a 5% FiO_2 nadir led to changes in all lipid profile parameters.[25] The moderate severity of intermittent hypoxia—both in terms of FiO_2 nadir and of hours of exposure per day—might be one reason for the absence of changes in lipid parameters in the present study. Similarly, the 8% FiO_2 nadir and 8 h of hours of exposure per day employed here might not have induced hypoxia severe enough to affect UCP2 expression.

In conclusion, our investigation of the effect of intermittent hypoxia on the expression of UCP2 mRNA in C57BL mice revealed that, after 35 days of exposure to intermittent hypoxia, there was no significant change in the expression of this regulatory protein. At the level of severity employed here, intermittent hypoxia causes changes in pancreatic function that might be unrelated to potential changes in the expression of UCP2 mRNA.

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Preventing smoking during pregnancy: the importance of maternal knowledge of the health hazards and of the treatment options available*

Prevenção do tabagismo na gravidez: importância do conhecimento materno sobre os malefícios para a saúde e opções de tratamento disponíveis

André Luís Bertani, Thais Garcia, Suzana Erico Tanni, Irma Godoy

Abstract

Objective: To examine the pattern of tobacco use and knowledge about tobacco-related diseases, as well as to identify popular types of electronic media, in pregnant women, in order to improve strategies for the prevention or cessation of smoking among such women. **Methods:** A cross-sectional study involving 61 pregnant women, seen at primary care clinics and at a university hospital, in the city of Botucatu, Brazil. For all subjects, we applied the Hospital Anxiety and Depression Scale. For subjects with a history of smoking, we also applied the Fagerström Test for Nicotine Dependence, and we evaluated the level of motivation to quit smoking among the current smokers. **Results:** Of the 61 pregnant women evaluated, 25 (40.9%) were smokers (mean age, 26.4 ± 7.4 years), 24 (39.3%) were former smokers (26.4 ± 8.3 years), and 12 (19.8%) were never-smokers (25.1 ± 7.2 years). Thirty-nine women (63.9%) reported exposure to passive smoking. Of the 49 smokers/former smokers, 13 (26.5%) were aware of the pulmonary consequences of smoking; only 2 (4.1%) were aware of the cardiovascular risks; 23 (46.9%) believed that smoking does not harm the fetus or newborn infant; 21 (42.9%) drank alcohol during pregnancy; 18 (36.7%) reported increased cigarette consumption when drinking; 25 (51.0%) had smoked flavored cigarettes; and 12 (24.5%) had smoked a narghile. Among the 61 pregnant women evaluated, television was the most widely available and favorite form of electronic media (in 85.2%), as well as being the form most preferred (by 49.2%). **Conclusions:** Among pregnant women, active smoking, passive smoking, and alternative forms of tobacco consumption appear to be highly prevalent, and such women seem to possess little knowledge about the consequences of tobacco use. Educational programs that include information about the consequences of all forms of tobacco use, employing new and effective formats tailored to this particular population, should be developed, in order to promote smoking prevention and cessation among pregnant women. Further samples to explore regional and cultural adaptations should be evaluated.

Keywords: Pregnancy; Health knowledge, attitudes, practice; Smoking; Mass media; Smoking cessation; Primary prevention.

Resumo

Objetivo: Examinar o padrão de consumo do tabaco e conhecimentos sobre as doenças relacionadas ao tabaco, assim como identificar os tipos mais populares de mídias entre gestantes para aprimorar estratégias para a prevenção e a cessação do tabagismo entre essas mulheres. **Métodos:** Estudo transversal com 61 gestantes atendidas em um hospital universitário e em unidades básicas de saúde em Botucatu, SP. A Escala Hospitalar de Ansiedade e Depressão foi aplicada a todas as participantes. Para aquelas com história de tabagismo, também foi aplicado o Teste de Fagerström para Dependência de Nicotina, e foi avaliado o grau de motivação para cessação tabágica nas fumantes. **Resultados:** Das 61 gestantes avaliadas, 25 (40,9%) eram fumantes (média de idade, 26,4 ± 7,4 anos), 24 (39,3%) eram ex-fumantes (média de idade, 26,4 ± 8,3 anos), e 12 (19,8%) nunca fumaram (média de idade, 25,1 ± 7,2 anos). A exposição passiva foi relatada por 39 gestantes (63,9%). Das 49 fumantes/ex-fumantes, 13 (29,6%) conheciam as consequências pulmonares do tabagismo; somente 2 (4,9%) conheciam os riscos cardiovasculares; 23 (46,9%) acreditavam que fumar não causa nenhum problema para o feto ou o recém-nascido; 21 (42,9%) consumiram álcool durante a gestação; 18 (36,7%) relataram aumento no consumo de cigarros quando bebiam; 25 (51,0%) experimentaram cigarros com sabores; e 12 (24,5%) fumaram narguilé. Entre as 61 gestantes avaliadas, a televisão foi o tipo de mídia mais disponível e favorita (85,2%), assim como a mais preferida (49,2%). **Conclusões:** Entre gestantes, o fumo ativo, o fumo passivo e o uso de formas alternativas de consumo de tabaco parecem ser altamente prevalentes, e tais mulheres parecem possuir poucos conhecimentos sobre as consequências do uso de tabaco. Programas educacionais que incluam informações sobre as consequências de todas as formas de uso de tabaco, utilizando formatos novos e efetivos para esta população específica, devem ser desenvolvidos para promover a prevenção/cessação do tabagismo entre gestantes. Amostras adicionais para explorar diferenças culturais e regionais são necessárias.

Descritores: Gravidez; Conhecimentos, atitudes e prática em saúde; Hábito de fumar; Meios de comunicação de massa; Abandono do hábito de fumar; Prevenção primária.

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Introduction

Although the prevalence of smoking in the general population is well known, few studies have addressed smoking in pregnant women. In the United States, the prevalence of maternal smoking during pregnancy is estimated to be 25%.[1] A study evaluating pregnant women seen at primary care units in the state of São Paulo, Brazil, showed that 19.2% actively smoked (during pregnancy and breastfeeding); 28.2% were active and passive smokers; and 16.8% were exposed to passive smoking only.[2] In 2011, another study, conducted in the Brazilian state of Rio Grande do Sul, evaluated anthropometric measurements of neonates born to 2,484 women and showed that, during pregnancy, 23.3% of those women had smoked and 28.9% had been continuously exposed to secondhand smoke.[3]

Anti-smoking policies in Brazil are quite advanced. The tobacco industry is required to label packages with warnings about the health consequences of smoking, and there are laws prohibiting smoking in collective and indoor environments. Direct and indirect merchandising and sponsorship by the tobacco industry are also prohibited.[4-6] However, the industry continues to employ strategies such as adding flavors to conventional cigarettes to change the taste and smell, in order to recruit new smokers from among women and adolescents. It should be borne in mind that flavored cigarettes and alternative forms of tobacco deliver all of the chemicals found in conventional cigarettes,[7] and the prevalence of the use of such products remains unknown.

The study and analysis of pregnant women and smoking, as well as of the characteristics of nicotine addiction and its adverse health consequences, are fundamental to developing tools for the prevention and treatment of smoking in this population. There have been few studies evaluating knowledge of the hazards of smoking among pregnant women in Brazil,[2,3,8] and none have evaluated technology preferences with the objective of designing interventions targeting such women. Therefore, the main objective of the present study was to examine the pattern of tobacco use and knowledge about tobacco-related diseases, as well as to identify the preferred forms of electronic media, in pregnant women, in order to improve strategies for promoting smoking prevention and cessation among such women.

Methods

Subjects

Between January and July of 2012, we recruited 61 pregnant women from among those attending routine appointments at the public prenatal care clinic of a university hospital and at primary care clinics in the city of Botucatu, Brazil. The study was approved by the Research Ethics Committee of the São Paulo State University Botucatu School of Medicine, also in the city of Botucatu. All participants (or their parents or legal guardians) gave written informed consent.

Study design and procedures

This was a descriptive cross-sectional study. The only exclusion criterion was refusal to participate. An investigator approached each pregnant woman while she was waiting to be seen and explained the aims of the study. The investigator was not a member of the health care team responsible for the treatment of the women recruited and visited the site only to conduct the interviews. All of the women invited agreed to participate and were directed to a room to be interviewed, in order to complete the study questionnaires. The interviews were conducted face-to-face, the investigator using a questionnaire developed specifically for the present study. The pregnant women freely answered questions about active and passive smoking, smoking habits during social activities, consumption of alcohol, use of alternative forms of smoking, and knowledge about the health hazards of smoking in general, as well as about the adverse health consequences of smoking during pregnancy, not only for the mother but also for the fetus and the newborn infant. In addition, all of the women completed the Hospital Anxiety and Depression Scale (HADS)[9]; those who were smokers or former smokers took the Fagerström Test for Nicotine Dependence[10]; and we assessed the motivational stage of change (level of readiness to quit smoking) using the model devised by DiClemente & Prochaska.[11] All personal information was kept confidential.

Statistical analyses

We used the chi-square test to compare the proportions and ANOVA with Tukey's test to compare means. Both evaluations were performed with a power of 80% and a level of significance of 5%.

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Results

Of the 61 pregnant women evaluated, 25 (40.9%) were smokers (mean age, 26.4 ± 7.4 years), 24 (39.3%) were former smokers (26.4 ± 8.3 years), and 12 (19.8%) were never-smokers (25.1 ± 7.2 years). The main characteristics of those three groups are presented in Table 1. Most of the women were married and were smokers or former smokers. Only 7 women (11.5%) were over 36 years of age. The predominant level of education was ≤ 9 years of schooling. Most of the women interviewed reported having been exposed to passive smoking, the prevalence of such exposure being highest among the smokers and never-smokers. Of the 25 smokers, 12 (49.2%) reported that their husband smoked, and 4 (14.7%) reported that at least one member of the household smoked. Abortion due to fetal malformation was reported only by women who were smokers or former smokers. Of the 18 women (29.7%) who had husbands who did not smoke, 10 (54.5%) were former smokers.

Among the 49 pregnant women who were smokers or former smokers, the age at smoking initiation ranged from 9 years to 25 years. Of the 8 women (16.3%) who had started smoking by 12 years of age, 7 (87.5%) were current smokers (p = 0.023). In contrast, we found no association between the age at smoking initiation and current smoking among the women who had started smoking after 12 years of age. The proportional distribution of the use of alternative forms of tobacco consumption—flavored cigarettes, clove cigarettes, water pipe (narghile), and electronic cigarettes—by the smokers and former smokers is presented in Table 2.

The proportion of women reporting wheezing was higher among the smokers than among the former smokers and never-smokers (87.5% vs. 12.5% and 0%, respectively; p = 0.030). In addition, a history of hypertension was observed only among the smokers and former smokers, of whom 14 (55.5%) and 11 (44.5%), respectively, reported having received such a diagnosis. Among women whose HADS scores were suggestive of anxiety or depression (Table 3), the majority were smokers. Five (18.4%) of the 25 smokers reported that they continued to smoke because of anxiety, whereas 3 (12.2%) reported smoking for pleasure.

Our findings related to how much knowledge pregnant women possess about the adverse health consequences of smoking were disappointing (Table 4). Most of the pregnant smokers and former smokers were unaware of the hazards that smoking poses to fetuses and newborn infants, as well as of tobacco-related diseases in general.

Regarding the motivational stage of change, we found that the proportion of smokers in the pre-contemplative stage was higher than was that of those in the contemplative stage (68% vs. 32%; p = 0.024). According to the results of the Fagerström Test for Nicotine Dependence, 15 (60%) of the smokers and 14 (58.3%) of the former smokers had a low degree of nicotine dependence. However, 12 (49%) of the smokers cited nicotine dependence as the main motivator for their continued smoking. We identified a reduction in smoking during pregnancy, in comparison with smoking before pregnancy (Figure 1). Of the 49 women with a history of smoking, 38 (77.5%) reported an increased desire to quit during pregnancy. Of the 24 former smokers, 12 (50%) reported that they had stopped smoking because they were pregnant. It is of note that 38 (77.5%) of the women with

Table 1 - Characteristics of the 61 pregnant women evaluated.

Variable	Smokers	Former smokers	Never-smokers
n (% of the sample as a whole)	25 (40.9)	24 (39.3)	12 (19.8)
Mean age (years), mean ± SD	26.4 ± 7.4	26.4 ± 8.3	25.1 ± 7.2
Married, n (%)	16 (64.0)	13 (54.2)	7 (58.3)
Level of education (years of schooling), n (%)			
≤ 9	14 (56.0)	10 (41.7)	4 (33.3)
10-12	8 (32.0)	9 (37.5)	7 (58.3)
> 12	3 (12.0)	5 (20.8)	1 (8.4)
Passive smoking, n (%)	18 (72.0)	11 (45.8)*	10 (83.3)
History of abortion, n (%)	5 (20.0)	7 (29.2)	4 (33.3)
Abortion due to fetal malformation, n (%)	3 (12.0)	2 (8.3)	0 (0.0)

*p = 0.049 vs. smokers and never-smokers.

a history of smoking did not know that smoking cessation treatments were available, and that 40 (65%) of the women interviewed expressed a desire to have more knowledge about the adverse health consequences of smoking. Alcohol consumption during pregnancy was reported by a considerable proportion of the women with a history of smoking (42.9%), and most (85.7%) of those women reported an increase in cigarette consumption when drinking.

In our sample, the electronic media available to pregnant women included video players (in 36.1%), radio (in 62.3%), and television (in 85.2%). Television was also the medium most preferred for relaxation/enjoyment (by 49.2%). Internet use was still somewhat limited in this population, being cited by only 21 (34.4%) of the 61 women interviewed.

Table 2 - Alternative forms of tobacco consumption during pregnancy, by smoking status.

Variable	Smokers	Former smokers
	(n = 25)	(n = 24)
Flavored cigarettes, n (%)	12 (48.0)	13 (54.2)
Clove cigarettes, n (%)	7 (28.0)	6 (25.0)
Narghile, n (%)	5 (20.0)	7 (29.2)
Electronic cigarettes, n (%)	2 (8.0)	0 (0.0)

Discussion

The main findings of the present study were that, among the pregnant women evaluated, there was a high prevalence of active and passive smoking during pregnancy; considerable usage of alternative forms of tobacco consumption during pregnancy; high levels of alcohol consumption during pregnancy; and limited knowledge of the adverse health consequences of smoking, including pregnancy outcomes for the fetus and newborn infant. On the basis of the preferences expressed by the interviewees, television appears to be the medium most well suited to delivering educational materials to this population (pregnant women).

We found a high (40.9%) prevalence of active smoking among pregnant women, and 72% of the pregnant smokers also reported being exposed

Table 3 - Levels of anxiety and depression among pregnant women, according to the Hospital Anxiety and Depression Scale scores, by smoking status.

Variable	Total	Smokers	Former smokers	Never-smokers
	(n = 61)	(n = 25)	(n = 24)	(n = 12)
Anxiety, n (%)				
Possible[a]	11 (18.0)	5 (20.0)	5 (20.8)	1 (8.3)
Probable[b]	13 (21.3)	7 (28.0)	2 (8.3)	4 (33.3)
Depression, n (%)				
Possible[a]	8 (13.1)	3 (12.0)	2 (8.3)	2 (16.7)
Probable[b]	5 (8.2)	4 (16.0)	0 (0.0)	1 (8.3)

[a]Hospital Anxiety and Depression Scale score of 8-10. [b]Hospital Anxiety and Depression Scale score of 11-21.

Table 4 - Knowledge of and beliefs about the health consequences of smoking for maternal, fetal, and neonatal outcomes, on the part of pregnant smokers and former smokers.

Variable	Smokers	Former smokers
	(n = 25)	(n = 24)
Maternal health		
Lung disease, n (%)	6 (24.0)	7 (29.2)
Abortion/placental damage, n (%)	2 (8.0)	6 (25.0)
Cardiovascular disease, n (%)	1 (4.0)	1 (4.2)
Cancer, n (%)	1 (4.0)	0 (0.0)
No problems, n (%)	15 (60.0)	10 (40.6)
Fetal/neonatal health		
Lung disease (%)	9 (36.0)	5 (20.8)
Gestational problems,* n (%)	6 (24.0)	6 (25.0)
No harm to the fetus/neonate	10 (40.0)	13 (54.2)

*Prematurity, malformation, or low birth weight.

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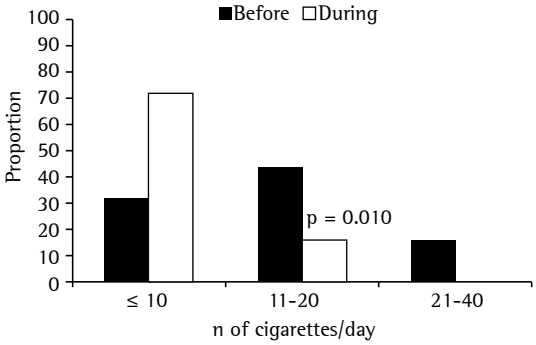

Figure 1 - Daily consumption of cigarettes before and during pregnancy among expectant mothers in the city of Botucatu, Brazil (n = 49).

to secondhand smoke during pregnancy. The prevalence of active smoking was higher than the 19.2-23.3% reported in the national and international literature.[1] It should be borne in mind that this study was not designed to determine the prevalence of smoking among pregnant women in general. In fact, some of the participants were recruited from a university hospital with a prenatal outpatient clinic primarily targeting women with high-risk pregnancies, which can be associated with other disorders that predispose to increased smoking. To our knowledge, there have been no previous studies evaluating the prevalence of smoking in this subgroup of pregnant women. However, this could explain, at least in part, the high prevalence of current smoking in our study sample and indicates the need to develop prevalence studies and offer individualized smoking cessation programs at such clinics. The prevalence of passive smoking in our sample (63.9%) is comparable to the 39.2-56.7% reported in other studies of pregnant women.[8,12]

Our results show that a high proportion of pregnant former smokers lived with a never-smoker husband, which is consistent with the findings of previous studies showing a tendency for pregnant women to stop smoking if they have a husband who has never smoked.[13] In addition, according to data in the literature and from the present study, pregnancy promotes smoking cessation, and that window of opportunity is not being taken advantage of, as evidenced by the fact that 77.5% of the smokers and former smokers interviewed in our study did not know that smoking cessation treatment was available.[14] Furthermore, at least two studies have reported that mothers feel guilty about smoking during pregnancy.[14,15] Therefore, a carefully presented appeal to consider smoking cessation treatment before or during pregnancy could be an effective strategy targeting this population of women.

We found that a high proportion of the pregnant women interviewed smoked flavored cigarettes or consumed tobacco in other alternative forms. The prevalence of those forms of tobacco consumption among pregnant women in Brazil remains unknown. Like traditional (cigarette) smoking, alternative forms of tobacco consumption have adverse health consequences.[16] Therefore, smoking cessation interventions should include information about alternative forms of tobacco use, and that information needs to be widely disseminated.

Of the pregnant women interviewed in the present study, fewer than 30% were aware of the effects that smoking has on respiratory health, and a similar proportion knew that smoking during pregnancy could lead to spontaneous abortion or damage the placenta. The consequences of maternal smoking for the fetus and newborn infant, such as prematurity, malformation, and low birth weight, were also known by only approximately 30% of the participants. Unfortunately, 40% of the smokers and 54.2% of the former smokers believed that smoking did not cause harm to the fetus or newborn infant. In addition, fewer than 6% of the women we interviewed were aware of the fact that smoking is associated with cardiovascular disease and cancer. These findings are consistent with those of studies showing that pregnant women possess only superficial knowledge of the health consequences of smoking during pregnancy.[12,15]

We found that the pregnant women evaluated in the present study presented with certain risk factors for smoking.[12,13] The majority had a low level of formal education, and alcohol consumption during pregnancy was common (reported by 42.9%). Freire et al.[17] also identified alcohol consumption during pregnancy in 31.3% of the pregnant smokers they evaluated. Similarly, Kroef et al.[18] showed that, among pregnant women, smokers and former smokers consumed more alcohol than did never-smokers. In the present study, 39.3% of the pregnant women evaluated had scores of the HADS that were suggestive of anxiety and 21.3% had HADS scores suggestive of depression. Anxiety disorders are common during pregnancy,[19,20] and depression

has been associated with difficulty in quitting smoking among women, a situation than can be compounded by pregnancy.[19,21] Park et al.[21] and Solomon et al.[22] both demonstrated that, in women who spontaneously stopped smoking during pregnancy, there was a positive association between depressive symptoms at the end of pregnancy and relapse to smoking in the postpartum period.[21,22]

Among the pregnant women evaluated in the present study, television, the internet, and radio were the most widely used forms of electronic media, television being the form preferred by the largest proportion of the participants. Studies have shown that sending text messages (via mobile phone) advising pregnant women to quit smoking is an effective way to encourage smoking cessation during pregnancy, as is promoting interaction among pregnant smokers via online social networks.[23,24] However, Bot et al.[25] evaluated the differences in internet usage by pregnant women with different levels of education and found that those who had a low level of education were less interested in receiving e-mails about health issues than were those who had a higher level of education. In view of our finding that 65% of the pregnant smokers in the present study expressed a desire to increase their knowledge of the health consequences of smoking, we believe that educational interventions might be beneficial to these smokers.

In conclusion, the results of our study indicate that there is a high prevalence of active and passive smoking among pregnant women and that such women have limited knowledge about the health consequences of smoking, during pregnancy and otherwise. Pregnancy provides a window of opportunity for promoting smoking cessation and should be viewed as an excellent opportunity to provide more information about the health hazards of smoking and to offer smoking cessation treatment to pregnant women. Educational programs that include information about the consequences of all forms of tobacco use, employing new and effective formats tailored to this particular population, should be developed. Despite large-scale media campaigns, the level of knowledge among pregnant women regarding the long-term consequences of tobacco use remains low, and the use of alternative forms of tobacco is high among such women. However, pregnant women expressed interest in learning more about the subject, and television might be a useful tool for delivering information to this population in an attractive and continuous manner.

Potential limitations of the present study include the small sample size and the fact that it was conducted in only one city. In addition, the study sample comprised high-risk pregnant women. Therefore, the results cannot be extrapolated to pregnant women in general or to other regions of Brazil. However, because all of the women invited to participate in the study agreed to be included, there was no selection bias.

We believe that our study has added to the body of information supporting the development and implementation of new tools to improve the treatment of smoking during pregnancy. The use of material tailored to pregnant smokers and delivered in the form of videos shown or distributed to pregnant women during prenatal visits to outpatient clinics might promote smoking prevention and cessation among such women.

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Cognitive impairment in COPD: a systematic review*

Comprometimento cognitivo em pacientes com DPOC: uma revisão sistemática

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Abstract

The objectives of this study were to characterize and clarify the relationships between the various cognitive domains affected in COPD patients and the disease itself, as well as to determine the prevalence of impairment in the various cognitive domains in such patients. To that end, we performed a systematic review using the following databases: PubMed, Scopus, and ScienceDirect. We included articles that provided information on cognitive impairment in COPD patients. The review of the findings of the articles showed a significant relationship between COPD and cognitive impairment. The most widely studied cognitive domains are memory and attention. Verbal memory and learning constitute the second most commonly impaired cognitive domain in patients with COPD. The prevalence of impairment in visuospatial memory and intermediate visual memory is 26.9% and 19.2%, respectively. We found that cognitive impairment is associated with the profile of COPD severity and its comorbidities. The articles reviewed demonstrated that there is considerable impairment of the cognitive domains memory and attention in patients with COPD. Future studies should address impairments in different cognitive domains according to the disease stage in patients with COPD.

Keywords: Pulmonary disease, chronic obstructive; Mild cognitive impairment; Hypoxia, brain.

Resumo

Os objetivos deste estudo foram caracterizar e esclarecer as relações entre os vários domínios cognitivos afetados em pacientes com DPOC e a doença em si, assim como determinar a prevalência de comprometimentos cognitivos em tais pacientes. Para tanto, foi realizada uma revisão sistemática utilizando as seguintes bases de dados: PubMed, Scopus e ScienceDirect. Os artigos incluídos forneciam informações sobre os comprometimentos cognitivos em pacientes com DPOC. A revisão dos achados de tais artigos mostrou uma relação significativa entre DPOC e comprometimento cognitivo. Os domínios cognitivos mais estudados são a memória e a atenção. Memória verbal e aprendizagem constituem o segundo domínio cognitivo mais comumente prejudicado em pacientes com DPOC. A prevalência de comprometimento da memória visuoespacial e da memória visual intermediária é 26,9% e 19.2%, respectivamente. Observamos que o comprometimento cognitivo está associado ao perfil de gravidade da DPOC e suas comorbidades. A revisão dos artigos demonstrou que há um comprometimento considerável dos domínios memória e atenção em pacientes com DPOC. Investigações futuras devem abordar os comprometimentos em diferentes domínios cognitivos em conformidade com o estágio da doença em pacientes com DPOC.

Descritores: Doença pulmonar obstrutiva crônica; Comprometimento cognitivo leve; Hipóxia encefálica.

Introduction

The hallmark of COPD is chronic airflow obstruction that has a systemic impact and a progressive evolution.[1] It is an important health problem that is estimated to become the fifth leading cause of disability and the third leading cause of death worldwide by 2020.[2] The prevalence of COPD in the global population is close to one percent and increases with age. Among individuals 40 years of age or older in the city of São Paulo, Brazil, its prevalence ranges from 6 to 15.8%.[3]

The typical profile of patients with COPD includes multiple comorbidities,[4,5] such as heart

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Table 1 - Characteristics of the articles selected.

Study	Design	Objective	Sample size and COPD severity	Characteristics of COPD participants	Intervention	Results/Conclusions
Dodd et al.[19]	Observational study	To assess neuropsychological performance in COPD patients hospitalized after an acute exacerbation and recovery, compared with patients with stable COPD and with healthy control subjects	110 participants: 30 COPD inpatients hospitalized following an exacerbation 50 outpatients with stable COPD 30 healthy control subjects	Mean age, 70 ± 11 years; 15 (50%) were female Mean age, 69 ± 8 years; 28 (56%) were female	-	In patients hospitalized with an acute COPD exacerbation, impaired cognitive function is associated with worse health status and longer length of hospital stay. Cognitive function might not improve with recovery
Chang et al.[20]	Cohort study	To determine the extent to which the co-occurrence of COPD and cognitive impairment leads to adverse health outcomes in older adults	3,093 patients: 431 with COPD only 29 with COPD and cognitive impairment 114 with cognitive impairment only 2,519 with neither COPD nor cognitive impairment	188 (43.7%) were 65-70 years of age; 210 (48.7%) were female 6 (21.3%) were 65-70 years of age; 10 (34.5%) were female	None	Patients with COPD and cognitive impairment had the highest rates of respiratory-related and all-cause hospitalizations and death
Dodd et al.[21]	Observational study	To evaluate whether there are significant differences between COPD patients and control subjects, in terms of white matter integrity and communication between gray matter resting-state networks, and to test the observed differences related to disease severity, comorbid cerebrovascular disease, and cognitive dysfunction	25 non-hypoxemic COPD patients 25 control subjects	Mean age, 67.8 ± 8.1 years; 11 (44%) were female	None	In stable, non-hypoxemic COPD, there is reduced white matter integrity throughout the brain and widespread disturbance in the functional activation of gray matter, which might contribute to cognitive dysfunction. White matter microstructural integrity is independent of smoking and comorbid cerebrovascular disease, but gray matter functional activation is not. The mechanisms remain unclear but could include cerebral small vessel disease caused by COPD
Villeneuve et al.[10]	Observational study	To determine the frequency and subtypes of MCI in COPD patients and to assess the validity of two cognitive screening tests (the MMSE and MoCA) in detecting MCI in COPD patients	45 patients with moderate-to-severe COPD 50 healthy control subjects	Mean age, 68.84 ± 8.43 years; 29 (64%) were female	None	In this preliminary study, a substantial proportion of COPD patients were found to have MCI. The MoCA was better than was the MMSE at detecting MCI in COPD patients.
Martin et al.[22]	Clinical trial	To determine the effect of hypoxia on cognitive performance in COPD patients with PaO_2 <6.6 kPa	10 patients with moderate-to-severe COPD	Mean age, 64 years; 3 (30%) were female	For a short period of time, patients breathed 21% O_2 when PaO_2 was < 6.6 kPa	Short-term exposure to hypoxia had no adverse effect on cognitive function
Pereira et al.[23]	Clinical trial	To evaluate the effect of a multidisciplinary pulmonary rehabilitation program on cognitive function in COPD patients, adjusting for potential confounders	34 patients with moderate-to-severe COPD 18 healthy control subjects	Mean age, 65.2 ± 7 years; 17 (50%) were female	3-month program of pulmonary rehabilitation	Even after adjusting for the sociodemographic factors that might affect cognitive function, the authors found that pulmonary rehabilitation improved cognitive performance in COPD patients. There were gender- and age-related differences in cognitive scores that persisted after rehabilitation
Klein et al.[24]	Cohort study	To explore the influence of COPD on attentional functions, learning, and logical thinking	60 COPD patients 60 control subjects	Mean age, 63.2 ± 9.8 years; 24 (40%) were female	None	In COPD patients, there was global impairment in cognitive functions that was negatively influenced by advancing age and increased in proportion to the degree of disease severity
Thakur et al.[25]	Cohort study	To elucidate the association between COPD and the risk of cognitive impairment, in comparison with control subjects without COPD	1,202 COPD patients 302 control subjects	Mean age, 58.2 ± 6.2 years; 691 (57.4%) were female	None	COPD is a major risk factor for cognitive impairment. In COPD patients, hypoxemia is a major contributor to cognitive impairment and regular use of home oxygen is a protective factor. Health care providers should consider screening COPD patients for cognitive impairment

Table 1 - Continued...

Study	Design	Objective	Sample size and COPD severity	Characteristics of COPD participants	Intervention	Results/Conclusions
Antonelli-Incalzi et al.[14]	Observational study	To assess whether certain neuropsychological patterns are associated with various limitations to physical independence in COPD patients	149 COPD patients	112 (75.2%) were over 65 years of age; 14 (9.4%) were female	None	Classic indicators of the severity of COPD showed no correlation with personal autonomy
Borson et al.[26]	Observational study	To model the relationship between respiratory failure and domains related to brain function, including low mood, subtly impaired cognition, systemic inflammation, and structural/neurochemical brain abnormalities	9 healthy control subjects 18 COPD patients, half of whom were oxygen-dependent	Mean age, 68.5 ± 8.0 years; 11 (64%) were female	None	COPD is associated with slight decreases in mood and cognition. Severe COPD is associated with chronic systemic inflammation and subtle cognitive deficits (on digit symbol coding tasks). Levels of oxygen desaturation appear to mediate specific changes in brain neurochemistry and structure that suggest sustained brain damage
Orth et al.[27]	Observational study	To analyze driving performance in COPD patients and healthy control subjects	17 COPD patients 10 healthy control subjects	Mean age, 55.2 ± 9.3 years	None	Compared with healthy control subjects, COPD patients are more likely to cause a traffic accident. Impaired driving performance in COPD patients cannot be predicted on the basis of the severity of the disease
Pinto de Lima et al.[28]	Observational study	To test the hypothesis that clinically stable COPD patients without overt cognitive symptoms can nonetheless have subtle cognitive impairment	30 COPD patients 34 control subjects	Mean age, 65 ± 8 years; 10 (33%) were female 24 (71%) were female	None	There might be subclinical encephalopathy in COPD, characterized by subtle impairment of global cognitive ability
Salik et al.[29]	Observational study	To determine the relationship between cognitive function and quality of life in COPD patients with mild hypoxemia and moderate airway obstruction	32 patients with moderate stable COPD 26 healthy subjects	Mean age, 66.7 ± 2.5 years; 14 (44%) were female	None	Cognitive function in COPD patients with hypoxemia might not be impaired despite their poor quality of life status
Antonelli-Incalzi et al.[30]	Observational study	To evaluate the prognostic role of cognitive impairment in patients with severe COPD	149 COPD patients who had undergone a period of in-hospital rehabilitation following an acute exacerbation	Mean age, 68.7 ± 8.5 years; 22 (16.4%) were female	None	Impaired drawing ability is a risk factor for mortality and its testing might improve the assessment of hypoxemic COPD patients
Corsonello et al.[31]	Observational study	To determine whether cancer is more disabling than are other chronic diseases that are highly prevalent in the elderly	6 groups of patients: Congestive heart failure (n = 832) Diabetes mellitus (n = 939) COPD (n = 399) Non-metastatic solid tumors (n = 813) Metastatic solid tumors (n = 259) Leukemia/lymphoma (n = 326)	178 (44.6%) were 65-79 years of age; 147 (36.8%) were female	None	Cognitive impairment was more prevalent in patients with congestive heart failure or COPD than in those with cancer
Antonelli-Incalzi et al.[32]	Observational study	To determine whether the neuropsychological performance of untreated patients with OSA conforms to a distinctive pattern	49 newly diagnosed, untreated OSA patients 27 patients with multi-infarct dementia 31 patients with mild-to-moderate dementia of the Alzheimer type 63 patients with severe COPD		None	A minority of newly diagnosed OSA patients had distinct neuropsychological impairment. The greater body mass index of cognitively impaired OSA patients indicates that the metabolic syndrome might also be causally related to the cognitive dysfunction

MMSE: Mini-Mental State Examination; MoCA: Montreal Cognitive Assessment; MCI: mild cognitive impairment; kPa: kilopascal; CHF: congestive heart failure; and OSA: obstructive sleep apnea.

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disease,[6] osteoporosis,[7] type 2 diabetes mellitus,[8] lung cancer,[9] and cognitive impairment.[10] In recent years, the clinical relevance of cognitive impairment has risen,[11] due to the increase in the prevalence of COPD and the growing interest in the aspects that determine functionality and treatment compliance[12,13] among patients with the disease.[14]

Although COPD and cognitive impairment have been studied separately (as individual diseases), there is growing evidence of a relationship between the two.[11] Hugg et al.[15] analyzed cognitive impairment in patients with COPD and found that such patients had a greater risk of developing cognitive impairment than did patients without COPD. The hypoxemia seen in some patients with COPD seems to be a crucial factor for cognitive impairment, because it affects the oxygen-dependent enzymes that are important in the synthesis of neurotransmitters such as acetylcholine.[16] Various studies have shown that cognitive impairment has a prevalence of 77% in patients with COPD and hypoxemia.[17]

The main hypotheses of this review were that there is a relationship between the various cognitive domains affected in COPD patients and the disease itself, and that the prevalence of impairment varies among the different cognitive domains. The objective of this review was two-fold: to characterize and clarify the relationship between the various cognitive domains affected in COPD patients and the disease itself; and to determine the prevalence of impairment in the various cognitive domains in such patients.

Methods

In this review of the literature, we adopted the classification of cognitive domains devised by Lezak.[18] According to that author, who is the current reference in neuropsychological assessment, the cognitive domains correspond to five key areas: perception; attention; memory and learning; executive function; and language. We adopted a systematic approach using the following search strings (comprising terms related to COPD and to the Lezak classification of cognitive domains): "cognitive impairment" AND "COPD"; "cognitive decline" AND "COPD"; "cognitive dysfunction" AND "COPD"; "hypoxia" AND "cognitive impairment" AND "pulmonary disease"; "cognitive impairment" AND "hypercapnia" AND "pulmonary disease"; "cognitive attention" AND "COPD"; "memory and learning" AND "COPD"; "memory learning" AND "COPD" AND "cognitive"; "perceptive function" AND "COPD"; "verbal language" AND "COPD"; and "executive functions" AND "COPD".

We systematically searched the following databases: PubMed, Scopus, and ScienceDirect. Searches were limited to studies in humans published in the last ten years in order to focus on the recent interest and scientific evidence in this area. The inclusion criteria were being a clinical trial, epidemiological study, observational study, cohort study, or case-control study; and providing information on the subject at hand (i.e., cognitive impairment in COPD patients). We excluded articles that dealt with subjects unrelated to this topic, those that were not available in full text, and those that were review articles or simple case reports, as well as those published in languages other than English, Spanish, or French. The article selection process is depicted as a flowchart in Figure 1.

Results

The search yielded 478 articles. After the abstracts had been reviewed, only 16 articles were selected for inclusion in the review. The characteristics of the selected articles are shown in Table 1. Our review of those studies revealed a significant relationship between COPD and cognitive impairment. It is important to point out that there is as yet no consensus regarding the definition of cognitive impairment in patients with COPD. Different operational definitions of such impairment among the studies reviewed made it difficult to evaluate that aspect across those studies.

Given the multiple classifications of cognitive domains and the complexity of the assessment tools available, we chose the classification proposed by Lezak,[18] which is one of the most complete and comprehensive such classifications devised to date. Table 2 shows the various tests used and the cognitive domains assessed in the selected articles.

Of the 16 studies selected, 14 were descriptive studies and two were experimental studies. Of the 14 descriptive studies, 11 were observational studies and three were cross-sectional studies.

Discussion

Various controlled studies have investigated the prevalence of cognitive impairment in

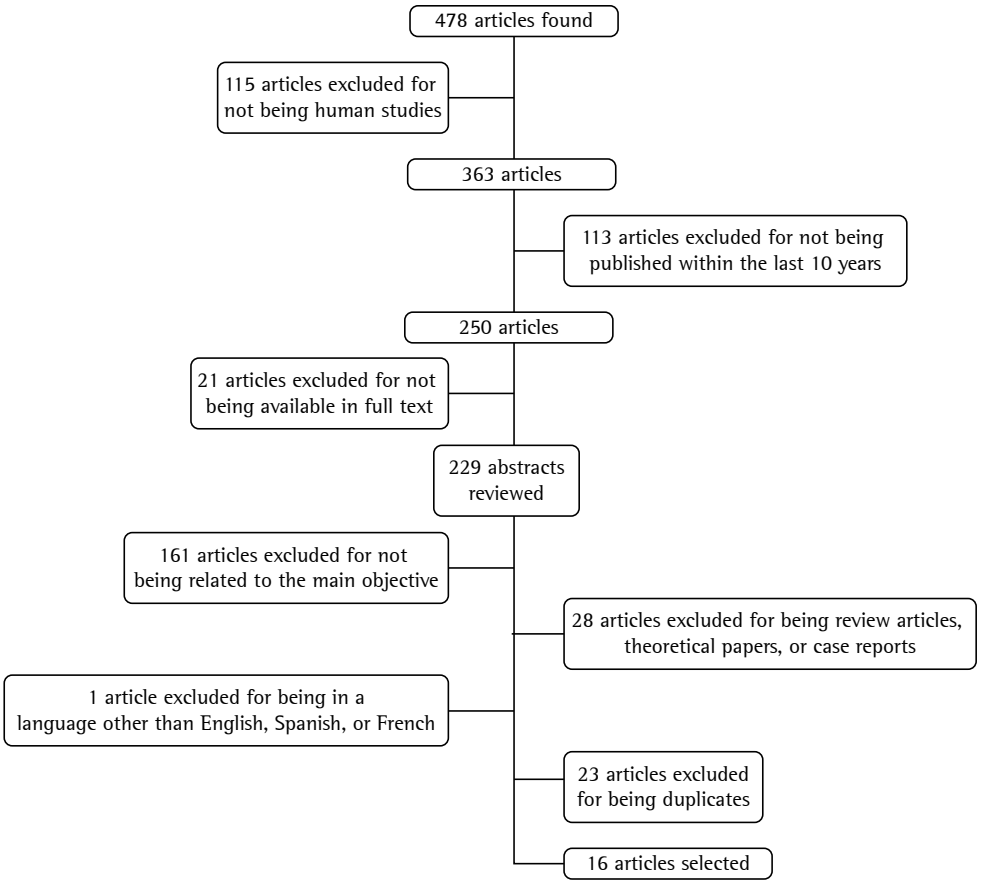

Figure 1 - Selection of the articles analyzed in this review.

COPD,[21,25,28] showing that prevalence to be higher in COPD patients than in healthy control subjects.[10,31] According to such studies, mild cognitive impairment is present in 36% of COPD patients and in 12% of subjects without COPD. In a study conducted by Antonelli-Incalzi et al.,[30] the prevalence of cognitive impairment and severe cognitive impairment in COPD patients was found to be 32.8% and 10.4%, respectively.

The prevalence of cognitive impairment in patients with COPD was found to be associated with the severity of the disease,[20,25] being 3.9% among patients with mild COPD, 5.7% among patients with moderate COPD, and 7.7% among patients with severe COPD. In fact, a relationship has been found between the Mini-Mental State Examination score and the severity of COPD ($r = -0.49$, $p < 0.001$).[28] However, the study conducted by Salik et al.[29] showed that cognitive function in COPD patients with mild hypoxemia was similar to that observed for healthy subjects. According to those authors, cognitive function is affected by hypoxemia only when the latter is severe. In addition, Grant et al.[17] reported a 77% prevalence of cognitive impairment in patients with hypoxemic COPD. The reasons for this variation across studies include differences in the degree of COPD severity and in the age of the patients included in the studies, as well as the use of different diagnostic criteria for cognitive dysfunction and different cognitive tests.

The studies included in our review had large sample sizes and included a great variety of patients, which reduces any bias in prevalence rates. It is known that COPD is associated with an increased risk of impaired cognitive function,[26] even when the data are adjusted for age, gender, smoking history, and level of education.[19,25] Villeneuve et al.[10] reported that level of education was the only variable for which there were significant differences among COPD patients with mild cognitive impairment, COPD patients without cognitive impairment, and healthy control subjects.[10] The authors ruled out strokes and

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other cardiovascular diseases (all of which are common among COPD patients) as risk factors. Low peripheral oxygen saturation (≤ 88%) has been strongly associated with a risk of cognitive impairment in patients with COPD, and the use of home oxygen therapy has been associated with a reduction in that risk.[25] Numerous studies have explored the relationship between COPD and cognitive impairment. While some studies have addressed this issue globally using screening tests, others have focused on the assessment of specific cognitive domains.[10,24,27]

Perception is a series of processes and activities through which we extract information about our environment, the actions we perform within it, and our own state. Perceiving the environment requires a proper combination of attention and perception. Therefore, even though attention and perception are considered separate areas in the Lezak classification, they are often assessed together. Hypothesizing that automobile accidents would be more common among drivers with COPD than among those without, Orth et al.[27] compared COPD patients with healthy control subjects, in terms of complex attentional and perceptual functions. The authors found that, in simulated driving situations, COPD patients showed lower concentration values and had a significantly higher number of accidents than did the healthy control subjects.[27] According to various studies,[10,24] attentional and executive functions are commonly impaired in the main subtype of mild cognitive impairment found in patients with COPD.

Learning implies acquiring information and therefore changes the state of memory. Verbal memory is one of the cognitive domains that are most frequently impaired in patients with COPD.[31] According to Villeneuve et al.,[10] verbal memory and learning is the second most commonly impaired cognitive domain in patients with COPD. In such patients, the prevalence of impairment in visuospatial memory and intermediate visual memory is 26.9% and 19.2%, respectively.[14] In patients with COPD and sleep apnea, verbal memory and visual memory are the most commonly affected cognitive domains,[30] although processing speed, working memory, and executive function are also affected ($p = 0.01$, $p = 0.02$, and $p \leq 0.001$, respectively).[21]

The term "executive functions", coined by Lezak, refers to skills involved in formulating goals, planning their achievement, and effectively performing behaviors.[18] The assessment of executive functions in patients with COPD has shown that such patients tend to have slower processing speeds.[19] Twenty percent of patients with exacerbated COPD exhibit a loss in processing speed that is significant enough to be considered pathological. Slower processing speed has been related to the duration of hospital stay, quality of life measured with the Saint George's Respiratory Questionnaire, and the number of COPD exacerbations.[19]

The ability to understand and communicate is determined by language. This mental process enables structured thinking, allowing an individual to make connections between ideas and mental representations. There have been studies evaluating cognitive function in a number of diseases,[30] including sleep apnea and COPD. Patients with COPD and sleep apnea have been found to perform more poorly on tests of verbal fluency and deductive thinking than do COPD patients without sleep apnea. There are data indicating that only 3% of COPD patients have a completely normal cognitive profile.[19]

We made cognitive impairment the focus of the present review because it is a common comorbidity in patients with COPD. The strength of our review is that it explored the relationship between COPD and cognitive impairment in the various cognitive domains over the last ten years, during which time a number of relevant clinical studies on this subject have been conducted. In addition, the studies included had large sample sizes. There have been a number of reviews of cognitive impairment in elderly people and COPD patients.[33-36] The review conducted by Schillerstrom et al.[33] addressed the impact of medical illness on executive function. In another review, Dodd et al.[11] explored the mechanisms that cause injury and dysfunction in the brain, discussing the methods used in order to evaluate cognition, gathering evidence on the nature and level of cognitive impairment in COPD. Another recent review, conducted by Schou et al.,[37] investigated the occurrence and severity of cognitive dysfunction in COPD patients, exploring the relationship between the severity of COPD and the level of cognitive function. In our review, we included nine new studies about COPD and cognitive impairment, conducted between 2009 and 2013, which were excluded from the review

Table 2 - Tests or batteries of tests used in the assessment of the cognitive domains under study in the articles selected.

Neuropsychological assessment instrument or function assessed	Cognitive domain						
	Perception	Attention	Memory and learning	Abstract thinking and executive function	Language	Intelligence	General (global screening)
Wechsler Test of Adult Reading[19,22]						X	
Mini-Mental State Examination[10,19-21,25,28-30]							X
Rey Complex Figure Test-Copy and Rey Complex Figure Test-Recall[19,21,22]			X				
Wechsler Memory Scale-III UK Word Lists[19]			X				
Delis-Kaplan Verbal Fluency test[19]					X		
Delis-Kaplan Trail Making Test[10,19,22]				X			
Wechsler Adult Intelligence Scale-III UK Letter-Number Sequencing[19,21]				X			
Wechsler Memory Scale-III UK Spatial Span[19,23]				X			
Wechsler Adult Intelligence Scale-III Digit Symbol[19,26]				X			
Wechsler Adult Intelligence Scale-III Symbol Search[19,21]				X			
Montreal Cognitive Assessment[10]							X
Digit Span Test (Wechsler Adult Intelligence Scale-III)[10,23]		X		X			
Digit Symbol coding test (Wechsler Adult Intelligence Scale-III)[10]		X		X			
Semantic Verbal Fluency[10]		X		X			
Letter verbal fluency (P, F and L)[10]		X		X			
Rey Auditory Verbal Learning Test[10,23]			X				
Block Design[10]	X						
Bells Test[10]	X						
Word Lists Learning, Delayed Recall, and Delayed Recognition (Wechsler Memory Scale-III)[21]			X				
Verbal Fluency-FAS task (Delis-Kaplan Executive Function System)[21,23]				X			
Stroop Color-Word Test[10,23]				X			
Attention Network Test[24]		X		X			
Standard Progressive Matrices[24]							
Verbal and Nonverbal Learning Test (part of the Vienna Test System)[24]			X				
Raven's Colored Progressive Matrices[14]	X						
Phonemic verbal fluency test[14]					X		
Corsi Block-Tapping task (visuospatial span)[14]	X		X				
Verbal word span[14]		X	X				
Rey Auditory 15-Word Learning test[14]			X				
Albert's test (visual exploration)[14]	X						
Copying geometrical drawings with or without landmarks[14]	X						
Immediate Visual Memory Test[14]			X				
Sentence construction[14]					X		
The Computer-Aided Risk Simulator (driving simulator test)[27]	X	X					
Dementia Rating Scale-2[26]							X
Wide Range Achievement Test-3[26]						X	
Logical memory subtest of the Wechsler Memory Scale-III[26]			X				
Mental Deterioration Battery[30]							X
10-item Hodkinson Abbreviated Mental Test[31]							X

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conducted by Schou et al.,[37] because they were not published within the date range set for the search of the literature in the latter.

One of the limitations of the present review is the great variety of outcome measures evaluated. However, our review of the literature clearly showed the existence of a relationship between COPD and cognitive impairment. That relationship appears to be determined by the severity of COPD and by its comorbidities.

The most widely studied cognitive domains are memory and attention, both of which have been explored with specific assessment tools and found to be considerably impaired in patients with COPD. Evidence suggests that a structured assessment of cognitive function should be a routine component of the evaluation of COPD patients. Future studies should explore impairment in the various cognitive domains in COPD patients at different stages of the disease.

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Lymphadenopathy and fever in a chef during a stay in Europe*

Linfadenomegalia e febre em chefe de cozinha durante viagem à Europa

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Abstract

This case illustrates a rare presentation (as lymphadenopathy and fever) of one of the most common zoonotic diseases worldwide—brucellosis—in a 22-year-old Brazilian male (a chef) who had recently returned to Brazil after having lived in and traveled around Europe for one year. The histopathology, clinical history, and response to treatment were all consistent with a diagnosis of brucellosis, which was confirmed by PCR in a urine sample. We also review some aspects of brucellosis, such as the clinical features, diagnosis, and management.

Keywords: Brucellosis; Fever; Lymph nodes; Brucella; Mononuclear phagocyte system; Granuloma.

Resumo

Ilustramos aqui um caso de uma apresentação atípica (na forma de linfadenomegalia e febre) de uma das doenças zoonóticas mais comuns no mundo — brucelose — em um paciente brasileiro de 22 anos (chefe de cozinha) que retornara ao Brasil recentemente após ter morado e viajado na Europa por um ano. A histopatologia, a história clínica e a resposta ao tratamento foram consistentes com o diagnóstico de brucelose, que foi confirmada por PCR em uma amostra de urina. Também revisamos alguns aspectos da brucelose, como manifestações clínicas, diagnóstico e tratamento.

Descritores: Brucelose; Febre; Linfonodos; Brucella; Sistema fagocitário mononuclear; Granuloma.

Introduction

The case reported here illustrates the differential diagnosis of febrile lymphadenopathy secondary to necrotizing granulomas. Lymphadenopathy and fever secondary to necrotizing granulomas can be a challenging clinical scenario. The differential diagnosis of necrotizing granuloma typically includes, but is not limited to, fungal or mycobacterial infections. Although bacteria such as *Brucella* spp. can cause necrotizing granulomas, they are often overlooked as causes of granulomatous lesions. When such bacteria represent a potential etiologic factor, a negative bacterial culture should be interpreted with caution, given that *Brucella* spp. are fastidious organisms. We also review various aspects of brucellosis, the most common zoonotic disease worldwide.

Case report

A previously healthy 22-year-old man was referred to our hospital with an 8-week history of cervical and mediastinal lymphadenopathy, fatigue, and intermittent fever. The patient reported no excessive sweating or weight loss. He had been living in Europe (in London) for one year, where he had been working as a chef, when his illness prompted him to return to Brazil.

On physical examination, we observed painless, rubbery bilateral anterior cervical lymph nodes, 2 cm in diameter, and a nonhealing sinus tract at the site of a previous fine needle aspiration that had been performed at another facility and had yielded an inconclusive result. There were no skin or oral lesions, the teeth were in good condition, and the patient had no respiratory

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complaints. A chest X-ray showed widening of the right paratracheal stripe, and a subsequent CT scan of the chest revealed enlarged mediastinal lymph nodes (Figure 1). The patient had a normal white cell count (6.5×10^9/L), with normal lymphocytes. His liver function was normal; an autoantibody panel was negative; he produced an induration of 20 mm (positive result) in response to a PPD skin test; and a cryptococcal antigen test was negative. In addition, serologic testing for HIV was negative, as were tests for histoplasmosis (immunodiffusion), toxoplasmosis (ELISA), tularemia (agglutination), and cat scratch disease (indirect fluorescence assay). An excisional cervical lymph node biopsy showed a suppurative (neutrophilic), necrotizing granulomatous lesion (Figure 2). However, on direct examination of the specimen, we identified no bacteria (Gram staining), fungi (Grocott methenamine silver staining), or acid-fast bacteria (Ziehl-Neelsen staining). Cultures for bacteria, mycobacteria, and fungi were also negative.

Despite the 20-mm PPD induration, mycobacterial infection does not typically present an exuberant inflammatory response manifesting as suppurative, necrotizing granulomatous lesions. Although the most common cause of such lesions is fungal infection, there have been reports in which suppurative, necrotizing granulomatous lesions have been attributed to infection with certain bacteria[1]: *Francisella tularensis* (tularemia); *Bartonella henselae* (cat scratch disease); *Actinomyces* spp.; *Burkholderia pseudomallei* (melioidosis); *Chlamydia trachomatis* (Lymphogranuloma venereum); and *Brucella* spp. (brucellosis).

A detailed history regarding exposures was taken. As a chef, the patient had a variety of gastronomic experiences during his stay in London and his travels around Europe (to Eastern Europe, Portugal, and Spain). He reported exposure to unpasteurized sheep cheese and to exotic raw meats. Therefore, we considered brucellosis a possible differential diagnosis. Because the bacterial culture results were negative, we employed PCR as an alternative method to reach the diagnosis. We performed PCR using primers targeting the *bcsp31* gene sequence for *Brucella* spp. (the B4/B5 primer pair) in urine. The PCR was positive for *Brucella* spp., which allowed us to confirm the suspected diagnosis of brucellosis, given that the histopathology, clinical history, and response to treatment (mentioned further on) were all consistent with that diagnosis.

Discussion

Brucellosis is a chronic granulomatous zoonosis caused by intracellular bacteria of the genus *Brucella*. It is transmitted to humans through contact with fluids from infected animals (especially through the consumption of mutton and beef, as well as of the milk of sheep and cows) or through direct contact with infected animal parts (such as the placenta, by inoculation through ruptures of skin and mucous membranes) or even by

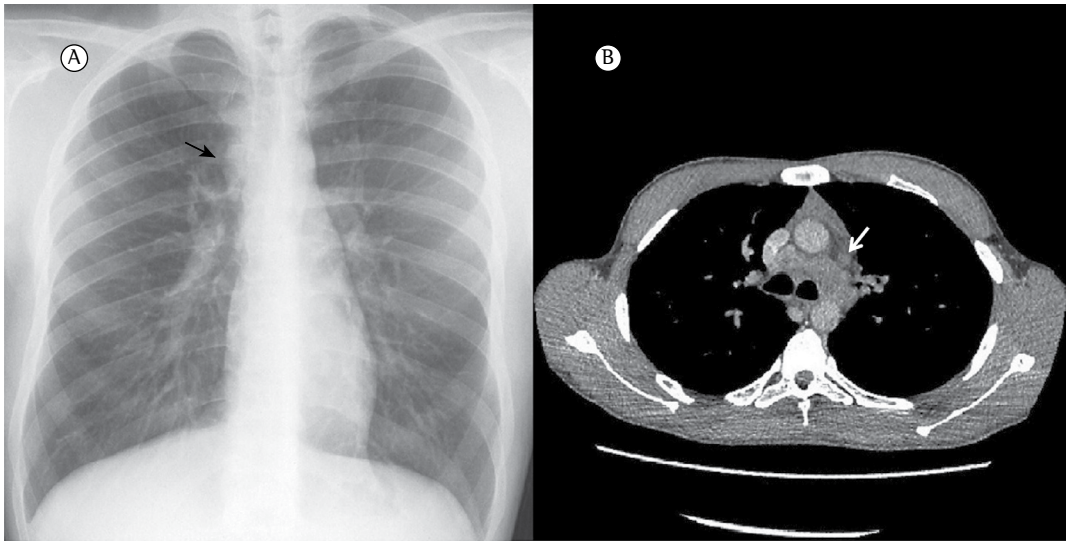

Figure 1 - (A) Chest X-ray, posteroanterior view, showing a widened paratracheal stripe (arrow). (B) High-resolution CT of the chest revealing enlarged mediastinal lymph nodes (arrow).

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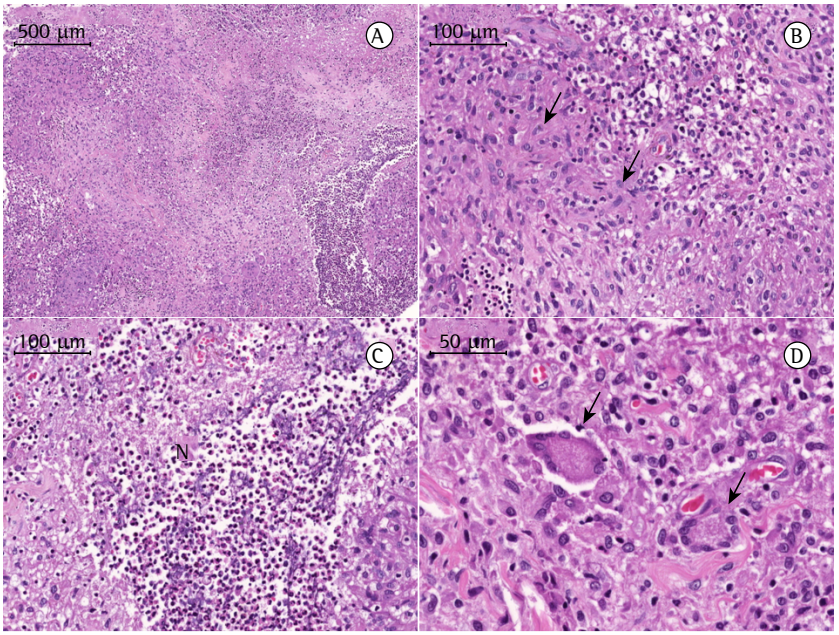

Figure 2 - Photomicrographs of a cervical lymph node biopsy sample. Lymphoid tissue is replaced by necrotizing granulomatous inflammation (panel A). Note palisading epithelioid cells (panel B, arrows), extensive neutrophil-rich suppurative necrosis (panel C, letter N), and scattered giant cells (panel D, arrows). Hematoxylin-eosin staining (magnification varies; see the scale bars displayed in the panels).

inhalation of aerosolized infectious particles.[2] Consumption of unpasteurized dairy products is the most common means of transmission.[2,3]

Human brucellosis is one of the most common zoonotic diseases worldwide. Although its epidemiology has drastically changed over the past decades and control of the disease has been achieved in a number of areas where it was traditionally endemic, the Mediterranean basin (around which our patient had been traveling) continues to be recognized as a region in which brucellosis is endemic.[3]

The wide spectrum of clinical manifestations of human brucellosis has earned it a place alongside syphilis and tuberculosis as one of the "great imitators". In patients with brucellosis, practically every organ and system of the human body can be affected. The physical examination findings are generally nonspecific, although lymphadenopathy, hepatomegaly, or splenomegaly is often present due to the tropism of *Brucella* spp. for the reticuloendothelial system. In addition, isolated lymphadenopathy is rare in human brucellosis. Because of the protean clinical manifestations, the cornerstone of making the clinical diagnosis of brucellosis is taking a detailed history and paying careful attention to epidemiological information. Special attention must also be paid to determining whether the patient has ingested contaminated dairy products or has been in contact with infected animals. Detailed patient interviews are crucial to making the diagnosis of human brucellosis, especially in urban and non-endemic areas, as well as when travelers acquire the disease abroad and become ill in non-endemic settings.[3,4]

The gold standard for the diagnosis of brucellosis is isolation of the bacteria from blood or tissue samples. Making a diagnosis of brucellosis can be quite challenging, because blood cultures or cultures of the tissue fragment are positive in only 15-70% of cases, as well as because the detection of *Brucella* spp. requires a prolonged incubation time.[5] Bone marrow cultures can increase the sensitivity by 15-20% over that of blood cultures.[4] However, in many cases, clinicians must use a wide range of nonspecific routine hematological and biochemical tests, together with *Brucella*-specific assays (serological and molecular techniques), in order to reach a definitive diagnosis.[6,7] Each of those tests has advantages and limitations, therefore requiring

careful interpretation of the results. Serological assays, which are mainly based on the identification of lipopolysaccharide antigens of *Brucella*, have high sensitivity but low specificity (as low as 64% in some reports), due to cross-reactivity with other bacterial species.[4,8] The fact that antibodies can be detectable for months after therapy further complicates the use of serological assays for the identification of relapse and reinfection. Nevertheless, a number of serological methods can be useful. One such method is serum agglutination testing, the modality for which there is the greatest amount of data in the literature. In an appropriate clinical scenario, a fourfold or greater increase in the *Brucella* agglutination titer between acute- and convalescent-phase serum samples, obtained ≥ 2 weeks apart, confirms a diagnosis of brucellosis. Absolute thresholds for serum agglutination testing should be individualized: positivity is defined as a titer of 1:160-1:320 in endemic regions and as a titer of 1:80 in non-endemic regions.[9] Other methods, such as ELISA, the direct antiglobulin (Coombs) test, and the immunocapture test, are available but do not seem to overcome the aforementioned problems.[9]

Another technique that has been increasingly used in the diagnosis of brucellosis is PCR. PCR is not a routine diagnostic method but can be performed on any clinical specimen and has been shown to have excellent sensitivity and specificity.[7,8,10-12] Genus-specific PCR targeting *bcsp31* seems to have greater sensitivity than do those targeting any other *Brucella* gene sequence available.[7] The sensitivity and specificity of PCR assays are both between 90% and 100%.[8,12] As in other infectious diseases, PCR testing is becoming an excellent alternative method for diagnosing brucellosis when standard methods have failed or are not available, especially when the clinical and histopathological aspects are consistent with the diagnosis.[9,13-15] A growing body of evidence indicates that PCR assays are accurate methods for the diagnosis of brucellosis, although there is a need for standardization before their widespread use as such can be recommended.

The goal of brucellosis treatment is the resolution of infection and the prevention of complications, relapses, and sequelae. The optimal treatment of uncomplicated brucellosis (without spondylitis, neurobrucellosis, or endocarditis) is based on a 6-week regimen of doxycycline, combined with streptomycin for 2-3 weeks or with rifampin for 6 weeks.[16] Although the streptomycin-containing regimen is slightly more efficacious in preventing relapse, parenteral administration of streptomycin complicates its use, and the doxycycline-rifampin regimen is therefore used more frequently, because of its convenience.[17,18] A 6-week regimen of quinolone plus rifampin is slightly more well tolerated than is that of doxycycline plus rifampin, and low quality evidence did not show any difference in overall effectiveness.[19] There is also some evidence that a three-drug regimen (involving the addition of trimethoprim-sulfamethoxazole to either of the abovementioned two-drug regimens, or a combination of streptomycin, rifampin and doxycycline) is an effective therapy in complex cases. Extended treatment (for at least 12 weeks) and the use of three-drug regimens should be considered in patients with complicated disease.[20]

In the case presented here, the patient was treated with doxycycline and rifampin. After 6 weeks, he presented complete resolution of fatigue and lymphadenopathy. At this writing, the patient has been followed for two years after the completion of treatment and there has been no evidence of relapse.

Our case illustrates a rare presentation of brucellosis, one of the most common zoonotic diseases worldwide. It also highlights the importance of taking a detailed epidemiological history as an important tool to guide clinicians to a correct diagnosis of infectious granulomatous diseases such as brucellosis.

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Congenital thoracic malformations in pediatric patients: two decades of experience

Malformações torácicas congênitas na infância: experiência de duas décadas

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To the Editor:

Congenital thoracic malformations constitute a heterogeneous group of developmental disorders, involving lung parenchyma, arterial supply, and venous drainage.[1] Their etiology is embryologic, and their clinical presentation and severity vary according to the degree of pulmonary involvement and their location in the thoracic cavity.[2] They can be asymptomatic—their diagnosis being based on incidental chest X-ray findings—or cause early and severe respiratory symptoms. [2,3] Although prenatal ultrasound has allowed intrauterine diagnosis of congenital thoracic malformations,[1,4] controversy remains regarding the nomenclature and treatment. Congenital thoracic malformations include pulmonary sequestration, congenital pulmonary airway malformations (formerly known as congenital cystic adenomatoid malformation), congenital lobar emphysema, bronchogenic cyst, congenital diaphragmatic hernia, diaphragmatic eventration, pulmonary vascular malformations, bronchial atresia, pulmonary hypoplasia, and pulmonary agenesis.[1] Chest X-rays can show localized hypertranslucency, cystic images, decreased volume in the right or left hemithorax, changes in the pulmonary vasculature, and condensation images. The objective of this letter is to report the clinical data and therapeutic management of patients with congenital thoracic malformations followed in the Pediatric Pulmonology Department of the Federal University of Bahia University Hospital, in the city of Salvador, Brazil, between 1991 and 2013.

This was a retrospective observational study (case series) of 26 patients with congenital thoracic malformations diagnosed radiologically, surgically, or both. Each medical chart was systematically analyzed. The study was approved by the local research ethics committee.

All patients had undergone chest X-rays. The presence of congenital thoracic malformations was confirmed by chest CT scans, in 24 children, and by contrast-enhanced examination of the esophagus, stomach, and duodenum, in 2 children. The following malformations were found: congenital lobar emphysema, in 6; pulmonary agenesis, in 5; congenital pulmonary airway malformations, in 4; pulmonary hypoplasia, in 3; cystic disease, in 2; congenital diaphragmatic hernia, in 2; bronchogenic cyst, in 1; lobar agenesis, in 1; pulmonary vascular malformations, in 1; and diaphragmatic eventration, in 1. Pulmonary agenesis is very rare, having occurred in 5 patients; of those, 4 had right lung agenesis, which is consistent with the literature,[5] with only 1 asymptomatic child. None of the patients had been diagnosed with pulmonary sequestration.

Of the 26 patients studied, 14 (53.8%) were male. All of the patients with congenital lobar emphysema were male, which is consistent with the literature.[6] Pulmonary agenesis and pulmonary hypoplasia were more common in female patients, which is inconsistent with the literature. Pulmonary agenesis was found in only 1 male patient.

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The mean age at diagnosis was 12.4 months (range: 0-120 months). Although prenatal diagnosis of congenital thoracic malformations has increased, only 3 patients had been diagnosed prenatally. This demonstrates the need for improving prenatal care.

Most of the patients with congenital thoracic malformations in the present study were symptomatic; that is, 22 (84.6%) of the 26 patients studied had at least one symptom (dyspnea, wheezing, tachypnea, or cyanosis). Of the symptomatic patients, 21 (95.4%) were symptomatic in the first year of life. Recurrent pneumonia occurred in 6 children, being more common in those with cystic disease (found on imaging studies).

Pulmonary agenesis (particularly right lung agenesis) can be associated with other congenital abnormalities.[5] Of the 26 patients studied, 11 had other malformations, including facial dysmorphism, heart disease, clubfoot, bilateral deafness, umbilical hernia, and inguinal hernia. All of the patients with pulmonary agenesis had other malformations, one of the patients having multiple birth defects and an incidental diagnosis of congenital thoracic malformation at the age of 7 months.

Abnormal development of the aortic arch during embryogenesis—which was not observed in the present study—results in pulmonary hypoplasia,[5] which in turn is a consequence of congenital diaphragmatic hernia. One patient had decreased pulmonary vascularization.

The only case of lobar agenesis involved the left upper lobe, with no other malformations. The patient was treated conservatively.

Pulmonary vascular malformations are characterized by abnormal communication between the pulmonary artery and vein, leading to right-to-left shunt.[7] The main symptoms are dyspnea, palpitation, fatigue, and epistaxis.[8] The patient who had pulmonary vascular malformations had recurrent pneumonia, which resolved after surgical treatment.

Congenital diaphragmatic hernia is a developmental defect of the diaphragm that allows abdominal viscera to reach the thoracic cavity. It usually causes symptoms at birth. In the present study, the 2 patients with diaphragmatic hernia were asymptomatic—which is very rare—having been diagnosed at ages 3 and 10 years. Both were referred for surgical correction.

Diaphragmatic eventration results from a congenital structural defect or phrenic nerve injury, which can be iatrogenic or due to traction during birth.[9] Although diaphragmatic eventration is usually asymptomatic, it can cause dyspnea and respiratory infection in infants.[9] The patient with diaphragmatic eventration presented with tachypnea, and the radiological findings were mistaken for pneumonia. The patient was asymptomatic after surgical correction.

Cystic disease is one of the most common congenital thoracic malformations.[2] In the present study, it was observed in 7 patients, 5 of whom underwent surgery. Of those 5 patients, 4 had congenital pulmonary airway malformations and 1 had bronchogenic cyst. Although congenital pulmonary airway malformations are more common in boys,[2] they were observed in two girls and two boys in the present study. After surgical treatment, 3 patients were classified as having type I malformation, i.e., large cysts (2-10 cm in diameter)—the most common type—and 1 was classified as having type II malformation, i.e., small cysts (0.5-2 cm in diameter). Figure 1 shows X-ray and CT findings of a child diagnosed with type I congenital airway malformations.

Bronchogenic cyst is a benign, congenital mediastinal malformation whose natural course is undefined; malignant transformation can occur in adults.[10] Although bronchogenic cyst is often asymptomatic, secondary infection and complications can occur.[10] One of the patients with cystic disease had recurrent pneumonia; after surgery, the presence of bronchogenic cyst was confirmed (Figure 2).

Congenital lobar emphysema results from bronchial or alveolar changes.[6] Although lobectomy is indicated for symptomatic patients, there is uncertainty regarding the treatment of asymptomatic patients.[6] In the present study, 4 patients with severe symptoms underwent lobectomy. All 4 had left upper lobe involvement, including the patient with bilateral disease (i.e., right and left upper lobe involvement). The two patients who were managed conservatively had right and left upper lobe lesions, respectively, and remained asymptomatic at follow-up.

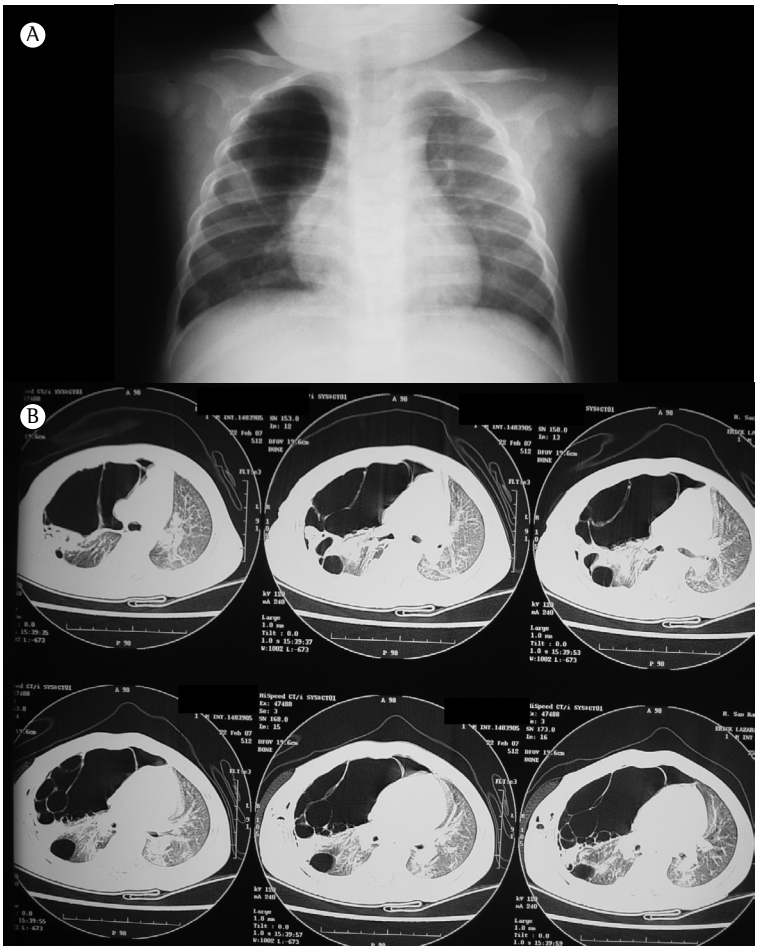

Figure 1 - Chest X-ray and CT scans of a 5-month-old patient with respiratory distress. In A, chest X-ray showing hypertranslucency in the right upper lobe, without mediastinal shift. In B, chest CT scans showing cystic images of varying sizes in the right upper lobe. The patient underwent right upper lobectomy. Histopathological examination confirmed the presence of congenital pulmonary airway malformation.

Most of the patients who underwent surgery progressed well. One patient had sepsis 48 h after having undergone lobectomy but responded favorably to antibiotic therapy. The only death was due to pneumonia, having occurred in the patient with pulmonary agenesis.

There is no consensus regarding the treatment of congenital thoracic malformations.[1] In some centers, surgical treatment is recommended for symptomatic patients only.[4] In others, early surgical resection is recommended in all cases because of the risk of complications.[1,4] Some authors recommend conservative treatment for asymptomatic patients because of the lack of data on long-term complications.[1] In the present study, asymptomatic or mildly symptomatic patients were treated conservatively.

Congenital lobar emphysema, pulmonary agenesis, and congenital pulmonary airway malformations were the most common congenital thoracic malformations in the study sample. Most of the patients had early symptoms, the most common clinical manifestations being respiratory distress and recurrent pneumonia. Regardless of the approach used, the prognosis was excellent.

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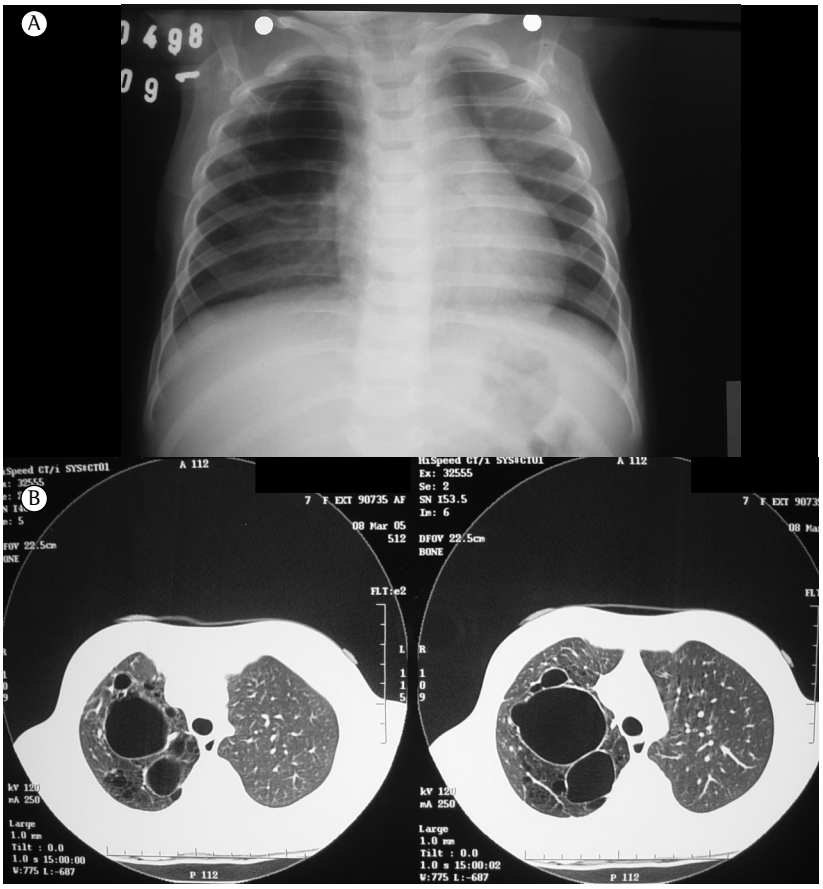

Figure 2 - Chest X-ray and CT scans of a patient with a prenatal diagnosis of cystic lung disease. In A, posteroanterior chest X-ray (taken at age 6 months) showing cystic images in the right upper lobe. In B, chest CT scans showing cystic images of varying sizes in the right upper lobe. The patient underwent right upper lobectomy. Histopathological examination confirmed the presence of bronchogenic cyst.

would also like to thank all of the surgeons who treated the patients studied.

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Cutaneous tuberculosis as metastatic tuberculous abscess

Tuberculose cutânea como abscesso tuberculoso metastático

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To the Editor:

Cutaneous tuberculosis (CTB) continues to be one of the most difficult diagnoses to make because of the wide variations in its clinical appearance, histopathology, immunology and treatment response.[1,2] The incidence of this disease has increased in the 21st century, due to a high incidence of HIV infection and multidrug-resistant pulmonary tuberculosis.[3,4]

Although CTB accounts for only 1.5% of all cases of extrapulmonary tuberculosis and 0.15% of all cases of skin disease, given the high prevalence of tuberculosis in many countries, these numbers are significant.[1,2] *Mycobacterium tuberculosis*, *M. bovis*, and the BCG vaccine can all cause CTB.[5]

In most cases, tuberculosis is transmitted via the airborne route, and skin manifestations are a result of hematogenous spread or direct extension from a focus of infection. However, primary inoculation can occur through direct introduction of the mycobacteria into the skin or mucosa of a susceptible individual by trauma or injury. The risk increases in the presence of HIV infection, intravenous drug abuse, diabetes mellitus, immunosuppressive therapy, malignancy, end-stage renal disease, or infancy.[5,6] Albeit a rare sign, CTB should be considered in the differential diagnosis of skin lesions, especially in individuals with a history of tuberculosis.

A 68-year-old male presented with a six-month history of weight loss and asthenia. He was a retired factory worker and former smoker, with a history of pulmonary tuberculosis in his youth (two distinct episodes, 20 years apart, the treatment regimens employed in those episodes being unknown), schizophrenia, osteoarticular pathology, and reflux esophagitis. The patient also presented with two anterior thoracic skin swellings (22 × 60 cm and 80 × 30 cm, respectively) that were painful on palpation, with an elastic consistency and without local warmth on the overlying skin (Figure 1). He reported that the swellings had first appeared one month earlier. He reported no fever or respiratory complaints. No lymph nodes were detected. A CT scan of the chest showed two liquid collections in the anterior chest wall, with a dystrophic aspect, together with thickening of the costal arch and the adjacent costal cartilage.

Diagnoses such as staphylococcal abscess, mixed bacterial infection, nocardiosis, atypical mycobacterial infections, and deep fungal infections were considered. A biopsy of one of the swellings showed granulation tissue with lymphocytes, plasma cells, and histiocytes, with suppurative areas and a fistulous tract. In sputum smears, staining for AFB was negative, although a PCR of a sputum sample was positive for *M. tuberculosis*. Serology for HIV was negative. The patient was referred to a center for the treatment of thoracic diseases, for evaluation and treatment.

Another CT scan of the pulmonary parenchyma revealed some fibrotic changes in both lung apices. Sputum smear staining for AFB was again negative, although a culture of the biopsy sample was positive for *M. tuberculosis*. Drug susceptibility testing showed that the strain was susceptible to isoniazid and rifampin, as well as to all of the first-line antituberculosis drugs tested.

The patient was started on four antituberculosis drugs, at doses adjusted for body weight—isoniazid (300 mg/day); rifampin (600 mg/day); pyrazinamide (1,500 mg/day); and ethambutol (1,000 mg/day).

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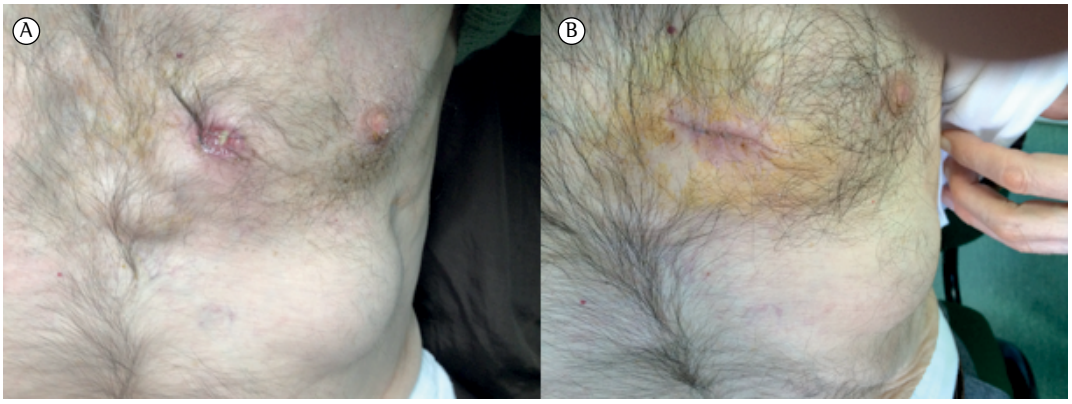

Figure 1 - Before and after treatment (photographs on the left and right, respectively).

Psychiatric evaluation was requested in order to adjust the regimen of treatment to take the schizophrenia into account. After two months of treatment, the tuberculosis treatment regimen was reduced to two drugs—isoniazid (300 mg/day) and rifampin (600 mg/day). At this writing, the patient has completed six months of treatment without major side effects and the skin lesions have improved (Figure 1).

The description of CTB includes dermatological manifestations of tuberculosis involving the skin, and early classifications of this disease were based on lesion morphology.[1,3,5] In patents with CTB, skin lesions are characterized by granulomatous inflammation, varying degrees of necrosis, and varying degrees of vasculitis; *M. tuberculosis* is identified by special staining, culture, or PCR.[3,5,6]

Despite being clinically similar, individual CTB lesions can present with different development, progression, and prognosis. On the basis of that knowledge, Tappeiner & Wolff proposed the most widely accepted CTB classification system, which is based on the mechanism of propagation—exogenous versus endogenous dissemination.[3,5] Exogenous inoculation occurs after the direct inoculation of *M. tuberculosis* into the skin of a person who is susceptible to infection. Endogenous infection occurs in patients who were previously infected. Exogenous transmission is significantly less common.[5] After that first classification, other authors introduced the concept of bacterial load, which is used in order to differentiate between the multibacillary form (in which mycobacteria are easily identified on histological examination) and the paucibacillary form (in which isolation of mycobacteria in culture is rare).[1,3,5] Chart 1 summarizes those two classification systems.

Here, we have reported the case of a patient ultimately diagnosed with metastatic tuberculous abscess, also known as tuberculous gumma, which is normally due to hematogenous spread of mycobacteria that remain latent until, for some reason (e.g., immunosuppression or malnutrition), the infection manifests itself, malnutrition being the probable trigger in our case. This form of CTB is characterized by non-tender and fluctuant subcutaneous abscesses, appearing as single or multiple lesions on the trunk, extremities, or head, which often invade the skin and break down.

Although making a clinical diagnosis of CTB is not always easy, it should be considered in all cases of chronic skin lesions, mainly in HIV-infected patients and in patients with history of pulmonary tuberculosis.[6] The differential diagnosis includes staphylococcal abscess, other mixed bacterial infections, sporotrichosis, nocardiosis, chromomycosis, leishmaniasis, atypical mycobacterial infections, deep fungal infections, syphilitic gumma, leprosy, and all forms of panniculitis.[2]

Supporting evidence for the clinical presentation includes epidemiological data, history of tuberculosis or contact with a tuberculosis patient, and histology (skin biopsy in most cases). Histology must include sputum smear testing for AFB, PCR, and culture for *M. tuberculosis*.[1-3,5,6] Isolating *M. tuberculosis* in culture is the only way to make a definitive diagnosis.

Tuberculous gumma is a multibacillary form of CTB that can occur without any underlying source of tuberculosis. Histology of CTB lesions reveals massive necrosis and abscess formation. Staining for AFB usually shows large quantities of mycobacteria.[1,3]

Chart 1 - Classifications for cutaneous tuberculosis.

Classification 1		
Mechanism of propagation	Dissemination	Types of lesions
Exogenous		Tuberculous chancre
		Tuberculosis verrucosa cutis
		Lupus vulgaris
Endogenous	Contiguous	Scrofuloderma
		Orificial tuberculosis
	Hematogenous	Acute miliary tuberculosis
		Metastatic tuberculous abscess
		Papulonecrotic tuberculid
		Lupus vulgaris
	Lymphatic	Lupus vulgaris
Classification 2		
Form	Type of lesion	
Multibacillary	Tuberculous chancre	
	Scrofuloderma	
	Tuberculosis orificialis	
	Acute miliary tuberculosis	
	Metastatic tuberculous abscess (tuberculous gumma)	
Paucibacillary	Tuberculosis verrucosa cutis	
	Lupus vulgaris	
	Tuberculids	

The antituberculosis drug regimens used in the treatment of pulmonary tuberculosis are adequate for treating CTB, because the bacillary load in CTB is usually much smaller than that occurring in pulmonary tuberculosis.[3,7,8] This include regimens of directly observed therapy, and the standard treatment regimen involves two months of quadruple therapy (isoniazid, rifampin, pyrazinamide, and ethambutol) followed by four months of double therapy (isoniazid and rifampin).[1]

It is extremely important to determine the past history of tuberculosis, given that patients with such a history are more likely to be infected with a strain of mycobacterium that is resistant to antituberculosis drugs. In the case presented here, a culture of the biopsy specimen was positive for *M. tuberculosis*, and drug susceptibility testing showed susceptibility to all of the first-line drugs tested. Surgical excision is sometimes necessary, not only as a diagnostic method, but also as an adjunct to pharmacological therapy.[4] A clinical response should be expected between weeks 4 and 6 of treatment,[1] as was observed in our case.

Although uncommon, CTB should be kept in mind in the differential diagnosis of skin lesions.

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Tracheobronchomalacia in a patient on invasive mechanical ventilation: the role of electrical impedance tomography in its detection and positive end-expiratory pressure titration

Traqueobroncomalácia em paciente sob ventilação mecânica invasiva: o papel da tomografia de impedância elétrica na sua detecção e na titulação da pressão expiratória final positiva

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To the Editor:

Tracheobronchomalacia (TBM) is a disorder caused by weakness of the tracheal and bronchial walls, together with softening of the supporting cartilage, resulting in excessive expiratory collapse.[1] Although some individuals with TBM are asymptomatic, others present with symptoms such as dyspnea, hemoptysis, wheezing, and chronic cough.[1-3] Because the symptoms are nonspecific, TBM can be easily overlooked or misdiagnosed as other obstructive airway diseases, including asthma and COPD.[4]

In TBM patients with acute respiratory failure, noninvasive ventilation is a therapeutic option, because positive end-expiratory pressure (PEEP) can prevent airway collapse.[5-7] Kandaswamy et al.[8] reported that, among patients with respiratory distress who failed weaning from mechanical ventilation or required reintubation in the ICU, the prevalence of TBM, identified on CT scans of the chest acquired only days before intubation, was 1.6%. However, to our knowledge, there have been no reports of TBM being diagnosed during invasive mechanical ventilation.

Electrical impedance tomography (EIT) is a noninvasive, radiation-free monitoring tool that provides real-time imaging of ventilation at the bedside. Here, we report a case in which the combination of CT and EIT scans of the chest allowed us to make the diagnosis of TBM and to determine the best PEEP titration for preventing airway collapse in an intubated patient.

A 66-year-old female was admitted to the emergency room complaining of breathlessness. She had a history of recurrent episodes of wheezing and dry cough, both of which partially improved after treatment with aminophylline and inhaled short-acting bronchodilators. Her past medical history included orotracheal intubation, for severe bronchospasm, five years prior. She reported no fever, sputum production, or other symptoms. She stated that she had not been exposed to any inhaled allergens, had no known allergies, and had no family history of asthma. She reported that she was not a tobacco user but had long been exposed to biomass smoke from cooking.

On physical examination, she was in respiratory distress, presenting with accessory muscle use, her RR was 28 breaths/min, and her SpO_2 was 96% while breathing room air. Examination of the lungs revealed prolonged expiration and diffuse wheezing.

The results of the radiographic assessment and laboratory exams were unremarkable. Partial symptomatic relief was achieved after inhalation therapy with ipratropium bromide and fenoterol, together with intravenous hydrocortisone. She was discharged home but returned to the emergency room with bronchospasm minutes later. Although she was then treated with additional doses of inhaled bronchodilators, as well as intravenous magnesium sulfate, her dyspnea worsened. A few hours later, she became comatose, requiring orotracheal intubation and admission to the ICU.

At ICU admission, the patient was deeply sedated with fentanyl and midazolam, was started on inhaled albuterol (400 μg/h), received

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intravenous hydrocortisone (200 mg every 6 h), and was started on continuous cisatracurium infusion. Respiratory mechanics were measured during volume-controlled ventilation; the PEEP was set at 5 cmH_2O; the FiO_2 was set at 40%; the RR was 12 breaths/min; the flow rate was set at 60 L/min; the inspiratory pause duration on plateau pressure was 2 s; and the tidal volume (10 mL/kg) revealed low lung compliance (26 mL/cmH_2O), high airway resistance (24 cmH_2O/L/s), and an intrinsic PEEP of 8 cmH_2O. The expiratory flow curve was indicative of airway obstruction (Figure 1). Chest X-rays performed 24 and 48 h after ICU admission showed atelectasis of the left lower lobe and of the right lower lobe, respectively, without any differences between the two time points, in terms of the ventilatory parameters.

At 48 h after ICU admission, an HRCT scan of the chest showed bilateral small pleural effusions with partial lower lobe atelectasis, and a reduction in the cross-sectional diameters of the trachea and main bronchi, mainly in the subsegmental divisions of the lower lobes, bilaterally, all of which is consistent with a diagnosis of TBM (Figure 1). On the basis of that working hypothesis, the patient was maintained on pressure-controlled ventilation and the PEEP level was changed from 5 cmH_2O to 15 cmH_2O, all other parameters remaining unchanged. The wheezing on auscultation suddenly disappeared, tidal volume increased from 227 mL to 398 mL, and the shape of the expiratory flow curve dramatically improved, no longer indicating flow limitation (Figure 1).

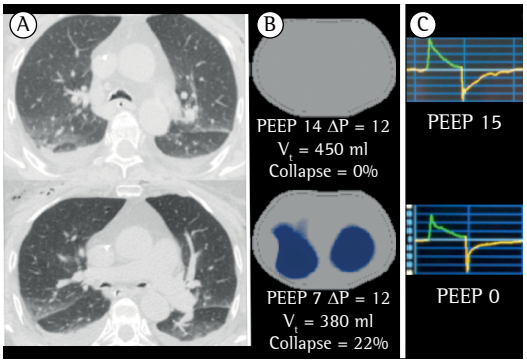

Figure 1 - In A, an HRCT scans of the chest showing bilateral small pleural effusions with partial lower lobe atelectasis, and a reduction in the cross-sectional diameters of the trachea and main bronchi, mainly in the subsegmental divisions of the lower lobes, bilaterally; in B, electrical impedance tomography scans showing that the use of a higher PEEP prevented airway collapse an expiratory flow curve indicative of airway obstruction; in C, an expiratory flow curve indicative of airway obstruction and a dramatically improved expiratory flow curve, no longer indicating flow limitation, after an increase in the positive end-expiratory pressure (PEEP).

In order to choose the PEEP level that would represent the best compromise—maintaining airway patency while avoiding lung overdistension—we titrated PEEP with EIT (Table 1). After a lung recruitment maneuver, we kept a constant driving pressure of 15 cmH_2O and decreased the PEEP level by 2 cmH_2O every 2 min until we reached a PEEP of zero. The PEEP level that allowed minimal lung overdistension and prevented airway collapse was 12 cmH_2O (Figures 1D and 1E).

The patient showed considerable improvement in her ventilation parameters. However, because of difficult weaning, she was tracheostomized at discharge.

The conventional approach to detecting TBM is by fluoroscopy or through direct observation on bronchoscopy, in which a narrowing of > 50% in the sagittal diameter of the trachea is considered diagnostic of the disorder.[4] Expiratory CT scans have been validated as a method to evaluate collapse of the airways, a 50% expiratory reduction in the cross-sectional area of the airway lumen being considered diagnostic of TBM in symptomatic individuals.[4,9-11] Although we cannot guarantee that, in the case presented here, the CT scan was obtained at full expiration, the clinical history and CT findings were highly suggestive of TBM. Our patient had also undergone bronchoscopy during a percutaneous tracheotomy performed in the ICU, with sedation and muscle paralysis. However, a detailed evaluation of the respiratory dynamics was not possible, because the patient was not breathing spontaneously.

Previous reports have addressed the importance of noninvasive ventilation to maintaining airway patency, decreasing pulmonary resistance,

Table 1 - Titration of positive end-expiratory pressure and the corresponding tidal volumes.

PEEP (cmH_2O)	V_T (mL)
13	450
11	440
9	420
7	380
5	327
3	230
ZEEP	144

PEEP: positive end-expiratory pressure; V_T: tidal volume; and ZEEP: zero end-expiratory pressure.

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improving expiratory airflow obstruction, and reducing the inspiratory transpulmonary pressures required to initiate airflow, thus decreasing the work of breathing.[5-7] To our knowledge, this is the first study to address the use of EIT in the ventilatory management of TBM in patients on invasive mechanical ventilation. The respiratory flow curves seen after we increased the PEEP helped show the importance of PEEP as a pneumatic stent to open the previously collapsed airways. In addition, the use of EIT allowed the bedside diagnosis of TBM and the titration of the PEEP. It is noteworthy that EIT was extremely helpful in that it informed decisions regarding changes in the ventilatory strategy, because high PEEP levels are not desirable in patients with obstructive lung disease, who are at a high risk for the development of dynamic hyperinflation. Coincidentally, the PEEP level that was set empirically was similar to that determined to be ideal based on the EIT analysis.

The lability of airway opening and closing in TBM predisposes patients to severe bronchospasm crises that are refractory to conventional therapy. Even for pulmonologists and critical care physicians, the diagnosis of TBM is a challenge. Therefore, it should be included in the differential diagnosis of refractory bronchospasm in ICU patients presenting with predisposing factors for TBM.

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Cutaneous focal mucinosis of the scalp and adenocarcinoma of the lung: association or coincidence?

Mucinose cutânea focal do couro cabeludo e adenocarcinoma do pulmão: associação ou coincidência?

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To the Editor:

Here, we present the case of a 62-year-old patient presenting with a three-month history of asymptomatic, flesh-colored, infiltrated plaques on the fronto-occipital scalp (Figure 1). The patient had a history of dyslipidemia and hypertension but reported no changes in medication in the last two years. Serial histopathological examination of the scalp plaques (over a two-year follow-up period) showed moderate dermal lymphocytic infiltrate with homogeneous deposition of mucin in the dermis. There were no alterations of the epidermis or pilosebaceous units, no eosinophils, no epidermotropism, and no granulomas (Figures 2A and 2B). Staining with Alcian blue showed mucin deposits arranged homogeneously in the dermis (Figure 2). The physical examination and the results of extensive laboratory tests (including serum and urine protein immunoelectrophoresis, auto-antibody screening, as well as tests of thyroid, liver, and renal function) were normal. A chest X-ray showed a mass in the upper lobe of the left lung. On the basis of the results of a CT scan and positron emission tomography scans (Figures 2C and 2D), the patient was diagnosed with primary adenocarcinoma of the lung. Examination of a transthoracic biopsy sample resulted in the tumor being classified as stage IIIA (T4N0M0). The patient was referred for cardiothoracic surgery (neo-adjuvant chemotherapy plus surgery with curative intent). At this writing (six months after surgery), there were no signs of recurrence of the adenocarcinoma and no new skin lesions, as well as slight improvement of the existing lesions.

Cutaneous focal mucinosis presents a histological reaction pattern, described in several diseases, in which abnormal focal deposition of mucin is found in the dermis. Cutaneous mucinosis can be classified in several ways: either primary or secondary to an associated disease (including malignancies, connective tissue disorders, and other reactive disorders); by the type of mucin; or by the pattern of distribution of the mucin (focal, follicular, or diffuse). The mucin can also be classified as epithelial or dermal, the two types differing in their composition, as well as in the staining techniques required in order to identify them. Epithelial mucins contain neutral and acid glycosaminoglycans and are hyaluronidase-resistant. They stain positively with periodic acid-Schiff and with Alcian blue at pH 2.5 but fail to stain with toluidine blue. Dermal mucins are periodic acid-Schiff-negative, show metachromatic purple staining with toluidine blue at pH 4.0, stain with Alcian blue at pH 2.5, and are hyaluronidase-sensitive.[1]

The etiology of cutaneous focal mucinosis is unknown. It is hypothesized to be a fibroblast disorder in which cytokines or immunoglobulins increase the synthesis of glycosaminoglycan by fibroblasts. The association with malignant disorders, as in our case, might be attributable to cytokine stimulation of fibroblasts and to tumor production of growth factors.[1] We conducted an extensive search of PubMed and found no other reports of cases of adenocarcinoma of the lung accompanied by cutaneous mucinosis.

In cases of focal mucinosis of the scalp, the differential diagnosis should include follicular mucinosis (not always present in alopecia) and mycosis fungoides. In the follicular subtype of mucinosis, the mucin is in the outer root sheath epithelium and sebaceous glands, with lymphocytic

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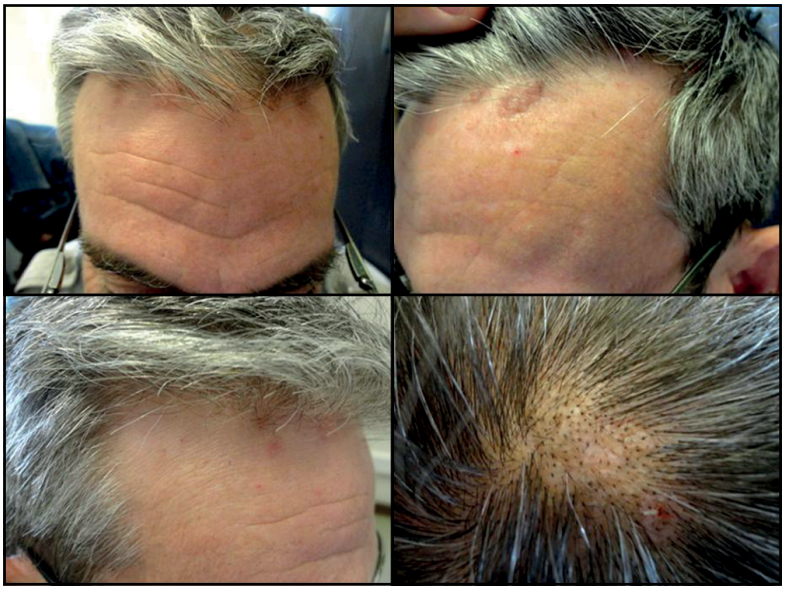

Figure 1 - Asymptomatic, flesh-colored, infiltrated plaques, located on the fronto-occipital scalp, which developed over a period of three months.

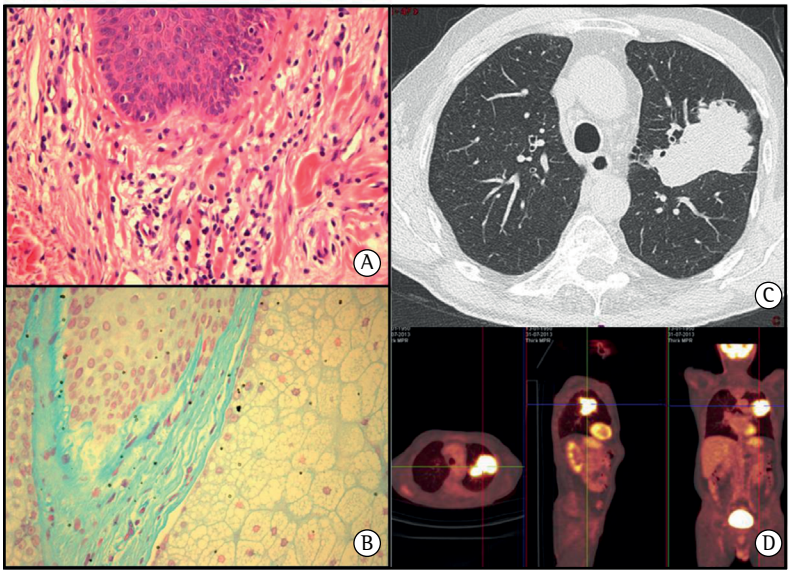

Figure 2 - Photomicrographs showing the results of the histopathological staining with H&E (magnification, ×40) and Alcian blue (magnification, ×40), in A and B, respectively. Note the homogeneous deposition of mucin (stained blue) in the dermis, with no alterations of the epidermis or pilosebaceous units, no eosinophils, no epidermotropism, and no granulomas. In C and D, respectively, a CT scan and positron emission tomography scans showing a primary adenocarcinoma in the upper lobe of the left lung.

infiltrate that is folliculotropic.[2] The deposition of mucin itself is rarely prominent, and it is thought that T cells stimulate the production of mucin by keratinocytes. In the case presented here, we detected mucins only in the dermis and the lymphocytic infiltrate was not folliculotropic.

Treatment for secondary cutaneous focal mucinosis requires treatment of the underlying disease. Although various therapeutic approaches have been tested in cases of primary cutaneous mucinosis, there is no consensus regarding the first-line therapy. Recent studies have indicated

that the disease has a chronic course, with recurrent or persistent lesions, in the majority of patients.[3] There is anecdotal evidence of the effectiveness of a number of therapies[4]: topical, intralesional, and systemic steroids; topical retinoids; systemic isotretinoin; dapsone; interferon; hydroxychloroquine and cyclophosphamide; methotrexate; psoralen plus ultraviolet A; antihistamines; minocycline; superficial X-ray radiation; photodynamic therapy; and pimecrolimus.

Cutaneous focal mucinosis can have a broad spectrum of clinical presentations. We presented this case in order to illustrate an unusual presentation of cutaneous focal mucinosis of the scalp (without follicular involvement) and to call attention to the importance of ruling out secondary associated malignant disorders, principally in elderly patients, in whom long-term follow-up can be required. To our knowledge, this is the first report of the combination of cutaneous focal mucinosis and adenocarcinoma of the lung.

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Abstracts

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

Chapter in a Book

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

Official Publications

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

Theses

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

Electronic publications

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

Homepages/URLs

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Custo Zero para seu paciente[1]

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

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

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

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