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HIGHLIGHT

The 40th anniversary of the JBP

Update on diagnosis and treatment of idiopathic pulmonary fibrosis

Inhalation therapy in mechanical ventilation

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

XXXVIII CONGRESSO BRASILEIRO DE PNEUMOLOGIA E TISIOLOGIA
IX CONGRESSO LUSO-BRASILEIRO DE PNEUMOLOGIA
XIV CONGRESSO BRASILEIRO DE ENDOSCOPIA RESPIRATÓRIA

REALIZAÇÃO

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Jornal Brasileiro de Pneumologia: forty years of history

Manuel Lopes dos Santos
Editor-in-Chief of the Journal of Pulmonology from 1975 to 1976.

The Brazilian Society of Pulmonology, founded in 1974, had various objectives, primarily to increase awareness of the specialty, to promote the exchange of new knowledge, and to publish the scientific production of pulmonologists working in Brazil. Therefore, we founded the Journal of Pulmonology, which would have to have, at its core, high quality technical and scientific content, with a view toward its later indexing as a scientific journal. It fell to me to be the first Director of the Journal. It is easy to imagine the various difficulties that had to be overcome for its publication to occur: the scarcity of economic resources, the obstacles to efficient communication, and the lack of computerization. Another problem to be overcome was related to the material to be published. To give the reader an idea of those difficulties, I paraphrase my editorial published in volume 2, issue 4 [1]:

> *"The three issues already published have given personality to the Journal, which has taken shape as a journal of high technical quality. However, it appears that our fellow pulmonologists do not like to publish. The current issue is, again, predominantly representative of the state of São Paulo. We hope that the upcoming conference in the city of Salvador will get them excited about writing and publishing, gracing our journal with their manuscripts, and that the new Director has no difficulty in obtaining quality scientific material for publication and does not need to explain the apparent provincialism of the official organ of the Brazilian Society of Pulmonology."*

The Brazilian Journal of Pulmonology has now gone far beyond its original goals. Having been indexed for SciELO and for MEDLINE/PubMed, the Journal is read and cited by those who are interested in the field of pulmonology. The various directors/editors who have followed me have succeeded, despite the hard work involved, in making it a vehicle that is widely and quite effectively distributed.

The Brazilian Journal of Pulmonology is celebrating its 40th anniversary this year. Congratulations! As the poet said: "Was it worth it? Everything is worth it if the soul is not too small."[a]

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[a] From "Mar Português" (Portuguese Sea) by the Portuguese author Fernando Pessoa.

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EDITORIAL

Jornal Brasileiro de Pneumologia: 40 years of tradition

Nelson Morrone
Editor-in-Chief of the Journal of Pulmonology from 1990 to 1994.

For humans, turning forty is almost a cause for despair, because it signals the end of youth as well as a less brilliant future. For a medical journal, however, 40 years of existence means that it has had a satisfactory history, and that, more importantly, it will have an increasingly bright future.

The Brazilian Journal of Pulmonology (BJP), which is celebrating its 40th anniversary, stands out today for a number of reasons, chief among which is that it disseminates research conducted by Brazilian and international experts. This internationalization reflects the maturity and dissemination power of the Journal. One important contribution to that internationalization, as well as to attracting researchers working in Brazil, was our acceptance for indexing by LILACS, PubMed/MEDLINE, and other databases. The online publication of all articles, in Portuguese and in English (in-house translation by the BJP), in parallel with the publication of a print version, in Portuguese, English, or Spanish, depending on the language of submission, is an invaluable achievement and confers considerable prestige. Changing the name of our Journal from the *Jornal de Pneumologia* (Journal of Pulmonology) to the *Jornal Brasileiro de Pneumologia* (Brazilian Journal of Pulmonology) undoubtedly made a considerable contribution to the prestige it currently enjoys.

Another truly important aspect of the BJP is that, unlike many publications, its online version is available for free. It therefore differs from other scientific journals in that it is not a source of revenue for the professional society that sponsors it—in our case the Brazilian Thoracic Association. This is clearly an important contribution to medical knowledge, with obvious advantages for patients, distinguishing our Journal from those that charge a fee for viewing an article.

The greatness of the BJP reflects the fact that numerous initial difficulties were surmounted, many by progress in general and other by advances in the field of information technology. For example, I remember that the government financed the publication of our Journal by providing an annual stipend, which was constantly devalued by inflation, and that we were prohibited from investing those funds. The reporting of expenditures was an onerous chore, given that even postage stamps had to be accounted for (a point of curiosity: a few years after leaving the BJP, I was fined by the tax authority because R$3.00, which is currently equivalent to less than US$1.00, had not been accounted for). This nuisance ended when we began to purchase a year's worth of printing paper all at once. Selling advertising space usually required the collaboration of several colleagues who had access to laboratories, given that the laboratories had little faith in the dissemination power of the BJP. It also should be noted that advertisements were not (and still are not) placed amid the scientific articles in the BJP.

The process of reviewing articles for publication was quite cumbersome, given that the articles were physically delivered to the Journal as hard copies, in at least quadruplicate (originals or photocopies), which then had to be mailed to at least three reviewers. In general, the review process took a few months per article. Today, it takes much less time. Long live the Internet!

The BJP was not always the journal of choice for Brazilian researchers wanting to publish their papers. Therefore, the availability of articles was not always ideal. To overcome that difficulty in the early days, considerable space was allocated to the publication of continuing education pieces, in various sections, in successive issues. However, the failure of some invited authors to meet their deadlines had a negative impact on the periodicity of the BJP. It was therefore decided that review articles would be written mostly by invitation, although unsolicited review articles were also welcome, and would be published in a single issue.

After the material had been fully reviewed and approved, it also took it a few weeks to be published because of technical difficulties involving the printing company the Journal was using at the time. Mailing was another cause of considerable delay. I get chills when I remember that, at the time, one of the directors (Dr. Bogossian) would spend hours at the post office.

The difficulties that have been overcome, some during my time at the journal and some during the terms of subsequent editors, are justification enough for continuing the tradition that is the BJP.

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Jornal de Pneumologia 1995-1998

Carlos Alberto de Castro Pereira[1]
Editor-in-Chief of the Journal of Pulmonology from 1995 to 1998.

Are you glad to have been appointed Editor? You will spend all of your already scarce free time on it, you will not think about anything else, you will lose some of your friends, and you will not make any new ones... Those were the words that Lock[1] said to me when I was about to become the new Editor of the *Jornal de Pneumologia*. When I did, in 1995, the journal had been in existence for 20 years and had come to be published every two months. At the time, Brazilian Thoracic Association Board of Directors made the decision that the Journal should be financially independent, requiring no expenditures by the Society. An increased number of advertisements allowed the journal to be published every two months. Subsequently, the journal was renamed the *Jornal Brasileiro de Pneumologia*.

Before accepting the position as Editor of the *Jornal de Pneumologia*, I read articles and texts on the topic of editing, I bought (and then repeatedly referred to) the American Medical Association Manual of Style,[2] and I read books and articles on clinical research, evidence-based medicine, and biostatistics. At the time, there were no associate editors or executive editors; that is, whenever an article was submitted to the journal, an initial evaluation was performed and a preliminary decision was made to reject it or send it to two reviewers. The reviewers were (and still are) anonymous, and this often resulted (and still results) in hasty, misguided opinions that were (and still are) sometimes expressed aggressively. I always participated in the review process, often studying the topic and sometimes disputing (or even overriding) the opinions of reviewers. I imagine that the current associate editors are specialists who review articles in their area of interest. However, I think it is time for peer review to be open and signed. Art, theater, and literary critics have the honesty and dignity to sign their published articles. Why should reviewers in the field of medicine remain anonymous? Are they afraid of losing their status as oracles? One randomized study[3] showed that signed reviews were of higher quality, more courteous, and more thorough than unsigned reviews. Reviewers who signed were more likely to recommend publication. Honest authors should not resent well-founded criticism and should welcome suggestions to improve their manuscripts.

The JBP suffers from a type of "schizophrenia" (as do other Brazilian medical journals). Brazilian authors, including Editors and Editorial Board members, prefer to submit their best studies to international journals that have greater visibility and impact. This hinders the development of the Journal and results in its being regarded as a second-rate journal. The solution is complex.

Between 1995 and 1998, the Journal published guidelines and special issues on spirometry, tuberculosis, pneumonia, asthma, and occupational diseases, all of which had a significant impact. It would be of great interest to determine how many of the original articles published in the Journal in the past 40 years have had an impact on clinical practice and have survived as relevant contributions.

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Gratitude for my time at the *Jornal de Pneumologia*

Thais Helena Abrahão Thomaz Queluz[1]
Editor-in-Chief of the Journal of Pulmonology from 1999 to 2002.

I was the editor of the Journal of Pulmonology from 1999 to 2002, a time during which the editor was also the Director of Communications of the Brazilian Thoracic Association (BTA), elected on a joint ticket in BTA elections. I worked in the administrations of Francisco Elmano Marques de Souza and Luiz Carlos Correia da Silva, both of whom lent me their full support. Both also accepted the fact that I chose not to encumber myself with other tasks related to the dissemination of information (the bulletins, the website, etc.) and opted to devote my time exclusively to the Journal of Pulmonology.

I was always a great admirer of the Journal of Pulmonology, which was the fruit of the labors of so many who came before me and one of the principal assets of the BTA—the "jewel in the crown". However, I noticed that authors working in our field of study in Brazil published their best work in journals with greater visibility, whereas they submitted their less important manuscripts, especially case reports, to the Journal of Pulmonology. The explanation for that is that our Journal was indexed only for LILACS, which encompasses only journals published in Latin America and the Caribbean. The Journal needed to be indexed for a database with greater international visibility. Envisioned and developed by Brazilians, the SciELO database was our target. For a journal to be included in SciELO, its editor has to apply, after which the journal is evaluated for a period of no less than two years. Once a journal has been indexed for SciELO, it is subject to ongoing evaluation. The evaluation process required rigorous attention to the timeliness of the publication of each issue of the Journal, a regular number of articles per issue, and a well-qualified editorial staff. To meet the challenge of organizing the editorial functions during that first year, I enlisted the aid of several researchers who were on the editorial staff and of various *ad hoc* reviewers. Some also volunteered to be responsible for series and review articles. To promote good interactions among the authors, the reviewers, and the editor, we took a pedagogical approach—the editor is not the "owner" of the journal; the authors and reviewers are not enemies. We are all researchers who want to show our work, our best work.

In 2001, the Journal of Pulmonology came to also be published online and, in September of 2002, was indexed for SciELO. By the end of my term as editor, we had published 24 issues, all of which were released promptly in the months listed on the cover, as well as 11 supplements. During that period, we evaluated 290 manuscripts and our rejection rate was approximately 30%.

I would like to thank the presidents of the BTA, as well as my colleagues, the reviewers, and the authors. In addition, I am especially grateful to Hugo Hyung Bok Yoo, the secretary of the Journal of Pulmonology, as well as to Enilze de Souza Nogueira Volpato and Rosemary Cristina da Silva, librarians at the Botucatu campus of São Paulo State University, for the technical consulting provided. I would also like to pay me respects to Priscilla de Cássia Bovolenta, the kind, efficient secretary who worked with me as well as with subsequent editors. Priscilla recently passed away at the age of 37, after a long battle against her disease. She will be missed.

The traits that are considered characteristic of a good editor are competence, integrity, impartiality, and the ability to withstand enormous pressure. I am quite grateful for those years as the editor of the Journal of Pulmonology, which provided me with an extensive education and allowed me to pursue those qualities. I am also very grateful to have achieved my objective of setting the Journal of Pulmonology on the path to greater visibility.

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My time at the JBP

Geraldo Lorenzi-Filho[1]
Editor-in-Chief of the Brazilian Journal of Pulmonology from 2003 to 2004.

Reflecting on the history of our Journal brings to mind the image of a long relay race with batons. I am extremely proud to be a part of this history. It all started when Professor Carlos Carvalho encouraged the residents to write a review. Publishing in the Journal of Pulmonology was a dream of mine. I recall the day I received the letter notifying me that, after extension, careful revision to address the concerns of the reviewers, my article had been accepted. That day remains clear in my memory. What a joy it was to become a member of such a select group. The careful reader will soon realize that 25 years have passed since that fateful day.[1] The years rolled by; I became enamored with research, earned my doctorate, did my postdoctoral work in Canada, and began to publish in other journals. However, the Journal of Pulmonology continued to occupy a special place in my little library. One night, Dr. Pereira called me at home. The invitation to become the editor of the Journal of Pulmonology was intoxicating. I had lost track of the passing time, and I realized that it was now my turn to lead. I drove to Botucatu to learn everything I could from the distinguished Professor Thais Queluz. The experience that I accumulated during my fleeting tenure as Editor (2003-2004) was unique and had a significant impact on my life. I dedicated myself body and soul to my new job. During my time as editor, I realized just how many instrumental people there were and just how much potential the Brazilian Thoracic Society had. I got involved with all aspects of the Journal, from copy editing to the advertising and financial aspects, as well as the proofreading of the Portuguese, the translation of the articles into English. We also created bylaws for the Journal itself and modified the bylaws of the Society, as well as redefining the role and clarifying the functions of the Editor. The format of the Journal changed, as did its name. After an extensive survey of all of our associates, the Journal of Pulmonology became the JBP. Passing the baton to Professor Baddini-Martinez, who worked actively on the Journal during my term as editor, made me certain that our dear child would be well cared for and would continue to flourish. The current status of the Journal proves that I was right.

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My time at the *Jornal Brasileiro de Pneumologia*

José Baddini-Martinez[1]
Editor-in-Chief of the Brazilian Journal of Pulmonology from 2005 to 2010.

When I took the reins of the Brazilian Journal of Pulmonology (BJP) in 2004, I was riding a wave of major proposals made by my predecessor, Geraldo Lorenzi Filho. Until that time, the publication of the Journal was the responsibility of a member of the Board of Directors of the Brazilian Thoracic Association (BTA)—the Director of Communications. I was charged with making a transition from that model to a new one. As part of that transition, I effectively became the first independent Editor-in-Chief of the BJP, dedicated exclusively to its production.

The next six years were a time of hard work—enthusiastic, productive work—during which I always had the full support of the BTA Board of Directors, captained by Mauro Zamboni, Antonio Carlos Lemos, and Jussara Fitterman. At that time, the imperative order of the day was for the BJP to be indexed for PubMed and for the Institute for Scientific Information (ISI) Web of Knowledge. A great deal of effort was put into standardizing the graphic layout and updating the editorial guidelines. Similarly, much energy was expended in order to ensure the punctuality and periodicity of the Journal, both of which are essential to a scientific journal becoming widely respected.

The following are my best memories of my time at the BJP:

- my participation in devising the Journal by-laws, which are still in effect
- the implementation of the (then) recently introduced system of online article submission
- the creation of a free-standing website, with texts in Portuguese, English, and Spanish
- my visit, together with Mauro Zamboni, to the National Library of Medicine, in Bethesda, Maryland[a]
- the festive announcement, made by Mauro Zamboni during the opening ceremonies of the XXXIII Congress of the BTA, held in the city of Fortaleza in 2006, of the long-coveted indexing of the JBP for PubMed
- the indexing of the Journal, in 2009, for the ISI Web of Knowledge, which was the initial step in the process that led to the calculation of our first impact factor, in 2011
- the establishment of a permanent[b] BJP office of administration at the BTA headquarters in Brasília

I have to admit that not all of the initiatives undertaken during my tenure at the JBP were successful. For example, the attempt to make the Journal a monthly publication was an exercise in frustration. Forgive me, my friends, but mistakes can be made, even with the best (if misguided) intentions.

One of the things that I realized during my time at the BJP was that, in fact, people and human relations are paramount. The major advances made at the BJP during that time occurred essentially because innumerable people were aware of the importance of the Journal and were imbued with an earnest desire to improve it. Researchers working in Brazil were aware of this need and graced us with their manuscripts. The members of the Editorial Board of the Journal always gave the best of themselves. The directors and staff of the BTA also contributed, either directly or indirectly, to supporting the efforts made by myself and my assistants.

I would be remiss if I did not acknowledge and express my gratitude to Luana Campos and Priscilla Bovolenta for their enormous contributions to overseeing the day-to-day activities of the BJP during my tenure.

This was a wonderful time in my life!

1. Departamento de Clínica Médica, Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo – FMRP-USP – Ribeirão Preto, Brasil.

[a] We were received by the then-Associate Director for Library Operations, Sheldon Kotzin, to whom we presented the BJP and who informed us of the *modus operandi* of submitting an application for a journal to be indexed for PubMed.

[b] Previously, the BJP office of administration was itinerant, operating in the city of residence of the current editor for the duration of his or her term.

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My time at the JBP

Carlos Roberto Ribeiro Carvalho[1]
Editor-in-Chief of the Brazilian Journal of Pulmonology from 2011 to 2014.

It has been a few months since I completed my term as Editor-in-Chief of the Brazilian Journal of Pulmonology (BJP), and it is great to be able to write about those four years, especially as our Journal completes its 40th year in publication.

In Brazil, being the editor of a scientific journal is an additional task to juggle, along with academic or health care activities. I remember the conversations I had, before my editorship, with the President of the Brazilian Thoracic Association (BTA)—Roberto Stirbulov—and with the Editor who preceded me—José Baddini Martinez. I was reluctant, because I was well aware of the huge workload and, especially, of the enormous responsibility that I would have going forward.

In my first Editorial, I emphasized the fundamental work of those who had preceded me, who had succeeded in getting the BJP indexed for the major international databases. I also emphasized how important it was that we (university professors and other health professionals in the field of respiratory medicine), work together to improve the scientific quality of our Journal, in order to gain more respect at the national and international level. I committed myself to leading this mission.

Between 2011 and 2015, the BJP experienced two contrasting occurrences. First, in June of 2012, the Journal received its first impact factor from Journal Citation Reports (JCR), an Institute for Scientific Information (ISI) Web of Knowledge database, and this was greatly celebrated. We had been monitoring the performance of the BJP in other databases, especially Scopus, which has its own metric (SCImago Journal Rank), and we expected to fare well in the ranking. In fact, the result was highly positive, placing us in a prominent position among Brazilian scientific journals (the BJP ranked third among medical journals) and in an admirable intermediate position among all respiratory journals worldwide.

In 2013, however, the BJP was excluded from the JCR list. The argument was that we had received an anomalously large number of citations in an article published in another Brazilian journal, which could artificially inflate our impact factor. That was a time of great tension. Our (temporary) exclusion led to a series of measures being taken by the *Coordenação de Aperfeiçoamento de Pessoal de Nível Superior* (CAPES, Office for the Advancement of Higher Education), the agency that evaluates graduate programs in Brazil, and this negatively impacted its tri-annual evaluation of several of our programs. What discomforted me greatly, and even made me a little angry, was that CAPES did not allow any of the editors of the journals that were excluded from that list an opportunity to present their side of the story. The BJP was unilaterally excluded from the CAPES journal ranking system (known as Qualis), despite the fact that it has been indexed for all other major scientific journal databases for all these years, that it continues to be indexed for the ISI database, that its published articles continue to be cited, that its citations continue to be computed, etc.

In the following year, the BJP was once more listed in JCR with an impact factor that remained among the highest in Brazil: the sixth highest among the 107 Brazilian journals indexed for the ISI database. However, because of the mechanism by which impact factors are calculated, ours will, over at least the next two years, continue to reflect the effects of the fact that we were penalized.

Finally, I would like to call attention to achievements that also took place in 2014. First, the BJP became available on PubMed Central (PMC), which is a free, full-text archive of biomedical and life sciences journal literature at the U.S. National Institutes of Health National Library of Medicine. Second, we began using the ScholarOne system of manuscript management, which is an agile platform for authors, reviewers, and editors. This was key to increasing the presence of the BJP on the international stage, as well as increasing our appeal to international authors and reviewers.

Those were four years of hard work and of mishaps that could only be overcome with the unconditional support of the BTA Board of Directors, as well as that of the Executive and Associate Editors of the BJP. Those were also years of victories—years that demonstrated the importance of having a Brazilian scientific journal, of international scope, via which to disseminate our work and earn the respect of researchers worldwide.

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The next 40 years

Rogério Souza[1]
Current Editor-in-Chief of the JBP.

Although having barely begun, my term as Editor-in-Chief of the JBP has been a time of intense learning.[a] It is quite interesting to reflect upon the evolution of the JBP since its founding 40 years ago.

Organizing ourselves as a scientific society concerned with the field of pulmonology was the impetus for the creation of a journal initially designed to disseminate knowledge related to that field and to strengthen us as a scientific community—incredibly, the journal continues to embody the essence of that original mission. The setting, however, has changed considerably. Given the incipient nature of respiratory science in Brazil at that time, the journal initially published articles that had already appeared in international journals, translating them to Portuguese for our national readership. As the field of pulmonology in the country developed, the JBP grew and came to be more representative of its readers. During that transitional phase, the forward thinking of the editors allowed the JBP to be indexed for various databases and even to obtain the bibliometric indices by which it can be compared with other journals in the field.[1]

During these last 40 years, our scientific society has also become stronger. The Brazilian Thoracic Association (BTA) began to develop its own guidelines, covering not only what is supported by the most robust scientific evidence but also taking into account aspects specific to Brazil in order to make them applicable in our country. [2,3] Several members of our society have come to be considered international authorities in their fields, the Editorial Board of the JBP itself is a reflection of that..

The field of respiratory science has now become firmly established in Brazil, a fact that is well represented by the BTA. Based on that fact, as well as on the fascinating trajectory of the JBP—as recounted by its former Editors-in-Chief—the current issue commemorates the first 40 years of the JBP.

I have begun to wonder what we want for the future; what kind of JBP do we want to have in the next 10, 20, or 40 years? One thing is certain: there is no simple answer. The JBP has several missions before it, and the setting in which it must complete those missions has become more complex. Its role in the dissemination of knowledge in the field of pulmonology is clear, but that role is now no longer limited to Brazil. It also plays an obvious role in promoting respiratory science at the national level, although that has become quite competitive in recent decades, which should be seen as good news. Therefore, there is a need for constant pondering. We must pursue the most recent advances in respiratory medicine without ceasing to be a portal for younger researchers who are still inexperienced in the art of presenting their findings, as well as creating an absolutely scientific environment within which they can discuss their studies with their peers.

We have to increase our international presence without losing the base that sustains us as a regional journal.[4,5] In that respect, there is a niche to be filled. If we look at all the scientific journals in the field of respiratory science, we see that there is only a small number of generalist journals with an impact factor of approximately 2.0. That number is further restricted if we consider only the journals that do not charge for access to their content or for paper submission, a standard we intend to maintain for several years to come. Our efforts therefore need to be directed to reach such a level that this exposure places us in an unequivocally prominent position ahead of other journals. Reviewing the editorials that precede this one, I see how far we have come. Audacious goals are realistic only if approached from a solid foundation. Over these last four decades, such a foundation was built by tireless teams of JBP staff members, captained by their respective Editors-in-Chief. It would be unfair to try to name them all, because I would certainly (although unintentionally) fail to mention someone. Therefore, I congratulate here all of the former Editors-in-Chief on what has been constructed, extending my congratulations to all those who assisted them. I also congratulate the current associate editors, without whom it would not be possible to plan future conquests. Finally, my congratulations go out to the entire editorial staff, with special recognition to the group of editorial assistants who made and make possible the day-to-day functioning of the JBP, excelling in maintaining the quality of the Journal throughout the process. It is all of those people, collectively, who have made and continue to make the JBP the reference that it is today. Happy 40th, JBP!

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Study of inhaler technique in asthma patients: differences between pediatric and adult patients

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ABSTRACT

Objective: Inhaler technique comprises a set of procedures for drug delivery to the respiratory system. The oral inhalation of medications is the first-line treatment for lung diseases. Using the proper inhaler technique ensures sufficient drug deposition in the distal airways, optimizing therapeutic effects and reducing side effects. The purposes of this study were to assess inhaler technique in pediatric and adult patients with asthma; to determine the most common errors in each group of patients; and to compare the results between the two groups. **Methods:** This was a descriptive cross-sectional study. Using a ten-step protocol, we assessed inhaler technique in 135 pediatric asthma patients and 128 adult asthma patients. **Results:** The most common error among the pediatric patients was failing to execute a 10-s breath-hold after inhalation, whereas the most common error among the adult patients was failing to exhale fully before using the inhaler. **Conclusions:** Pediatric asthma patients appear to perform most of the inhaler technique steps correctly. However, the same does not seem to be true for adult patients.

Keywords: Administration, inhalation; Aerosols/administration & dosage; Asthma/prevention & control.

INTRODUCTION

Inhaler technique comprises a set of procedures for drug delivery to the respiratory system. The oral inhalation of medications is the first-line treatment for lung diseases, and metered-dose inhalers (MDIs) are one of the drug delivery systems most frequently used by patients.[1] The use of oral medications offers many advantages, because these medications act directly on the airways and require administration of lower doses, with no gastric changes.[2] Using the proper inhaler technique ensures sufficient deposition of drug particles in the distal airways, optimizing drug effectiveness and reducing possible side effects.

One of the determinants of the effectiveness of inhaled medications is the ability of the patient to adhere to good inhaler techniques.[3] For some patients, that can be difficult, and the prescription of medication should therefore always be accompanied by appropriate inhaler technique training delivered by a health professional. Thus, it is possible to reduce the number of inhaler technique errors and minimize the clinical consequences of poor drug delivery.

The first therapeutic aerosol devices were developed in the 1950s[4] and consisted of nebulizers and atomizers containing anticholinergics for treatment of asthma.[5] Despite the long time since development and the wide use of these devices, inhaler technique errors continue to be common among respiratory patients,[6] reducing the benefits of inhaled medications. In Chile, Solís et al.[7] observed that only 12.5% of the mothers of hospitalized infants have a correct inhaler technique. However, it is unknown whether this trend is reflected in adult patients, given that the elderly are more likely to make inhaler technique errors.[8] This promotes the assessment of inhaler technique by age group, because tailoring education to the needs of each patient could significantly improve disease management. The purposes of the present study were to assess inhaler technique in pediatric and adult patients with asthma; to determine the most common errors in each group of patients; and to compare the results between the two groups.

METHODS

This was a descriptive cross-sectional study conducted in the region of Valparaíso, Chile, between March and May of 2014. The sample consisted of male and female patients with a diagnosis of asthma based on spirometry, in accordance with the Global Initiative for Asthma criteria.[9] The ages of the participants ranged from 5 to 90 years, and the sampling was non-probabilistic (purposive). Patients had to meet the following inclusion criteria: being enrolled in and attending follow-up visits as part of an asthma program in clinics in the region of Valparaíso, regardless of smoking status; having received a prescription for a bronchodilator and having been instructed on the proper use of their inhaler (practical demonstration by a nurse, physician, or kinesiologist at each follow-up appointment); and being able to self-administer inhaled medication. We

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excluded patients who had a respiratory comorbidity or any concomitant condition that could directly affect inhaler technique (prostration, oxygen dependence, or altered cognitive status).

All participants gave written informed consent, and the study was approved by the Research Ethics Committee of the University of Santo Tomás at Viña del Mar School of Kinesiology.

For comparative purposes, the patients were divided into two groups: pediatric patients (5-18 years); and adult patients (19-90 years). The volunteers were recruited during their follow-up appointments at the health facilities. On that occasion, they were scheduled to undergo assessment one week later. On the assessment day, they were asked to use their inhaler as usual. All volunteers used their own valve spacer (appropriate to their age). They received no additional instruction, coaching, or correction during inhaler use. The medication administered was albuterol (100 μg; Fesema®; Laboratorio ETEX, Santiago, Chile), used as rescue medication and delivered with an MDI.

Inhaler technique was assessed using a protocol described by Melani,[10] as shown in Table 1. This protocol documents the performance of ten essential inhaler technique steps by means of closed dichotomous response options (well performed/poorly performed). All assessments were made by two investigators with ten years of experience in the follow-up of asthma patients. After assessment, all patients were given supplemental instruction on inhaler technique by a health professional, in the form of a demonstration.

On the basis of a study of inhaler technique in pediatric patients,[11] which reported an 89.1% completion rate for "hold breath for 10 seconds", we calculated that, in order to achieve an alpha of 5%, a statistical power of 80%, and an estimation error of 6%, a sample size of at least 104 patients was required. Allowing for a loss of 10%, we determined that the minimum sample size needed was 115 patients.

For data analysis, we used descriptive statistics, calculating the number of errors per patient and the percentage of completion for each step of the protocol. The results were tabulated and analyzed with Microsoft Excel 2010. Differences between the percentages of errors made by each group were determined by the equivalence test for two proportions. Values of $p < 0.05$ were considered significant.

RESULTS

The total number of patients selected was 270. We excluded seven patients, for the following reasons: prostration (n = 2); oxygen-dependence (n = 2); Alzheimer's disease (n = 2); and sequelae of pulmonary tuberculosis (n = 1). The final sample therefore consisted of 263 patients: 135 pediatric patients and 128 adult patients. Of those, 44.1% were male. All patients had been diagnosed with bronchial asthma.

Table 1. Inhaler use protocol described by Melani.[10]

1. Remove the cap from the inhaler
2. Shake the inhaler before use
3. Exhale before using the inhaler
4. Insert the inhaler into the spacer
5. Hold the inhaler upright with the mouthpiece at the bottom during use
6. Take only one puff at a time
7. Actuate the inhaler in the first half of inhalation
8. Inhale slowly while actuating the inhaler
9. Continue to inhale after actuation
10. Hold breath for 10 seconds

The general characteristics of the participants are shown in Table 2. In the pediatric group, the most well-represented age group was the 13- to 18-year group, with 63 patients, whereas the 61- to 75-year group was predominant, with 51 patients, in the adult group.

Table 3 shows the types of errors made by the pediatric and adult patients. The most common errors in the pediatric group were failing to execute a 10-s breath-hold after inhalation (in 8.1%) and failing to continue to inhale after actuation (in 6.1%). In the adult group, 53.1% failed to exhale before using the inhaler, whereas 46% failed to execute a 10-s breath-hold after inhalation.

Table 4 shows the frequency of correct and incorrect inhaler technique, by patient age group. In the 61- to 75- and 76- to 90-year age groups, the frequency of incorrect technique was greatest (48 and 35 patients, respectively). Significant differences were found in the frequency of incorrect technique between the pediatric and adult groups.

DISCUSSION

The results of the present study show that most of the pediatric patients used correct inhaler techniques. The most common errors were failing to execute a 10-s breath-hold after inhalation (in 8.1%) and failing to continue inhaling after actuation of the device (in 6.1%). Among the adult patients, the most common errors were failing to exhale before using the inhaler (in 53.1%) and failing to execute a 10-s breath-hold after inhalation (in 46%). Crompton et al.[11] stated that poor inhaler technique in older patients might be due to cognitive impairment and their inability to retain the instructions received from the medical team. It is important to point out that, although the protocol used in our study is a guide for correct inhaler technique in adult patients, we found that pediatric patients appear to have better inhaler technique.

These results are consistent with what was described by Flor et al.[12] Studies of inhaler technique have established that the most common errors are, in order of incidence, as follows: poor coordination between actuation and inhalation; an insufficient breath-hold after inhalation; excessive inhalation flow; failing

Table 2. General characteristics of the sample.

Age, years	n[a]	Male gender, %[b]	Characteristic				
			Mean[c]				Tobacco consumption, %[b]
			Age, years	FEV_1[d]	FVC[d]	FEV_1/FVC[d]	
Pediatric patients							
5-6	8	87.5	6.0 ± 0.5	82 ± 20	100 ± 9	72 ± 9	0.0
7-8	13	76.9	7.0 ± 0.5	81 ± 15	98 ± 8	70 ± 8	0.0
9-10	21	47.6	9.0 ± 0.5	81 ± 7	99 ± 7	70 ± 9	0.0
11-12	30	50.0	12.0 ± 0.5	79 ± 14	99 ± 10	71 ± 5	0.0
13-18	63	47.6	14.0 ± 0.5	79 ± 19	101 ± 8	72 ± 7	30.0
Adult patients							
19-30	12	58.3	23 ± 0.7	78 ± 10	101 ± 18	71 ± 8	25.0
31-45	6	50.0	34.0 ± 0.6	82 ± 9	102 ± 15	69 ± 11	33.3
46-60	25	48.0	51.0 ± 0.6	80 ± 10	99 ± 19	70 ± 7	28.0
61-75	51	49.0	67.0 ± 0.7	81 ± 12	98 ± 18	71 ± 9	29.4
76-90	34	52.9	79.0 ± 0.5	79 ± 15	95 ± 15	69 ± 9	14.7
Total	263	100.0					

[a]Number of patients in each age group. [b]Proportion for each age group. [c]Values expressed as mean ± SD. [d]Percentage of predicted value.

Table 3. Frequency and percentages of inhaler technique errors observed in the pediatric and adult groups.

Type of error	Pediatric group		Adult group	
	n[a]	%[b]	n[a]	%[b]
Failing to exhale before using the inhaler	5	3.7	68	53.1
Failing to hold breath for 10 s	11	8.1*	59	46.0*
Failing to take only 1 *puff* at a time	4	3.0	37	28.0
Failing to continue to inhale after actuation of the inhaler	8	6.1	35	26.5
Failing to actuate the inhaler in the first half of inhalation	4	3.0	30	22.7
Failing to shake the inhaler before use	0	0.0	25	18.9
Failing to inhale gently and deeply while actuating the inhaler	4	3.0	14	10.6
Failing to insert the inhaler into the spacer	1	0.7	11	8.6
Failing to hold the inhaler upright with the mouthpiece at the bottom during use	0	0.0	2	1.5

[a]Number of patients who made the error. [b]Proportion within each group. *p < 0.001 (equivalence test for two proportions).

to shake the canister vigorously before use; failing to continue to inhale after actuation; pressing the canister down several times during the course of a single inhalation; exhaling during actuation; and failing to hold the inhaler upright.[13]

Other authors have observed that the rate of inhaler technique errors decreases when devices other than MDIs are used.[14] However, drug delivery effectiveness is similar when inhaler technique is correct,[15] regardless of the device used.

Poor inhaler technique has clinical consequences ranging from minor to critical.[6,10] Under this criterion, the results of our study allow us to state that the most frequent error made by the pediatric patients (made by 13 subjects) would moderately affect drug deposition in the lung, whereas the most frequent error made by the adult patients (made by 90 subjects) would slightly affect this deposition. As for specific consequences, the poor inhaler technique observed in the two groups of patients can affect drug delivery to the distal airways and prevent drug deposition on the respiratory epithelium.[16] The clinical implication of these results is that, in patients with poor inhaler technique, there is a waste of inhaled medication. Consequently, there would be an increase in the economic costs associated with the disease, an increase in the risk of side effects, and a reduction in treatment effectiveness.

Respiratory patient education is a critical factor in the proper use of medications.[17] Asthma patient education programs substantially improve adherence and inhaler technique.[18] All participants in our investigation regularly attend their follow-up appointments, and, at each such opportunity, they are instructed in the proper use of their medications. Nevertheless, our results show that errors in inhaler use persist. These mistakes are considered either unintentional (patients not noticing that their inhaler technique is poor) or intentional (patients knowingly using the incorrect inhaler technique).[18] In addition, there is clear evidence that inhalers are underused among asthma patients.[19] In this aspect, one of the limitations of our study was that we did not delve into the causes of the observed errors, which would have made it possible to provide each patient with specific supplemental instruction on the proper administration of the medication.

In our sample, we found that approximately 30% of the adult patients were smokers. Although this proportion is lower than observed among adults in Chile

Table 4. Frequency of correct/incorrect inhaler technique, by age group.

Age (years)	Correct technique	Incorrect technique
Pediatric patients	n	n
5-6	5	3
7-8	12	1
9-10	14	7
11-12	19	11
13-18	49	14
%	73.4	26.6*
Adult patients		
19-30	9	3
31-45	0	6
46-60	1	24
61-75	3	48
76-90	1	35
%	9.4	90.6*

*p < 0.05 (equivalence test for two proportions).

(40.6%),[20] it is significant, given that smoking affects asthma control.[21] Therefore, tobacco consumption in these patients would further increase the difficulty in controlling the disease.

Recent studies suggest that better results would be obtained by tailoring inhaler prescription to suit the characteristics and functional capabilities of each patient.[22] It has been observed that even individuals with correct inhaler technique can make errors if they are reassessed over time,[23] which makes it mandatory to provide patients with ongoing education in the administration of inhaled medications. Many times there are factors that hinder this learning process, such as limited duration of appointments, a lack of knowledge on the part of health care personnel about the correct steps of the inhaler technique, and the technical language used in teaching the technique.[16] Therefore, it is necessary to use new methods to provide patients with supplemental instruction on correct inhaler use, such as videos or illustrative leaflets that can promote the retention of information by patients.[24] In addition, it is necessary that supplemental instruction on inhaler use protocols be properly provided to health personnel and included in asthma clinical guidelines, which rarely address the administration of inhaled medications.[25]

In conclusion, we found that most pediatric asthma patients appear to have correct inhaler technique. However, the same does not seem to be true for approximately 90% of adult patients, among whom the most common error was failing to exhale before using the inhaler. We suggest that asthma patients, especially those who are older, should be given supplemental instruction on inhaler technique through the use of new methods, so that they can administer their medications properly.

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Diagnostic value of endobronchial ultrasound-guided transbronchial needle aspiration in various lung diseases

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ABSTRACT

Objective: Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is a new method for the diagnosis and staging of lung disease, and its use is increasing worldwide. It has been used as a means of diagnosing lung cancer in its initial stages, and there are data supporting its use for the diagnosis of benign lung disease. The aim of this study was to share our experience with EBUS-TBNA and discuss its diagnostic value. **Methods:** We retrospectively analyzed the results related to 159 patients who underwent EBUS-TBNA at our pulmonary medicine clinic between 2010 and 2013. We recorded the location and size of lymph nodes seen during EBUS. Lymph nodes that appeared to be affected on EBUS were sampled at least twice. We recorded the diagnostic results of EBUS-TBNA and (for cases in which EBUS-TBNA yielded an inconclusive diagnosis) the final diagnoses after further investigation and follow-up. **Results:** We evaluated 159 patients, of whom 89 (56%) were male and 70 (44%) were female. The mean age was 54.6 ± 14.2 years among the male patients and 51.9 ± 11.3 years among the female patients. Of the 159 patients evaluated, 115 (84%) were correctly diagnosed by EBUS. The diagnostic accuracy of EBUS-TBNA was 83% for benign granulomatous diseases and 77% for malignant diseases. **Conclusions:** The diagnostic value of EBUS-TBNA is also high for benign pathologies, such as sarcoidosis and tuberculosis. In patients with mediastinal disorders, the use of EBUS-TBNA should be encouraged, primarily because it markedly reduces the need for mediastinoscopy.

Keywords: Sarcoidosis; Tuberculosis, pulmonary; Lung neoplasms; Bronchoscopy; Mediastinoscopy; Endosonography.

INTRODUCTION

Endosonography was initially used in the staging of gastrointestinal tract malignancies.[1] In the 1990s, it was adapted for use in bronchial diseases. In patients with lung disease, its uses now include tumor staging; the diagnosis of central (parenchymal) masses; and the detection of mediastinal or hilar lymphadenopathy. Endobronchial ultrasound (EBUS) enables the visualization of lymph node structure, thus allowing the pulmonologist to evaluate and sample lymph nodes. Consequently, minimally invasive staging of lung cancer has advanced considerably. In addition, tumor invasion of the tracheobronchial wall can be assessed more accurately with EBUS than with CT. The accuracy of EBUS in making this distinction is 94%, compared with 51% for CT.[2] Lymph node stations 2, 4, 7, 10, and 11 can be sampled by EBUS. If EBUS is combined with esophageal ultrasound, lymph node stations 5, 8, and 9 can also be sampled. Therefore, the combination of esophageal ultrasound and EBUS can be seen as the first and best test in patients with suspected lymph node metastasis. [3] There are studies showing that this is a good alternative to mediastinoscopy.[4,5]

In patients with malignant disease or granulomatous diseases such as tuberculosis and sarcoidosis, EBUS can contribute to the diagnosis. In a recent meta-analysis, the diagnostic accuracy of EBUS-guided transbronchial needle aspiration (EBUS-TBNA) for sarcoidosis was shown to be 54-93%.[6] In tuberculosis, for which EBUS is also diagnostic, EBUS-TBNA has been shown to have a sensitivity of 85%.[7]

In the evaluation of airway disease, EBUS has emerged as a technique that has great potential for development. Different diagnostic values for EBUS have been reported in various studies. The aim of this study was to determine the diagnostic value of EBUS-TBNA, its contribution to the diagnosis of different diseases, and the factors that determine the magnitude of that contribution.

METHODS

Patients and procedures

In this study, we retrospectively analyzed 159 patients in whom EBUS-TBNA was used at our pulmonary medicine clinic between 2010 and 2013. In patients with mediastinal/hilar lymphadenopathy, EBUS-TBNA was performed in order to evaluate the etiology. Lymphadenopathy was defined as a finding of one or more lymph nodes with a short-axis diameter of ≥ 10 mm on CT or high

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18F-fluorodeoxyglucose uptake on positron emission tomography/CT. All of the patients evaluated gave written informed consent. Patients fasted for at least 4 h before the procedure. The preparation process included local anesthesia with lidocaine hydrochloride (Xylocaine®) and sedation with midazolam just prior to the EBUS procedure, which was performed with a convex-probe ultrasound-guided fiberoptic bronchoscope (BF-UC160F-OL8; Olympus Medical Systems, Tokyo, Japan). All EBUS-TBNA procedures were performed by the same pulmonologist. The location and size of the lymph nodes seen during EBUS were recorded. Lymph nodes that appeared to be affected were sampled at least twice. The samples were sent for histopathological assessment. Rapid onsite cytopathological examination was not performed. If EBUS-TBNA did not lead to a diagnosis, the patients underwent mediastinoscopy, open lung biopsy, or transthoracic needle aspiration (TTNA), according to the situation. In patients with pathological diagnosis of chronic granulomatous inflammation, the diagnosis of tuberculosis or sarcoidosis was determined from the EBUS-TBNA results. This determination was made on the basis of the presence of necrosis in the samples; clinical symptoms; the history of contact with tuberculosis cases; microbiological evaluation; tuberculin skin test results; and additional biochemical features. Samples were classified as containing insufficient material if they contained no lymphocytes. The cytology of a sample was classified as benign (normal) if it presented mature lymphocytes or anthracosis, without malignant cells or granulomas. The final diagnosis was based on the cytology, surgical results, or clinical follow-up. We recorded all diagnoses resulting from EBUS-TBNA. For the patients with inconclusive EBUS-TBNA results, the final diagnoses were recorded as those made after surgery, TTNA, or at least 6 months of follow-up (i.e., bacteriological and clinical outcomes). Patients were grouped by final diagnosis: malignant disease; benign disease; or inconclusive (normal cytology/anthracosis or insufficient material).

Statistical analysis

For statistical analysis of the data, we used the Statistical Package for the Social Sciences, version 15.0 for Windows (SPSS Inc., Chicago, IL, USA). We used descriptive statistics, including mean, standard deviation, and frequency. The lymph node size that supported the EBUS-TBNA-determined diagnosis was calculated via ROC analysis. Values of $p < 0.05$ were considered statistically significant.

RESULTS

Of the 159 patients evaluated by EBUS-TBNA in the present study, 89 (56%) were male and 70 (44%) were female. The mean age was 54.6 ± 14.2 years for the male patients and 51.9 ± 11.3 years for the female patients. Patients enrolled in the study were similar in terms of gender and age distribution ($p = 0.13$).

The EBUS-TBNA-determined diagnoses were as follows: sarcoidosis (in 43 patients); tuberculosis (in 14); malignancy (in 33); and normal cytology/anthracosis (in 58). In addition, EBUS-TBNA resulted in one patient being diagnosed with nocardiosis and another being diagnosed with a cyst in the subcarinal area. In 92 of the 159 patients, the EBUS-TBNA procedure was diagnostic. In 9 patients, the EBUS-TBNA samples were classified as containing insufficient material. Further investigation (surgery, TTNA, or follow-up) of those 9 patients revealed one case of sarcoidosis and one case of malignancy, the remaining seven cases being lost to follow-up. In the analysis of the EBUS-TBNA samples, the cytology was categorized as normal in 58 patients. Further evaluation and assessment of this group yielded the following diagnoses: sarcoidosis ($n = 6$); tuberculosis ($n = 5$); malignancy ($n = 9$); nocardiosis ($n = 1$); and normal cytology/anthracosis ($n = 22$). The remaining 15 patients were lost to follow-up, and the final diagnoses were therefore unknown. Of the 159 patients evaluated, 114 (83%) were correctly diagnosed using EBUS-TBNA. That group included those diagnosed with sarcoidosis or tuberculosis, as well as those in which the cytology was categorized as malignant (true positive) or benign (true negative). Figure 1 details the distribution of the final diagnoses.

Of the 50 patients receiving a final diagnosis of sarcoidosis, 43 (86%) were diagnosed with EBUS-TBNA, as were 14 (74%) of the 19 patients receiving a final diagnosis of tuberculosis. In the sarcoidosis and tuberculosis group, when we considered those 69 cases collectively (as the benign granulomatous disease category), EBUS-TBNA had a diagnostic accuracy of 83%. Among the 159 patients analyzed, the final diagnosis was malignancy in 43. In 33 (77%) of those patients, the diagnosis was based on the EBUS-TBNA findings. Among the remaining 10 patients (i.e., the 23% that were not diagnosed with EBUS-TBNA), there were seven cases of lung malignancy, two cases of hematologic malignancy (plasmacytoma and lymphoma, respectively), and one case of esophageal cancer. Therefore, for malignancy, EBUS-TBNA had a negative predictive value of 92% and an accuracy of 94%. The distribution of the final diagnoses and the diagnostic accuracy of EBUS-TBNA for each are given in detail in Table 1. The diagnostic accuracy of EBUS-TBNA was found to be similar for benign and malignant pathologies ($p = 0.39$). No serious complications (requiring early termination of the procedure) were found to have occurred during the use of EBUS-TBNA.

When we evaluated factors that might affect the diagnostic accuracy of EBUS-TBNA, neither age nor gender were found to have any such effect ($p = 0.05$ and $p = 0.43$, respectively). The number and size of lymph nodes detected using EBUS-TBNA are given in detail in Table 2. In the presence of enlarged mediastinal (N2) lymph nodes, the likelihood of obtaining a diagnosis with EBUS-TBNA increased significantly ($p = 0.013$). Enlargement of hilar lymph nodes had no such effect

(p= 0.065). The ROC analysis, performed in order to assess the contribution of lymph node size to the likelihood of diagnosis, revealed that, for obtaining an EBUS-TBNA-based diagnosis of granulomatous disease or malignancy, a finding of lymph nodes with a short-axis diameter ≥ 16.5 mm had a sensitivity of 60% and a specificity of 76% (Figure 2). For that cut-off value, the positive predictive value was 71%, the negative predictive value was 66%, and the area under the curve was 0.728. When that lymph node size cut-off value was applied, the diagnostic accuracy of EBUS-TBNA was 69% (p < 0.001).

Table 1. Final diagnoses and diagnostic accuracy of endobronchial ultrasound-guided transbronchial needle aspiration.

Type of disease	Final diagnosis	Definitive diagnosis by EBUS-TBNA
	n	n (%)
Malignant	43	33 (77)
Non-small cell lung cancer	32	26 (81)
Small cell lung cancer	7	6 (86)
Other[a]	4	1 (25)
Benign	72	59 (82)
Sarcoidosis	50	43 (86)
Tuberculosis	19	14 (74)
Other[b]	3	2 (67)

EBUS-TBNA: endobronchial ultrasound-guided transbronchial needle aspiration. [a]Lymphoma (n = 2); plasmacytoma (n = 1); and esophageal cancer (n = 1). [b]Nocardiosis (n = 2); and cyst (n = 1).

DISCUSSION

Although EBUS-TBNA is a new method, its use in the diagnosis and staging of lung diseases has become increasingly widespread. With EBUS-TBNA, it is possible to sample a lesion while it is being displayed by the ultrasound probe. This method has been used for lung cancer staging. It has also been shown to be diagnostic for benign lung diseases.[3-7] In the present study, we found that the overall diagnostic accuracy of EBUS-TBNA (regardless of the etiology) was 83%. Similarly, Choi et al.[8] reported that EBUS-TBNA had an overall diagnostic accuracy of 83.9%. Evaluating our cases over the last four years, we found that EBUS-TBNA has been well tolerated and has proven to be a reliable diagnostic method with few complications. The purpose of the present study was to share our experience regarding the diagnostic value of EBUS-TBNA.

Table 2. Lymph node number and size detected by endobronchial ultrasound.

Lymph node	n	Short-axis diameter mm[a]
2R	4	8.25 (5-35)
2L	0	
4R	55	14.5 (5-41)
4L	19	10.1 (4-50)
7	101	17 (3-42)
10R or 11R	45	14 (6-35)
10L or 11L	57	15 (4-45)
Total	281	

[a]Values expressed as median (min-max).

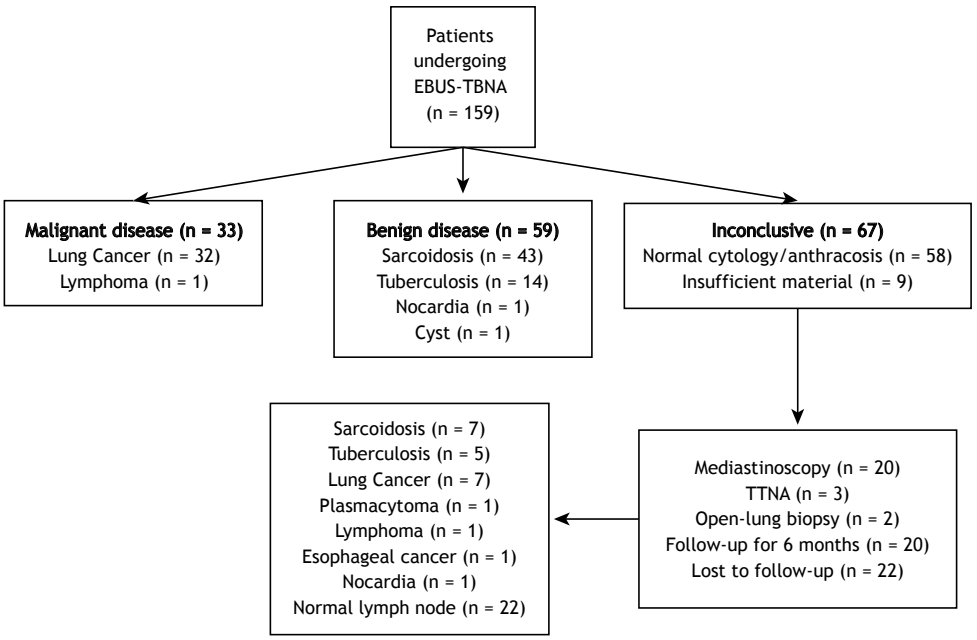

Figure 1. Flow diagram of the diagnoses made by endobronchial ultrasound-guided transbronchial needle aspiration and by other methods. EBUS-TBNA: endobronchial ultrasound-guided transbronchial needle aspiration, TTNA: transthoracic needle aspiration.

In the diagnosis of sarcoidosis, EBUS-TBNA is often used, because it can preclude the need for conventional TBNA or, in some cases, mediastinoscopy.[4,5,9] The use of EBUS-TBNA guarantees that the sample was taken from the targeted lymph nodes. Therein lies its superiority over conventional TBNA.[10,11] In addition, EBUS-TBNA is not as invasive as is mediastinoscopy. Various levels of diagnostic accuracy in sarcoidosis have been reported for EBUS-TBNA. A recent meta-analysis found that the reported diagnostic accuracy of EBUS-TBNA in sarcoidosis ranged from 54% to 93%.[6] In our study, that level was 86%, which is in agreement with the findings of other studies in the literature. Navani et al.[12] evaluated patients with suspected sarcoidosis using EBUS-TBNA and reported a diagnostic accuracy of 88%. When those same patients underwent transbronchial lung biopsy, mucosal biopsy, and BAL via standard bronchoscopy, the diagnostic accuracy increased to 93%. The variability in the reported levels of diagnostic accuracy across studies might reflect the level of experience of the pulmonologist performing the EBUS-TBNA or that of the pathologist, as well as the difference between studies in which rapid onsite cytopathological examination was performed and those in which it was not.

In another benign disease, tuberculosis, EBUS-TBNA is also used as a diagnostic method. Sun et al.[7] and Cetinkaya et al.[13] reported the sensitivity of EBUS-TBNA in tuberculosis to be 85% and 79%, respectively,[7,13] compared with the 74% found in the present study. The diagnostic accuracy of EBUS-TBNA is lower for tuberculosis than for sarcoidosis, and conventional TBNA has a diagnostic accuracy of 65% for tuberculosis.[14] Ren et al.[15] found that, in patients with suspected mediastinal tuberculous lymphadenitis, standard bronchoscopy had a sensitivity of 18.1% and a specificity of 100%. When the authors added EBUS-TBNA to standard bronchoscopy, those values rose to 80% and 92.3%, respectively.[15] Therefore, EBUS-TBNA seems to contribute to the diagnostic accuracy in patients with tuberculous lymphadenitis and mediastinal lymph node enlargement. In the present study, we also found the diagnostic accuracy of EBUS-TBNA to be lower for tuberculosis than for sarcoidosis. The prominent necrosis in paucibacillary tuberculosis could explain that finding. Dhooria et al.[16] reported that one can distinguish between tuberculosis and sarcoidosis on the basis of EBUS images. Accordingly, when combined with a positive tuberculin skin test result, the heterogeneous echotexture of the internal structure or necrotic appearance seen via EBUS can diagnose tuberculosis with a specificity of 98% and a positive predictive value of 91%.[16]

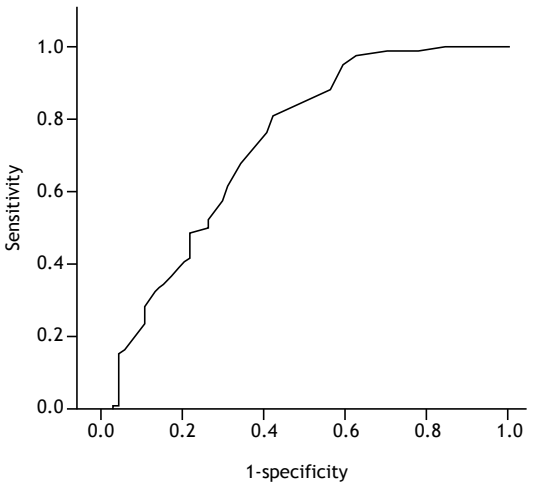

Figure 2. ROC curve analysis: when a lymph node size (short-axis diameter) cut-off value of 16.5 mm was applied, the sensitivity and specificity of endobronchial ultrasound (for a diagnosis of granulomatous disease or malignancy) were 76% and 60%, respectively. Diagonal segments are produced by ties.

One recent study reported that EBUS-TBNA has a diagnostic accuracy of 93.9% for malignancy,[8] compared with only 77% in the present study. That same study reported that the diagnostic accuracy of EBUS-TBNA was higher for malignant diseases than for benign diseases (93.9% vs. 70.6%, $p < 0.001$). In our study, the diagnostic accuracy of EBUS-TBNA for benign granulomatous disorders was not significantly different from that observed for malignant disease (83% vs. 77%, $p > 0.05$). Memoli et al.[17] showed that increased lymph node size supports an EBUS-based diagnosis of malignancy. Abu-Hijleh et al.[18] suggested that lymph node size has little effect on diagnostic accuracy or sensitivity of EBUS-TBNA. In contrast, when lymph node size exceeds 20 mm, the negative predictive value decreases. Those authors found that samples taken from lymph nodes ≥ 20 mm in size always contained sufficient material for analysis. The same authors reported that samplings of the 4R, 4L, 7, 10/11R, and 10/11L lymph nodes did not differ in terms of diagnostic accuracy.[18] Tedde et al.[19] showed that identifying lymphadenopathy in multiple lymph nodes and sampling subcarinal lymph nodes provides a higher diagnostic yield in EBUS-TBNA. Those authors reported that EBUS-TBNA has a diagnostic accuracy of 57% for malignancy. In the present study, lymph nodes with a short-axis diameter ≥ 16.5 mm were found to be more diagnostic in the histopathological evaluation than were those with smaller diameters. We also found that the diagnostic accuracy of EBUS-TBNA was better when there was mediastinal lymph node enlargement than when there was hilar lymph node enlargement. In a study conducted by Cetinkaya et al.,[20] the sensitivity of EBUS-TBNA was lower in the region of lymph node 4L than in those of the other lymph nodes. The authors reported that the overall diagnostic accuracy of EBUS-TBNA was not affected by the number of lymph nodes sampled, the number of times a lymph node region was sampled, or lymph node size.[20]

In our study sample, we noted that EBUS-TBNA provoked only minor complications, such as mild hypoxia, tachycardia, and minor hemorrhage. None of

those complications changed the course of the procedure or led to additional treatment or hospitalization. We can therefore assert that the procedure can be used safely in all adult age groups. Similar studies in the literature have also reported that EBUS-TBNA is safe and causes no severe complications.[8,20-23]

In conclusion, EBUS-TBNA is a proven method in the diagnosis and staging of malignancy. The diagnostic accuracy of this method is also high in benign pathologies such as sarcoidosis and tuberculosis. It is a method that is well-tolerated and minimally invasive, with a low rate of complications and high diagnostic accuracy. The use of EBUS-TBNA should be encouraged as the first procedure of choice for mediastinal and hilar lung pathologies, because it markedly reduces the need for mediastinoscopy.

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Sarcopenia in COPD: relationship with COPD severity and prognosis

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ABSTRACT

Objective: To evaluate the prevalence of sarcopenia in COPD patients, as well as to determine whether sarcopenia correlates with the severity and prognosis of COPD. **Methods:** A cross-sectional study with COPD patients followed at the pulmonary outpatient clinic of our institution. The patients underwent dual-energy X-ray absorptiometry. The diagnosis of sarcopenia was made on the basis of the skeletal muscle index, defined as appendicular lean mass/height^2 only for low-weight subjects and adjusted for fat mass in normal/overweight subjects. Disease severity (COPD stage) was evaluated with the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria. The degree of obstruction and prognosis were determined by the **B**ody mass index, airflow **O**bstruction, **D**yspnea, and **E**xercise capacity (BODE) index. **Results:** We recruited 91 patients (50 females), with a mean age of 67.4 ± 8.7 years and a mean BMI of 25.8 ± 6.1 kg/m^2. Sarcopenia was observed in 36 (39.6%) of the patients, with no differences related to gender, age, or smoking status. Sarcopenia was not associated with the GOLD stage or with FEV_1 (used as an indicator of the degree of obstruction). The BMI, percentage of body fat, and total lean mass were lower in the patients with sarcopenia than in those without ($p < 0.001$). Sarcopenia was more prevalent among the patients in BODE quartile 3 or 4 than among those in BODE quartile 1 or 2 ($p = 0.009$). The multivariate analysis showed that the BODE quartile was significantly associated with sarcopenia, regardless of age, gender, smoking status, and GOLD stage. **Conclusions:** In COPD patients, sarcopenia appears to be associated with unfavorable changes in body composition and with a poor prognosis.

Keywords: Sarcopenia; Body composition; Pulmonary disease, chronic obstructive; Severity of illness index.

INTRODUCTION

It is well known that COPD is a highly prevalent disease, affecting up to 10% of adults over the age of 40, with high rates of morbidity and mortality.[1] It is associated with various extrapulmonary disorders, such as cardiovascular disease, osteoporosis, cachexia, and anemia. Previous studies have indicated an association between low BMI and shorter survival in COPD patients.[2,3] However, more recent data demonstrate that specific unfavorable changes in body composition, especially a decrease in lean mass, can be more reliable predictors of mortality than is low BMI alone.[4,5] In patients with COPD, such changes have been shown to be related to exercise intolerance, impaired quality of life, and increased mortality.[6] Few studies in the literature have correlated the prevalence of sarcopenia with indices of COPD severity. In addition, to date, there have been no studies correlating sarcopenia with the prognosis of COPD or correcting sarcopenia by the BMI to avoid misdiagnosis in overweight patients.

In COPD patients over 50 years of age, there is a reduction of 1-2% per year in muscle mass.[4] In addition, among those in the 50- to 60-year age group and those over 60 years of age, muscle force has been shown to decline by 1.5% and 3.0% per year, respectively.[4] This phenomenon, known as sarcopenia, is an important indicator of frailty syndrome. Sarcopenia has been shown to occur in approximately 5-13% of all individuals over 65 years of age,[7] as well as in 20-40% of all COPD patients, which might include even the 10-15% of COPD patients who are of normal weight.[2]

In patients with COPD, a decrease in exercise capacity is the main factor limiting activities of daily living and is directly related to an increased risk of exacerbations.[8] It has been suggested that such a decrease is the best predictor of early mortality in COPD.[3] The degree of exercise capacity impairment (exercise intolerance), which results from factors such as impaired pulmonary function, limitation of gas exchange, and skeletal muscle dysfunction, is related to COPD severity. In the presence of dyspnea, such alterations lead to further impairment of physical activity, initiating a vicious cycle, also known as a downward spiral.[6,8]

The aim of this study was to evaluate the prevalence of sarcopenia in COPD patients. We also attempted to determine whether sarcopenia correlates with indices of COPD severity and with its prognosis.

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METHODS

Patients and procedures

This was a cross-sectional study involving 96 consecutive COPD patients, all over 50 years of age, treated at the Pulmonary Outpatient Clinic of the Federal University of Paraná *Hospital de Clínicas*, in the city of Curitiba, Brazil, between January of 2010 and December of 2011. The diagnosis of COPD was made on the basis of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria[9]: persistent progressive airflow limitation; and an increased chronic inflammatory response to noxious particles or gases in the airways and lungs, as evidenced by a post-bronchodilator FEV_1/FVC ratio < 0.70 on spirometry.[9] The inclusion criteria were having smoking-related COPD, having undergone pulmonary function testing with a spirometer (KoKo PFT; nSpire Health, Longmont, CO, USA), and having a post-bronchodilator FEV_1/FVC ratio < 0.70. We excluded patients for whom any of the required test results were unavailable, as well as those who were taking drugs that can reduce lean mass and those who had any other disease known to affect body composition. The study was approved by the *Hospital de Clínicas* Ethics Committee on Human Research, and all participating patients gave written informed consent.

We collected clinical data, including lifetime smoking history, quantified in pack-years[10]; history of exacerbations in the last year; FEV_1; the modified Medical Research Council dyspnea scale score[11]; the score on the COPD Assessment Test, which quantifies the overall impact that COPD has on health status[12]; and the six-minute walk distance.[13]

The patients were classified by the percentage of predicted FEV_1 (i.e., the degree of obstruction): ≥ 80% (mild); 50-79% (moderate); 30-49% (severe); and < 30% (very severe).[9] The severity (clinical stage) of COPD was determined according to the GOLD criteria[9]: post-bronchodilator FEV_1; history of exacerbations in the last year; and symptoms such as dyspnea (measured by modified Medical Research Council dyspnea scale or COPD Assessment Test). On the basis of those criteria, each patient was categorized as having COPD that was at GOLD stage I, II, III, or IV.[9] We evaluated COPD prognosis using the **B**ody mass index, airflow **O**bstruction, **D**yspnea, and **E**xercise capacity (BODE) index, stratifying the patients into four quartiles, the fourth being the most severe.[14]

Weight (in kg) was measured, with the patients wearing light clothing, on a digital electronic scale (Toledo do Brasil, São Bernardo do Campo, Brazil) with a maximum capacity of 200 kg and an accuracy of 50 g. Height (m) was measured while the patients were standing with their back straight, heels together, and arms at their sides. On the basis of the BMI, the patients were classified as underweight (BMI < 22 kg/m^2), normal weight (BMI ≥ 22 and < 27 kg/m^2), or overweight/obese (BMI ≥ 27 kg/m^2), according to the categories established by Lipschitz et al.,[15] which are the most suitable for use in middle-aged and elderly individuals.

For the assessment of body composition, all patients underwent dual-energy X-ray absorptiometry (DXA) in a whole-body scanner (Lunar Prodigy; GE Medical Systems, Madison, WI, USA), used in conjunction with enCORE 2002 software (GE Medical Systems). The software provides data about lean body mass (bone mass plus fat-free mass), bone-free lean mass (lean mass minus fat-free mass), fat mass, and bone mineral density.

Densitometric diagnosis of sarcopenia

The criteria for a diagnosis of sarcopenia by DXA were initially defined by Baumgartner et al.[16] in a study involving a large sample of elderly individuals in the state of New Mexico. However, using those criteria, the authors found that the prevalence of sarcopenia was underdiagnosed, probably due to the high proportions of overweight and obese individuals in the population studied. Newman et al.[17] proposed new methods for defining sarcopenia, by adjusting height and the appendicular lean mass (ALM) by the fat mass, which resulted in prevalence rates that were higher than those obtained with the former criteria.[17,18] However, those authors found that the former criteria continued to be superior for diagnosing sarcopenia in underweight patients. In two recent studies conducted in Brazil, Domiciano et al.[19] and Figueiredo et al.[20] compared the two sets of criteria and concluded that the cut-off BMI value of 22 kg/m^2 defined the choice of criteria to be used for the densitometric diagnosis of sarcopenia.

For the purpose of the densitometric diagnosis of sarcopenia, we used both systems of determining ALM: using the skeletal muscle index (SMI), calculated as ALM (in kg) relative to height squared in meters (ALM/height^2), with cut-off values of 7.26 kg/m^2 and 5.45 kg/m^2 for men and women, respectively, hereafter referred to as the Baumgartner criteria[16]; and calculating ALM (in kg) relative to height in meters and adjusted for total body fat mass (in kg), hereafter referred to as the Newman criteria.[17] The residuals of the regression were used in order to identify individuals with a lean mass lower than the value predicted for a given fat mass (given by an equation derived from the model). A positive residual would indicate a relatively muscular individual, whereas a negative residual would indicate an individual with sarcopenia. The equations derived from the model were as follows:

for men

$$ALM \text{ (in kg)} = -28.15 + 27.49 \times height \text{ (in m)} + 0.1106 \times fat\ mass \text{ (in kg)}$$

for women

$$ALM \text{ (in kg)} = -19.78 + 20.00 \times height \text{ (in m)} + 0.1554 \times fat\ mass \text{ (in kg)}$$

The 20th percentile of the distribution of residuals was used as the cut-off value for the diagnosis of sarcopenia, according to the ALM adjusted for fat

mass, as previously defined.[17,18] In our patient sample, that cut-off value corresponded to residuals of −2.021 for men and −1.082 for women. To make the densitometric diagnosis of sarcopenia, we applied the Baumgartner criteria for individuals with a BMI < 22 kg/m^2 and the Newman criteria for individuals with a BMI ≥ 22 kg/m^2.[21]

Statistical analysis

Data are presented as mean ± SD, except where otherwise specified. All statistical analyses were performed with the SPSS Statistics software package, version 20.0 (IBM Corporation, Armonk, NY, USA). For the variables evaluated, the normality of the data distribution was evaluated with the Kolmogorov-Smirnov test. For comparisons of quantitative variables between two groups, we used the Student's t-test for independent samples or the nonparametric Mann-Whitney test. For comparisons among three or more groups, we used one-way ANOVA and the least significant difference test for multiple comparisons or the nonparametric Kruskal-Wallis test. In the preliminary statistical analysis, we used Fisher's exact test and the chi-square test to assess the association between two qualitative variables. Values of $p < 0.05$ were considered statistically significant.

For multivariate analysis, we used logistic regression, considering sarcopenia as the response (dependent) variable and the following as explanatory (independent) variables: age (≤ 67 or > 67 years), female gender, GOLD stage III or IV, BODE quartile 3 or 4, and current smoking. For each variable, in the presence of the other variable included in the model, we tested the null hypothesis that the probability of sarcopenia is equal for the two classifications of the variable (lack of association between the variable and sarcopenia), versus the alternative hypothesis of different probabilities. We calculated the p values of the statistical tests, as well as odds ratios with their corresponding 95% confidence intervals.

RESULTS

Of the 96 patients evaluated, 5 were excluded because they did not perform all of the required tests. Therefore, the final sample comprised 91 patients (50 women and 41 men), with a mean age of 67.4 ± 8.7 years and a mean BMI of 25.8 ± 6.1 kg/m^2. Twenty-five patients (27.4%) were classified as normal weight, 28 (30.7%) were classified as underweight, and 38 (41.7%) were classified as overweight. The overall mean percentage of total body fat mass was 32.3 ± 11.7% (37.8 ± 15.8% in women and 25.6 ± 7.1% in men; $p = 0.000$), and the overall mean SMI was 6.57 ± 1.1 (6.17 ± 5 for women and 7.05 ± 5.3 for men, $p = 0.000$). The mean smoking history was 60 ± 41.4 pack-years. Sixteen patients (17.6%) were current smokers at enrollment in the study.

On the basis of the FEV_1 values, the degree of obstruction was classified as mild in 16 (17.6%) of the patients, moderate in 33 (36.3%), severe in 29 (31.9%), and very severe in 13 (14.3%). Among the 91 patients evaluated, COPD was classified as GOLD stage I in 15 (16.5%), as GOLD stage II in 22 (24.2%), as GOLD stage III in 34 (37.4%), and as GOLD stage IV in 20 (22%). Stratified by the BODE index, 36 patients (39.6%) were in the first quartile, 29 (31.9%) were in the second quartile, 15 (16.5%) were in the third quartile, and 11 (12.1%) were in the fourth quartile.

We found that BMI did not correlate significantly with FEV_1 ($p = 0.509$), GOLD stage ($p = 0.114$), or BODE quartile ($p = 0.114$). Sarcopenia was diagnosed in 36 patients (39.6%): 16 women and 20 men. When we stratified that result by BMI, we found that sarcopenia was present in 5 (20.0%) of the 25 normal weight patients, 23 (82.1%) of the 28 underweight patients, and 8 (21.1%) of the 38 overweight patients. Figure 1 shows the number of patients with sarcopenia, by BMI, according to the set of criteria used in making the diagnosis. There were no significant differences in the prevalence of sarcopenia in relation to gender ($p = 0.276$), age ($p = 0.309$), or smoking history ($p = 0.464$). The mean SMI was 5.86 ± 0.7 in the patients with sarcopenia (5.38 ± 0.42 in women and 6.25 ± 0.57 in men), compared with 7.03 ± 1.0 in those without (6.54 ± 0.89 in women and 7.81 ± 0.77 in men), the difference between the two groups being significant ($p < 0.001$). As can be seen in Table 1, the patients with sarcopenia also showed lower BMI ($p < 0.001$), lower percentage of total body fat ($p = 0.01$), and lower total lean mass ($p < 0.001$).

There was no association between the prevalence of sarcopenia and the severity of COPD, as determined by GOLD stage and FEV_1 (Figures 2A and 2B). There was a tendency toward an association between the prevalence of sarcopenia and the BODE quartile ($p = 0.06$). As depicted in Figure 3A, 11 patients (30.5%) were in the first quartile, 9 (31%) were in the second, 8 (60%) were in the third, and 9 (63.6%) were in the fourth. Figure 3B shows that the prevalence of sarcopenia among the patients in quartile 3 or 4 was 61.4%, significantly higher than the 30.7% seen among those in quartile 1 or 2 ($p = 0.009$; OR = 3.89; 95% CI: 1.21-12.46). The multivariate analysis showed that, regardless of age, gender, GOLD stage, and smoking status, the BODE index was significantly associated with sarcopenia (Table 2).

DISCUSSION

In our sample of COPD patients, there was a high prevalence of DXA-diagnosed sarcopenia, which was found to correlate with a poor prognosis. In patients with COPD, various factors have been shown to be associated with a worse prognosis, a higher number of hospitalizations, and shorter survival; chief among such factors is changes in body composition.[4] Low BMI has been associated with acute exacerbations, mortality, and loss of lean mass in COPD patients.[5] In

the present study, we confirmed that a loss of lean body mass is associated with lower BMI in COPD patients. However, we did not find BMI to be associated with COPD severity or a worse prognosis, which is in agreement with the findings of recent studies demonstrating that reduced lean mass is a better predictor of mortality in COPD patients than is low BMI alone, the former reducing survival by up to 50%.[22]

In our study, the overall prevalence of sarcopenia was 39.6%, which is consistent with the literature on COPD patients, in which the reported prevalence is 20-40%.[5,22] Cesari et al.[23] diagnosed sarcopenia in 30% of the COPD patients evaluated; when the authors adjusted for fat mass, that rate rose to 42.5%, a difference that was primarily attributed to the increased proportion of obese patients diagnosed. When we applied the Baumgartner criteria, we diagnosed sarcopenia in 37 patients (40.6%), compared with only 19 patients (21.0%) when we applied the Newman criteria. That was mainly due to the fact that the mean BMI in our sample was lower than that reported in the other studies cited. For overweight and obese patients, adjusting for fat mass (i.e., applying the Newman criteria) was especially important, because it increased the prevalence of sarcopenia by 8% over that obtained when the Baumgartner criteria were applied. This demonstrates the importance of making this adjustment, which can prevent underdiagnosis.

The loss of lean body mass in patients with COPD has previously been shown to be associated with lower BMI,[6] and we confirmed that. However, sarcopenia also occurs in approximately 20% of normal-weight, overweight, and obese patients. One study showed that a decrease in muscle mass occurs in 21% of normal-weight patients with COPD,[24] and another

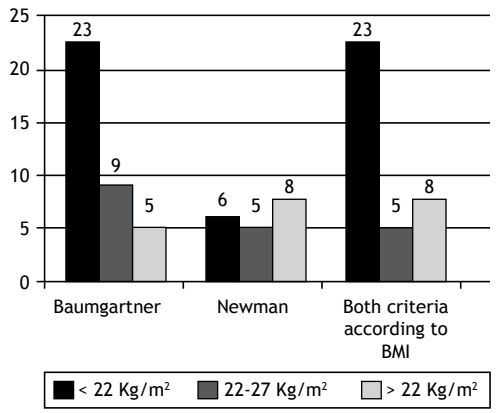

Figure 1. Number of patients with sarcopenia, by BMI, depending on the set of criteria used for the diagnosis: (left) the criteria by Baumgartner et al.[16] in all patients; (center) the criteria by Newman et al.[17] in all patients; and (right) the criteria by Baumgartner et al.[16] for patients with a BMI < 22 kg/m² and the criteria by Newman et al.[17] for patients with a BMI ≥ 22 kg/m².

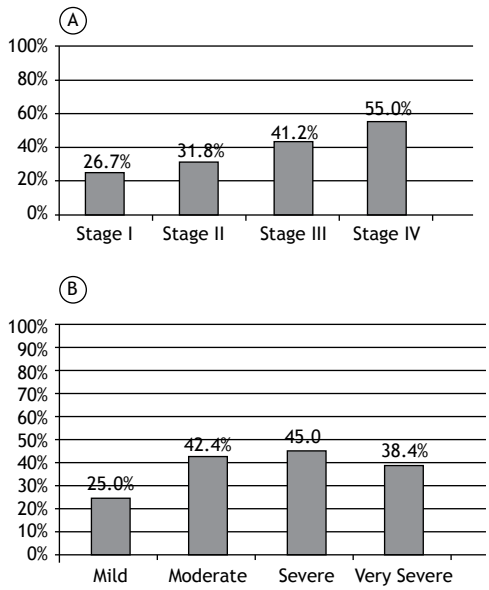

Figure 2. Prevalence of sarcopenia, diagnosed with dual-energy X-ray absorptiometry, among COPD patients (N = 91), by COPD severity (GOLD stage, in A) and degree of obstruction (FEV_1, in B). Sarcopenia did not correlate significantly with GOLD stage (p = 0.305) or FEV_1 (p = 0.599). Degree of obstruction (FEV_1): Mild (≥ 80%); Moderate (50-79%); Severe (30-49%); and Very severe (< 30%).

Table 1. Differences between COPD patients with and without sarcopenia.[a]

Variable	Sarcopenia (n = 36)	No sarcopenia (n = 55)	p
Age, years	68.6 ± 10.4	66.6 ± 7.46	0.309
BMI, kg/m²	22.2 ± 4.9	28.2 ± 5.6	< 0.001*
% Total BF	28 ± 14.2	35.1 ± 8.8	0.01*
Lean mass, kg			
Arms	4.6 ± 1.2	3.9 ± 1.0	0.003*
Legs	11.1 ± 2.0	13.6 ± 3.2	< 0.001*
Total	37.4 ± 6.4	44.1 ± 9.3	< 0.001*
Skeletal muscle index[b]			
All patients	5.86 ± 0.7	7.03 ± 1.0	< 0.001*
Women	5.38 ± 0.42	6.25 ± 0.57	< 0.001*
Men	6.54 ± 0.89	7.81 ± 0.77	< 0.001*

% Total BF: percentage of total body fat. [a]Results expressed as mean ± SD. [b]Appendicular lean mass/height².

showed that 10-15% of COPD patients with a normal or high BMI have sarcopenia.[25]

Cigarette smoking is one of the mechanisms involved in the increased protein catabolism in COPD, as demonstrated in various epidemiological association studies on smoking and sarcopenia.[26] Although there is controversy in the literature, one study demonstrated an association between smoking history and a loss of lean mass in COPD patients,[27] whereas others have shown no such association.[28,29] In the present study, we observed no association between smoking history and sarcopenia. One possible explanation for that finding is that patients with COPD show a high, persistent inflammatory state, with elevated levels of TNF-α, which is involved in the physiopathology of sarcopenia, independently of the smoking history.[27]

In our sample of COPD patients, we found that a diagnosis of sarcopenia correlated with lower BMI, a reduction in the overall percentage of body fat, lower total lean mass, and the SMI. These findings are consistent with those of other studies of sarcopenia in patients with and without COPD,[30,31] an annual reduction in muscle mass of 1-2% over 50 years having been shown to occur in COPD patients.[32] A loss of lean body mass occurs by several mechanisms, such as TNF-α-mediated motor neuron death, hormonal changes, nutritional status, and an increase in inflammatory factors. In our study, we detected no increase in the prevalence of sarcopenia with advancing age, which is in agreement with the findings of other studies of COPD.[33,34] One possible explanation for this is that the severity of the disease and the elevated levels of inflammatory cytokines, present from the onset of COPD, contribute to a greater loss of lean mass, regardless of age.[35]

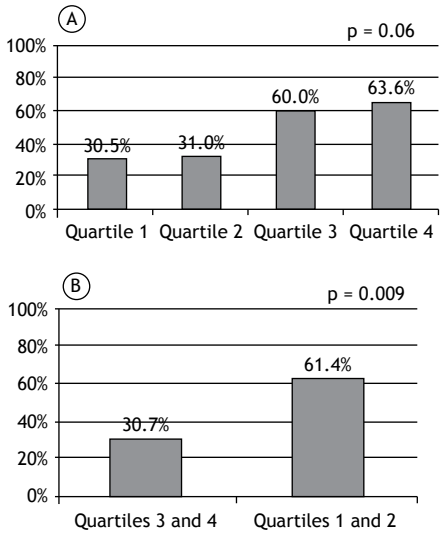

Figure 3. Proportion of patients diagnosed with sarcopenia by densitometry according to the quartiles of the **B**ody mass index, airflow **O**bstruction, **D**yspnea, and **E**xercise capacity (BODE) prognostic index, grouped by quartile (in A) and pooled (in B) into a less severe group (quartiles 1 and 2) and a more severe group (quartiles 3 and 4).

In the present study, neither the GOLD stage nor the degree of obstruction (FEV_1) was found to correlate with a diagnosis of sarcopenia. The number of patients studied and the distribution of the severity grades could explain that lack of correlation. In contrast with our findings, Ischaki et al.[36] showed that, in COPD patients, a greater loss of lean body mass translates to greater disease severity, as quantified by GOLD criteria and FEV_1. However, those authors assessed body composition using bioelectrical impedance analysis, which is less reliable than is DXA.[16] In another recent study, lower lean mass was also associated with worse FEV_1, although, again, body composition was assessed by bioelectrical impedance analysis.[37]

The BODE index, a prognostic parameter, considers exercise capacity, which can affect lean mass. We observed a trend toward a higher prevalence of sarcopenia among COPD patients in the higher BODE quartiles, and there was a statistically significant difference between those in the lower quartiles and those in the higher quartiles. In our multivariate analysis, the BODE index was significantly associated with sarcopenia, which was more prevalent among the patients with a worse prognosis (in quartile 3 or 4). To our knowledge, there have been no other studies investigating this association. A reduction in lean mass leads to exercise intolerance, which has been described as an essential factor for impairing quality of life, increasing the frequency of exacerbations/hospital admissions, and increasing mortality.[4] This confirms that sarcopenia is associated with a worse prognosis in COPD.

One limitation of our study is that we did not assess muscle strength. However, various studies have demonstrated a correlation between reduced lean body mass and decreased muscle strength.[38] In addition, this limitation was likely offset by the fact

Table 2. Multivariate analysis in which sarcopenia was the dependent variable.

Variable	Reference	p*	OR	95% CI
Age	≤ 67 years	0.055	2.80	1.06-7.37
Gender	Female	0.266	1.69	0.66-4.31
Clinical stage	GOLD stage III or IV	0.744	1.19	0.41-3.42
Smoking status	Current smoking	0.138	2.57	0.73-9.13
BODE index	Quartile 3 or 4	0.02*	3.89	1.21-12.46

GOLD: Global Initiative for Chronic Obstructive Lung Disease; and BODE: **B**ody mass index, airflow **O**bstruction, **D**yspnea, and **E**xercise capacity. *Wald test (logistic regression) level of significance, $p < 0.05$.

that we applied the BODE index, which takes exercise capacity into account.

The results of the present study demonstrate that the prevalence of sarcopenia, as diagnosed by DXA, which is currently considered the gold standard method, was high in a sample of patients with COPD. Ours was a pioneering study in that we correlated the prevalence of sarcopenia with the BODE index quartile. The impairment and loss of lean mass are common and worrisome; as COPD extrapulmonary manifestations, they cause a reduction in exercise capacity. This can also result in even more pronounced loss of muscle mass, thus initiating a vicious cycle. Therefore, early diagnosis of sarcopenia, through the analysis of body composition, can facilitate the implementation of interventions aimed at preventing the deterioration of lean body mass and improving quality of life in patients with COPD.

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ORIGINAL ARTICLE

Determining respiratory system resistance and reactance by impulse oscillometry in obese individuals

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ABSTRACT

Objective: To evaluate peripheral respiratory system resistance and reactance (Rrs and Xrs, respectively) in obese individuals. **Methods:** We recruited 99 individuals, dividing them into four groups by body mass index (BMI): < 30.0 kg/m^2 (control, n = 31); 30.0-39.9 kg/m^2 (obesity, n = 13); 40.0-49.9 kg/m^2 (severe obesity, n = 28); and ≥ 50.0 kg/m^2 (morbid obesity, n = 13). Using impulse oscillometry, we measured total Rrs, central Rrs, and Xrs. Peripheral Rrs was calculated as the difference between total Rrs and central Rrs. All subjects also underwent spirometry. **Results:** Of the 99 individuals recruited, 14 were excluded because they failed to perform forced expiratory maneuvers correctly during spirometry. The individuals in the severe obesity and morbid obesity groups showed higher peripheral Rrs and lower Xrs in comparison with those in the two other groups. **Conclusions:** Having a BMI ≥ 40 kg/m^2 was associated with a significant increase in peripheral Rrs and with a decrease in Xrs.

Keywords: Obesity; Airway obstruction; Oscillometry; Respiratory function tests.

INTRODUCTION

Obesity currently poses a major risk to human health, affecting more than 600 million people worldwide[1] and constituting a predisposing factor for other health problems, including respiratory diseases, cardiovascular diseases, osteoarticular diseases, diabetes, and hyperlipidemia.[2]

Thoracic and abdominal adipose tissue accumulation results in reduced respiratory system compliance and, consequently, increased respiratory effort. In addition, reduced expiratory reserve volume (ERV) and functional residual capacity result in a decrease in lung elastic recoil pressure. The aforementioned factors can play a role in reducing peripheral airway caliber and increasing respiratory system resistance (Rrs) in obese individuals.[3-6] In addition, increased circulating leptin levels are associated with reduced airway caliber and predispose to increased bronchial hyperresponsiveness.[7,8]

A variant of the forced oscillation technique, impulse oscillometry (IO) is a noninvasive, effort-independent method for assessing respiratory mechanics.[9] Previously studied in clinical practice, IO involves the application of pressure pulses of single or multiple frequencies to the airways, allowing measurement of Rrs, respiratory system impedance, and respiratory system reactance (Xrs).[4,10,11]

One of the advantages of IO over other methods is that it allows differentiation between central Rrs and peripheral Rrs.[11] In addition, the fact that IO requires no patient effort and minimal patient cooperation makes it easier to perform than spirometry or plethysmography.[12,13]

The objective of the present study was to evaluate peripheral Rrs and Xrs by IO in individuals with varying degrees of obesity.

METHODS

This was an exploratory, comparative observational study conducted between June of 2007 and March of 2010 in the *Laboratório de Função Pulmonar* of the *Hospital das Clínicas* of the *Universidade Federal de Pernambuco*, in the city of Recife, Brazil. The study was approved by the local research ethics committee (Protocol no. 0316.0.172.000-07). All participants gave written informed consent.

We recruited 99 individuals between 18 and 60 years of age, dividing them into four groups by body mass index (BMI): < 30.0 kg/m^2 (control, n = 31); 30.0-39.9 kg/m^2 (obesity, n = 13); 40.0-49.9 kg/m^2 (severe obesity, n = 28); and ≥ 50.0 kg/m^2 (morbid obesity, n = 13). Only 12 participants had FVC or FEV_1/FVC values below 80% of predicted, 3 of whom were in the control group and 9 of whom were in the severe obesity group.

Individuals with a history of pulmonary disease were excluded, as were those with signs and symptoms of recent pulmonary disease (wheezing on auscultation, cough, or dyspnea), those with a history of smoking, those with chest X-ray changes, those with neurological

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disease, those with musculoskeletal disease, and those who failed to perform forced expiratory maneuvers correctly during spirometry.

Anthropometric data (weight and height) were obtained with the use of an electronic scale (Metalúrgica Arja, São Paulo, Brazil), whereas IO and spirometric parameters were obtained with the MasterScreen IO system (Jäeger, Würzburg, Germany). All tests were performed with the individuals sitting comfortably with both feet flat on the floor, breathing through a plastic mouthpiece, and using a nose clip. The IO system was calibrated daily before data collection, by the variable flow method with a 3-liter syringe (Jäeger).

Spirometry was performed in accordance with the American Thoracic Society guidelines.[14] We evaluated slow vital capacity (SVC), ERV, inspiratory capacity, FVC, FEV_1, FEV_1/FVC, and $FEF_{25-75\%}$. For SVC, inspiratory capacity, and FEV_1, the highest values obtained from three acceptable maneuvers were selected, whereas $FEF_{25-75\%}$ was obtained from the maneuver with the highest sum of FVC and FEV_1. The data obtained were compared with the predicted values for the Brazilian population.[15]

During IO, patients were instructed to keep their lips around the mouthpiece and breathe normally for 40 s while pressing their cheeks together in order to prevent movement and reduce the upper airway shunt effect. The harmonic frequencies of the sound waves ranged from 5 Hz to 35 Hz, and pressure never exceeded 5.98 cmH_2O (0.5 kPa). We measured total Rrs (5 Hz), central Rrs (20 Hz), Xrs (5 Hz), and resonant frequency (Fres). Peripheral Rrs (also known as frequency dependence of resistance) was calculated as the difference between total Rrs and central Rrs. Low-frequency Xrs is associated with the peripheral airways, which is why Xrs was measured at a frequency of 5 Hz.[16]

To ensure reliability, measurements were repeated until consistency was > 0.7 for a frequency of 5 Hz and > 0.9 for a frequency of 20 Hz, a maximum of five maneuvers being performed.[10]

The Kolmogorov-Smirnov test was used in order to assess the distribution of variables. Fisher's exact test was used in order to compare categorical variables. One-way ANOVA and the Kruskal-Wallis test were used in order to compare variables between groups. The chi-square test was used in order to evaluate nominal variables, and Tukey's post hoc test was used in order to determine the pairs of groups that differed from one another. GraphPad Prism, version 4 (GraphPad Software Inc., San Diego, CA, USA), and Microsoft Office Excel 2007 were used.

RESULTS

A total of 99 individuals participated in the present study. Although all individuals were able to perform IO maneuvers correctly, 14 failed to perform forced expiratory maneuvers correctly during spirometry and were therefore excluded. Of those 14 individuals, 2 were in the control group, 2 were in the obesity group, 5 were in the severe obesity group, and 5 were in the morbid obesity group.

Table 1 presents the general characteristics of the 85 individuals who remained in the study, by group. There were no differences among the groups regarding age. With regard to gender, females predominated in the control, severe obesity, and morbid obesity groups.

Table 2 shows an intergroup comparison of mean spirometric values (in % of predicted) in the study population. Both FVC and FEV_1 were significantly lower in the morbid obesity group than in the control and obesity groups; SVC was significantly lower in the morbid obesity group than in the obesity group; and ERV was significantly lower in the severe obesity and morbid obesity groups than in the control and obesity groups.

Table 3 shows an intergroup comparison of mean IO values in the study population. Total Rrs and peripheral Rrs were highest in the severe obesity and morbid obesity groups. This shows that peripheral Rrs is the major factor responsible for an overall increase in Rrs. In addition, Xrs was lowest in the severe obesity and morbid obesity groups. There was a slight negative association between peripheral Rrs and ERV ($R = -0.32$; $p < 0.01$).

DISCUSSION

Obesity is a major risk factor for pulmonary complications arising from changes in lung volumes

Table 1. General characteristics of the study population (N = 85), by group.[a]

Characteristic	Group[b]				p
	Control (n = 31)	Obesity (n = 13)	SO (n = 28)	MO (n = 13)	
Gender*					
Male	9 (29.1)	8 (61.5)	4 (14.2)	5 (38.4)	0.1825
Female	22 (70.9)	5 (38.5)	24 (85.8)	8 (61.6)	0.5826
Age, years**	31.8 ± 11.3	39.6 ± 9.2	34.8 ± 12.4	34.1 ± 6.9	0.1924
BMI, kg/m²**	24.2 ± 3.0	32.6 ± 2.7	45.5 ± 2.7	56.7 ± 5.2	< 0.0001

SO: severe obesity; MO: morbid obesity; and BMI: body mass index. [a]Values expressed as n (%) or mean ± SD. [b]Control group: BMI < 30.0 kg/m²; obesity group: BMI = 30.0-39.9 kg/m²; SO group: BMI = 40.0-49.9 kg/m²; and MO group: BMI ≥ 50.0 kg/m². *Chi-square test. **One-way ANOVA and Tukey's post hoc test.

Table 2. Spirometric variables (in % of predicted) in the study population (N = 85).[a]

Variable	Group[b]			
	Control (n = 31)	Obesity (n = 13)	SO (n = 28)	MO (n = 13)
FVC	97.6 ± 15.5	100.6 ± 12.5	90.6 ± 12.2	81.9 ± 14.3*†
FEV_1	97.4 ± 12.1	99.5 ± 14.9	90.6 ± 12.6	82.4 ± 16.6*†
FEV_1/FVC	84.6 ± 7.4	81.4 ± 7.9	83.4 ± 6.2	84.3 ± 6.7
$FEF_{25-75\%}$	98.3 ± 19.1	106.2 ± 29.0	95.3 ± 27.4	83.1 ± 29.0
ERV	121.6 ± 35.7	111.8 ± 53.0	73.3 ± 27.6*†	52.3 ± 26.2*†
IC	96.7 ± 26.4	114.7 ± 16.2	110.9 ± 19.6	106.7 ± 29.3
SVC	100.7 ± 15.8	104.9 ± 17.2	97.9 ± 10.8	88.4 ± 16.2¶

SO: severe obesity; MO: morbid obesity; ERV: expiratory reserve volume; IC: inspiratory capacity; and SVC: slow vital capacity. [a]Values expressed as mean ± SD. [b]Control group: BMI < 30.0 kg/m^2; obesity group: BMI = 30.0-39.9 kg/m^2; SO group: BMI = 40.0-49.9 kg/m^2; and MO group: BMI ≥ 50.0 kg/m^2. *p < 0.01 vs. control group. †p < 0.01 vs. obesity group. ¶p < 0.05 vs. obesity group. One-way ANOVA and Tukey's post hoc test.

Table 3. Impulse oscillometry variables in the study population (N = 85).[a]

Variable	Group[b]			
	Control (n = 31)	Obesity (n = 13)	SO (n = 28)	MO (n = 13)
Total Rrs, $cmH_2O/L/s$	4.3 ± 1.1	4.5 ± 1.5	5.6 ± 1.7*	6.0 ± 1.2†
Total Rrs, % of predicted[c]	130.2 ± 36.6	136.5 ± 39.7	163.0 ± 54.0¶	185.6 ± 46.0†**
Central Rrs, $cmH_2O/L/s$	3.7 ± 1.0	3.7 ± 1.2	4.2 ± 1.4	4.4 ± 1.1
Central Rrs, % of predicted[c]	135.1 ± 38.2	133.9 ± 39.7	146.3 ± 51.7	161.9 ± 48.0
Peripheral Rrs, $cmH_2O/L/s$	0.5 ± 0.4	0.7 ± 0.4	1.4 ± 0.6*†	1.6 ± 0.4*†
Fres, Hz	13.5 ± 3.6	16.2 ± 2.6	19.2 ± 3.1*.**	20.4 ± 3.9*.**
Xrs, $cmH_2O/L/s$	−1.3 ± 0.4	−1.6 ± 0.9	−2.0 ± 0.8¶	−2.1± 0.9¶

SO: severe obesity; MO: morbid obesity; Rrs: respiratory system resistance; Fres: resonant frequency; and Xrs: respiratory system reactance. [a]Values expressed as mean ± SD. [b]Control group: BMI < 30.0 kg/m^2; obesity group: BMI = 30.0-39.9 kg/m^2; SO group: BMI = 40.0-49.9 kg/m^2; and MO group: BMI ≥ 50.0 kg/m^2. [c]Calculated on the basis of Pelosi et al.[20] *p < 0.01 vs. control group. †p < 0.01 vs. obesity group. ¶p < 0.05 vs. control group. **p < 0.05 vs. obesity group. One-way ANOVA and Tukey's post hoc test.

and peripheral Rrs and can lead to increased work of breathing and reduced gas exchange.[17-19]

The results of the present study show reduced SVC and FEV_1 in severely obese or morbidly obese individuals (Table 2), as reported elsewhere.[20-23] In addition, analysis of IO parameters revealed a strong association of the degree of obesity with increased peripheral Rrs and reduced Xrs (Table 3).

Fat deposition in the neck, thorax, and abdomen can lead to reduced lung volumes, resulting in reduced elastic recoil pressure of the lung and of the walls of the smaller bronchi, as well as in reduced airway caliber. In addition, the mechanical disadvantage imposed on the diaphragm by an increase in abdominal pressure leads to reduced ERV. The aforementioned factors, together with extrinsic airway compression, result in expiratory airflow limitation in obese individuals.[3]

In obese individuals, functional residual capacity is more markedly reduced than is residual volume; consequently, there is a marked reduction in ERV. Therefore, in obese individuals, tidal breathing occurs at low lung volumes. Under such conditions, some airways tend to narrow or even close during exhalation.[24] The association between IO variables and plethysmography variables should be evaluated in order to confirm the relationship between reduced lung volume and airway narrowing.

One advantage of IO over other methods for evaluating respiratory mechanics, such as spirometry and whole-body plethysmography, is that IO does not require forced expiratory maneuvers (which can affect bronchial tone), therefore requiring minimal patient cooperation.[13] In this regard, we were able to measure IO parameters correctly in 14 obese patients who failed to perform forced expiratory maneuvers correctly during spirometry.

Zerah et al.[5] used plethysmography in order to study lung volumes and respiratory mechanics in 46 individuals with no history of lung disease and found increased airway resistance and reduced lung volumes in those whose BMI was ≥ 30 kg/m^2. Oliveira et al.[4] used IO and found increased airway resistance in 25 obese individuals who were compared with 25 non-obese individuals. However, neither group of authors stratified patients by BMI. This was done in the present study, which showed that the aforementioned changes occur predominantly in severely obese or morbidly obese individuals, i.e., those whose BMI is ≥ 40 kg/m^2. In addition, we differentiated between central Rrs and peripheral Rrs, which clearly showed the role that the small airways play in airflow limitation in such patients, as demonstrated by increased Fres and peripheral Rrs.

Both Fres and peripheral Rrs as measured by IO, which are considered to be small airway markers,[25-27] can detect increased peripheral Rrs.[16] Friedman et al.[28] evaluated IO data from residents and area workers who inhaled dust and fumes from the World Trade Center disaster and found increased total Rrs and increased peripheral Rrs, which were associated with increased exposure to dust and fumes, as well as with lower respiratory symptoms.

In patients with mild to moderate asthma, Yamaguchi et al.[29] found reduced peripheral Rrs after 12 weeks of treatment with inhaled hydrofluoroalkane-134a beclomethasone dipropionate, which has ultrafine particles; however, no changes were observed in $FEF_{25-75\%}$. These findings suggest that IO is more sensitive to measure the response to asthma and COPD treatment than are other methods.[30]

A complex concept, Xrs incorporates lung elastic recoil properties. Low-frequency Xrs has been correlated with peripheral airway obstruction. At low frequencies, there is passive lung distension, increased lung compliance, reduced elastic recoil pressure, and reduced Xrs.[13] Xrs at 5 Hz expresses Xrs as a whole, being reduced in patients with restrictive lung disease and in those with chest wall disease.[13,16] Our comparative analysis revealed a significant reduction in Xrs in severely obese and morbidly obese individuals. This finding reflects the association between obesity and reduced Xrs, given that none of the study participants had abnormal chest X-ray findings or a history of collagen disease.

Our results show that individuals with a BMI ≥ 40 kg/m² can have normal spirometry results despite significant changes in respiratory mechanics, which are detected by IO. Reduced lung volume resulting from the interdependence of tissue structures reduces small airway diameter, increasing small airway resistance. Future studies will soon be able to show real, volume-corrected obstruction, combining IO data with residual volume and functional residual capacity as determined by plethysmography.

In this context, the clinical relevance of IO is evident, given that it is an accurate, noninvasive method for evaluating changes in respiratory mechanics (Rrs and Xrs) in the early stages of disease. The findings of the present study show the importance of drawing treatment plans aimed at reducing airway resistance and, consequently, improving lung function in obese individuals, especially those with respiratory symptoms. In addition, IO is an alternative method for evaluating patients who are unable to perform the required respiratory maneuvers for spirometry and plethysmography.

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ORIGINAL ARTICLE

Lung function and left ventricular hypertrophy in morbidly obese candidates for bariatric surgery

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ABSTRACT

Objective: To look for correlations between lung function and cardiac dimension variables in morbidly obese patients, in order to test the hypothesis that the relative size of the small airways is independently correlated with left ventricular hypertrophy. **Methods:** This was a retrospective study involving 192 medical records containing a clinical protocol employed in candidates for bariatric surgery between January of 2006 and December of 2010. **Results:** Of the 192 patients evaluated, 39 (10 males and 29 females) met the inclusion criteria. The mean BMI of the patients was 49.2 ± 7.6 kg/m^2, and the mean age was 35.5 ± 7.7 years. The FEF_{25-75}/FVC, % correlated significantly with left ventricular posterior wall thickness and relative left ventricular posterior wall thickness, those correlations remaining statistically significant ($r = -0.355$ and $r = -0.349$, respectively) after adjustment for weight, gender, and history of systemic arterial hypertension. Stepwise multivariate linear regression analysis showed that FVC and FEV_1 were the major determinants of left ventricular mass (in grams or indexed to body surface area). **Conclusions:** A reduction in the relative size of the small airways appears to be independently correlated with obesity-related cardiac hypertrophy, regardless of factors affecting respiratory mechanics (BMI and weight), gender, or history of systemic arterial hypertension. However, FEV_1 and FVC might be important predictors of left ventricular mass in morbidly obese individuals.

Keywords: Obesity; Spirometry; Echocardiography; Body mass index.

INTRODUCTION

Obesity is an isolated risk factor for cardiovascular disease; it can lead to cardiac hypertrophy followed by dilated cardiomyopathy, predisposing to fatal arrhythmias.[1] Obesity also causes organ-specific changes, which are due to a direct mechanical effect of the adipose tissue or occur systemically through humoral mediators and metabolic adjustments that change heart hemodynamics and geometry, as well as possibly lung function.[1-3]

A recent epidemiological study[4] found a relationship between lung function and left ventricular mass (LVM), although the relationship differed between genders. Functional effects of obesity that are associated with being male or female are common in pulmonary function testing, since fat concentrated in the chest (android obesity) could lead to deeper changes in lung function than could fat concentrated in the hips (gynecoid obesity). In contrast, another study, which had a case-control design and involved children with and without metabolic syndrome, found no relationship between lung function and LVM.[5]

Recent evidence suggests that inflammatory mediators act independently of confounding variables on cardiac remodeling in obese individuals,[2,6] as well as on lung function,[7,8] primarily at the level of the small airways. In contrast, there is evidence of purely mechanical cardiopulmonary effects, with no effect of inflammatory mediators,[9,10] or an interaction of mechanical and inflammatory factors in cases of lung function and asthma associated with obesity.[11]

Therefore, the primary objective of this exploratory study was to look for correlations between lung function and cardiac dimension variables, in order to test the hypothesis that regardless of being a purely mechanical or gender-related factor, the relative size of the small airways (dysanapsis), as measured indirectly by the ratio of $FEF_{25-75\%}$ to FVC (FEF_{25-75}/FVC, %), is correlated with left ventricular hypertrophy (remodeling), since the small airways are especially susceptible to mechanical-inflammatory interactions and bronchial hyperreactivity. Similarly, we aimed to determine the degree of association between lung function and ventricular mass in the study population, with the goal of guiding future studies related to common mechanisms of cardiac and pulmonary impairment in morbid obesity. To the best of our knowledge, based on our review of currently available databases (Bireme, SciELO, PubMed, Cochrane Library, and Google Academic), this is the first study to investigate this relationship in morbidly obese individuals.

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METHODS

We planned this study based on secondary data obtained from a bariatric surgery outpatient clinic, which is a state referral center for this type of surgery. In this retrospective study, we reviewed the medical records of all obese individuals who were candidates for bariatric surgery between January of 2006 and December of 2010, with the total number of individuals being 192. Individuals underwent a standardized clinical assessment, which was based on an instrument designated "clinical assessment form for obese patients" (a protocol at the department of bariatric surgery), in which detailed information was obtained on anthropometric parameters, degree of obesity, comorbidities, and pressure levels, among other clinical data and relevant tests, assessed by physicians, nutritionists, and nurses working in that department.

The aim of the medical record review was to systematically collect the following clinical data on and test results for morbidly obese individuals (BMI ≥ 40 kg/m^2)[12]: (i) anthropometry; (ii) simple spirometry; (iii) M-mode echocardiography; (iv) reporting of bronchial asthma (diagnosis and/or treatment); (v) reporting of current or former smoking; and (vi) reporting (diagnosis and/or treatment) of systemic arterial hypertension (SAH). Asthma was defined as reporting of a current or prior medical diagnosis. Current or former smoking refers to a longer than 1-year history of smoking, regardless of the number of pack-years. SAH was defined as a current drug treatment for SAH or at least two arterial blood pressure measurements ≥ 140/90 mmHg. Data on the forms, as well as test results, were only accepted if they had been properly recorded within 1 year before surgery. Only 45 patients met all of the above inclusion criteria, of whom 3 were excluded because of an echocardiographic report of acoustic window impairment caused by obesity and 3 were excluded because they did not meet the spirometry quality criteria. The main reasons for exclusion of the remaining cases were not being diagnosed with morbid obesity (136 individuals) and being a morbidly obese patient with no spirometric data (4 individuals), no echocardiographic data (5 individuals), or neither (2 individuals).

Anthropometric data were obtained by using a stadiometer and a scale for obese individuals, and BMI was calculated by the formula weight/height^2 (in kg/m^2). Waist circumference values were not collected, since such values were lacking in many cases. The study was approved by the Human Research Ethics Committee of the Federal University of Mato Grosso do Sul and was in compliance with the Declaration of Helsinki.

Spirometry with forced expiratory maneuver was performed in the pulmonary function section of the department of pulmonology of the university. All tests met the acceptability criteria established in the Brazilian guidelines for pulmonary function testing,[13] and values were corrected to body temperature, pressure saturated. All tests were performed with a Vitatrace VT 130 spirometer (Pró Médico Ltda., Rio de Janeiro, Brazil), with individuals in a sitting position and wearing a nose clip. The equipment was always calibrated in the morning, in accordance with the manufacturer instructions, and the tests were always conducted by one of two trained spirometry technicians belonging to the department of pulmonology. At least three acceptable maneuvers were always performed, and instantaneous flow was expressed as that obtained from the one maneuver with the highest sum of FVC (in L) and FEV_1 (in L/min). The reference values used were those of Pereira et al.,[14] and the mean ± SD of the study population was recorded.

Echocardiography was performed by two cardiologists, who used a Nemio 17-2005 echocardiograph (Toshiba, Tokyo, Japan). Those two cardiologists, one of whom is one of the present authors, work specifically in the echocardiography section of the hospital. For the purposes of this study, only data acquired in M-mode were collected; left ventricle end-diastolic volume (LVDV) and LV end-systolic volume (LVSV) were indirectly measured using the Teicholz formula, and LVM was calculated using the formula by Devereux et al.[15] The measurements were obtained from parasternal LV cross-sections at the level of the papillary muscles. Left atrial (LA) dimensions, LV end-diastolic diameter (LVDD), and LV end-systolic diameter (LVSD) were also measured. We used as criteria for LVM indexation both height to the power of 1.7 (LVM/m$^{1.7}$), which is a criterion recommended for obese individuals, and height squared (LVM/m^2). Relative LV posterior wall thickness (RLVPWT) was obtained by dividing LV posterior wall thickness (LVPWT) by LVDD.

The results are expressed as mean ± SD or frequency. Our sample size calculation (PASS software, version 11; NCSS LLC, Kaysville, UT, USA) showed that 40 individuals would be enough to provide a power of 80% for a significant correlation coefficient of 0.40 at $\alpha = 0.05$ (FEF_{25-75}/FVC, % vs. LVM/LVPWT/RLVPWT). For multiple linear regression analysis (based on LVM), 40 individuals would be necessary to provide a power of 98% and an $r^2 = 0.37$, in a model with four independent variables (weight, FEV_1, FVC, and FEF_{25-75}/FVC, %). The categorical variables reporting of smoking, reporting of asthma, and reporting of SAH were also computed, and gender and reporting of SAH were coded as a binary variable for purposes of statistical adjustment. Correlations between various spirometric and echocardiographic variables were assessed by Pearson's correlation test. Only LVM and LVPWT required log transformation to fit a normal distribution. The relationship between reporting of asthma (diagnosis and/or treatment) or current/former smoking and FEF_{25-75}/FVC, %, below or above the lower limit of the normal range, was assessed by Fischer's exact test. The relationship between FEF_{25-75}/FVC, % and LVPWT/RLVPWT was tested by partial correlation analysis, adjusted for weight, gender, and SAH, which

are traditionally the most important determinants of LV hypertrophy in obesity. In order to determine which variable would be the best predictor of LVM (dependent variable), we tested a stepwise multivariate linear regression model, in which the independent variables were only the variables showing a significant correlation ($p < 0.05$) with LVM, whether indexed or not. For all calculations and graphs, we used the IBM SPSS Statistics software package, version 20.0 (IBM Corp., Armonk, NY, USA). Results were considered significant at the level of $p \leq 0.05$.

RESULTS

Of the 45 patients for whom all data were originally available for inclusion, 6 were excluded because of reported failures in M-mode echocardiography or in pulmonary function testing, which did not meet quality criteria. The anthropometric and demographic data of the 39 patients included in the study are shown in Table 1. Females predominated in the study (74.3%), the mean age of the participants was 35.5 ± 7.7 years, and 8 participants were considered super-obese (BMI > 55 kg/m^2). Asthma and ever smoking were reported by 7 and 6 individuals, respectively. SAH (diagnosis and/or treatment) was reported to be present in 21 individuals (54%). Only 1 individual reported both asthma and smoking. The main spirometric and echocardiographic parameters are shown in Table 2. The mean spirometric values were above 80% of predicted. The mean values of LA diameter, LVM, and LVM/m^2 were increased relative to normal mean values for the Brazilian population.[16]

The various correlations between the echocardiographic and spirometric variables are shown in Table 3. No correlation was found between BMI and any of the spirometric variables studied. Chief among the significant correlations is the weak direct relationship between BMI and the variables LVDD($r = 0.359$; $p < 0.05$), LVSD ($r = 0.387$; $p < 0.05$), LVDV ($r = 0.387$; $p < 0.05$), and LVSV ($r = 0.425$; $p < 0.01$). A moderate inverse correlation was found between FEF_{25-75}/FVC, % and the variables of LV remodeling (Table 3) in the univariate analysis, and this correlation remained statistically significant for LVPWT ($r = -0.355$; $p < 0.05$) and RLVPWT ($r = -0.349$; $p < 0.05$) even after adjustment for weight, gender, and SAH (Figures 1A and 1B, respectively). The correlation between indexed LVM (in g/m$^{1.7}$) and FEF_{25-75}/FVC, % was borderline for statistical significance ($p = 0.05$; Figure 1C). Interestingly, FEF_{25-75}/FVC, % did not correlate with the variables of LV internal diameter or LV volume. No correlation was found between $FEF_{25-75\%}$ and any of the echocardiographic variables. Fischer's exact test showed no statistically significant association between FEF_{25-75}/FVC, %, below or above the lower limit of the normal range, and reporting of asthma or smoking ($p > 0.05$ for both).

Stepwise multiple linear regression analysis (Table 4) showed that the variation in LVM among morbidly obese individuals is better predicted by FVC (in L), which explained 36.9% ($p < 0.0001$) of the variation in LVM in the study population. The best predictor of LVM indexed to height squared and LVM indexed to height to the power of 1.7 was FEV_1 (in L/min; $p < 0.05$ for both; Table 4).

DISCUSSION

This retrospective study shows there is an independent association between the relative size of the small airways (FEF_{25-75}/FVC,%) and echocardiographic parameters of ventricular hypertrophy in morbidly obese individuals.

Table 1. Characteristics of the individuals included in the study (N = 39).[a]

Characteristic	Result
Age, years	35.5 ± 7.7
Height, cm	163.1 ± 9.1
Weight, kg	131.4 ± 25.9
BMI, kg/m^2	49.2 ± 7.6
BS, m^2	2.3 ± 0.3
Gender (M/F), n/n	10/29
Asthma (Y/N), n/n	7/32
Smoking (Y/N), n/n	6/33
SAH (Y/N), n/n	21/18

BS: body surface; M: male; F: female; Y: yes; N: no; and SAH: systemic arterial hypertension. [a]Values expressed as mean ± SD, except where otherwise indicated.

Table 2. Spirometric and echocardiographic parameters (N = 39).

Parameter	Result
Spirometry	
FEV_1, L	2.8 ± 0.6
FEV_1, % predicted	87.9 ± 11.8
FVC, L	3.4 ± 0.8
FVC, % predicted	88.4 ± 11.7
FEV_1/FVC, %	83.1 ± 6.4
FEF_{25-75}/FVC, %	99.5 ± 30.2
Echocardiography	
LA, mm	36.2 ± 4.1
ST, mm	11.6 ± 4.4
LVPWT, mm	10.7 ± 2.3
RLVPWT	0.2 ± 0.1
LVDD, mm	48.2 ± 4.1
LVSD, mm	29.6 ± 3.7
LVDV, mL	108.9 ± 21.7
LVSV, mL	34.9 ± 11.2
LVM, g	248.3 ± 84.9
LVM, g/m$^{1.7}$	106.7 ± 30.4
LVM, g/m^2	92.1 ± 26.1

LA: left atrium; ST: septal thickness; LVPWT: left ventricular posterior wall thickness; RLVPWT: relative left ventricular posterior wall thickness; LVDD: left ventricular end-diastolic diameter; LVSD: left ventricular end-systolic diameter; LVDV: left ventricular end-diastolic volume; LVSV: left ventricular end-systolic volume; and LVM: left ventricular mass.

Table 3. Univariate correlations of anthropometric and spirometric variables with transthoracic echocardiography variables (M-mode) in the sample as a whole (N = 39).

Parameter	LV hypertrophy						LV diameter/volume				
	LVM, g	LVM, g/m²	LVM, g/m$^{1.7}$	ST, mm	LVPWT, mm	RLVPWT	LA, mm	LVEDD, mm	LVESD, mm	LVEDV, mL	LVESV, mL
Anthropometry											
BMI, kg/m²	0.175	0.192	0.227	0.078	0.092	−0.046	0.069	0.359*	0.387*	0.387*	0.425‡
Weight, kg	0.476†	0.293	0.312	0.160	0.360*	0.169	0.380*	0.447†	0.476†	0.455‡	0.556‡
Spirometry											
FEV_1, L	0.590‡	0.388*	0.401*	0.162	0.389*	0.212	0.473†	0.406†	0.388*	0.386*	0.488‡
FEV_1, % predicted	0.147	0.232	0.154	0.110	−0.029	−0.102	0.015	0.217	0.196	0.238	0.162
FVC, L	0.584†	0.346*	0.380*	0.164	0.429‡	0.264	0.513‡	0.365*	0.315	0.366*	0.418†
FVC, % predicted	0.087	0.159	0.256	0.071	−0.017	−0.061	0.019	0.133	0.048	0.194	0.038
FEV_1/FVC, %	0.003	0.077	0.040	−0.002	−0.114	−0.145	−0.082	0.118	0.197	0.047	0.167
FEF_{25-75}/FVC, %	−0.397*	−0.275	−0.318†	−0.054	−0.453‡	−0.404‡	−0.168	0.009	0.041	−0.057	−0.020

LV: left ventricular; LVM: LV mass; ST: septal thickness; LVPWT: LV posterior wall thickness; RLVPWT: relative LV posterior wall thickness; LA: left atrium; LVDD: LV end-diastolic diameter; LVSD: LV end-systolic diameter; LVDV: LV end-diastolic volume; and LVSV: LV end-systolic volume. *p < 0.05; †p = 0.05; ‡p < 0.01.

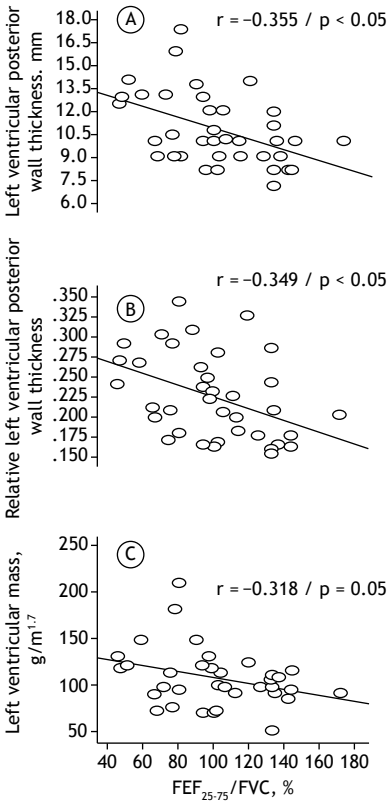

Figure 1. Correlation of FEF_{25-75}/FVC, %, adjusted for the variables weight, gender, and systemic arterial hypertension, with left ventricular posterior wall thickness, in A; with relative left ventricular posterior wall thickness, in B; and with left ventricular mass adjusted for body size in obese individuals, in C.

In addition, FVC (in L) and FEV_1 (in L/min) were found to be important predictors of LVM in grams or indexed to body surface area.

Both LVM and LV internal diameters are increased in obesity, regardless of SAH.[17] In our study, we found no relationship of BMI with LVM in grams or indexed to body surface area or with LVPWT, but we found a relationship of BMI with LV internal diameters and LV volumes, which is consistent with the literature.[2,17] This positive association is likely to be due to increased preload and increased cardiac output, causing ventricular dilatation, which could later progress to LV remodeling.[18]

The literature shows inconsistent associations between BMI and spirometric results, with some studies showing an association[19] and others not showing any.[20] This is probably due to differences in gender ratio among studies, since the android type of obesity favors the correlation between BMI and lung function, unlike the gynecoid phenotype, which does not produce excessive accumulation of fat mass in the chest. In our study, females predominated (74%), which partly explains the lack of correlation between any spirometric variable and BMI.

The relationships of FVC, FEV_1, and $FEF_{25-75\%}$ with LVM and LVPWT have been studied in (non-obese) elderly individuals with cardiovascular disease, and the results differ among studies in regard to the direction of the correlation, with correlations being positive[21] or negative,[22] which more strongly reflects loss of lung function associated with advanced age and with the effects of SAH and pulmonary hypertension, as well as with the pulmonary restrictive effects of cardiomegaly. One study[4] showed an inverse relationship between LVM and FVC in nonsmoking females and a direct relationship between LVM and FVC in nonsmoking males under 60 years of age. The fact that most of our sample consists of females (74%) suggests that, in morbidly obese individuals, the direction of the correlation may be different for some lung function variables.

FEF_{25-75}/FVC, % is a measure that corrects to some extent for the large variability found in $FEF_{25-75\%}$ alone and reflects changes predominantly in the small airways, being adjusted for lung size on the basis of FVC.[17] The correlations of FEF_{25-75}/FVC, % with LVM indexed

Table 4. Stepwise multiple linear regression for the dependent variable left ventricular mass (in grams or indexed to body surface area; N = 39).

Dependent variable	Predictor variable	Beta	95% CI	Adjusted R^2	p
LVM, g	FVC, L	0.60	0.43-1.13	0.369	< 0.001
LVM, g/m^2	FEV_1, L/min	0.38	0.29-2.8	0.126	< 0.05
LVM, $g/m^{1.7}$	FEV_1, L/min	0.40	0.2-1.3	0.161	< 0.05

LVM: left ventricular mass.

to body surface area (in $g/m^{1.7}$) and with LVPWT/RLVPWT, correlations that remained after adjustment for weight, gender, and SAH, possibly reflect the direct mechanical effects of obesity, but may also suggest that there are other independent (inflammatory or lipotoxic) mechanisms.

Since research on the subject is scarce, there is limited evidence that the small airways are independently affected by obesity, as has been reported in nonsmoking males.[23] The hypotheses raised in that study[23] include an increase in blood volume in obese individuals, causing bronchial vessel congestion; the presence of increased levels of very-low-molecular-weight lipoproteins, which could trigger the release of histamine; and altered lipoprotein metabolism in obesity, which could elicit and amplify these effects.

Recent data in the literature also indicate that obesity is characterized by hyperresponsiveness to methacholine, predominantly in the small airways,[24] and that this hyperresponsiveness correlates better with FEF_{25-75}/FVC, %.[25] On this point, a recent study suggests that groups of obese individuals with hyperresponsiveness are associated with greater LVM.[26] Small airway hyperresponsiveness in obese individuals also could be partially explained by dysanapsis (which is assessed indirectly by FEF_{25-75}/FVC, %), a term coined by Green et al.[27] to explain the large interindividual variability in airway size, regardless of lung parenchyma size. An important predictor of LVM, BMI correlated directly with cardiac size and mass in several studies, although lean body mass remains a better predictor of LVM.[2,28,29] This retrospective study found no correlations between BMI and LVM (in grams or indexed to body surface area), which is in agreement with another study,[30] and this is possibly due to differences in obesity phenotypes, prevalence of SAH, and number of individuals studied.

Of note in our study is the fact that FVC (in L) was the best predictor of variation in LVM (in g), explaining 37% of this variation in the study population, which suggests that reduced lung volume may be an important variable in establishing a predictive model for LVM in obese individuals in future studies. In turn, LVM correlates with cardiovascular morbidity and mortality.

Among the limitations of our study is the fact that our sample was small, consisting of candidates for bariatric surgery, was limited by the criterion of including only morbidly obese and super-obese individuals, and was based on criteria that were unclear in the medical charts, such as the diagnosis of asthma or SAH. In addition, data on diabetes were not collected, although the relationship between diabetes and LVM is inconsistent in the literature. Other important limitations were the limited acoustic window in the analysis of M-mode echocardiographic variables in obese individuals and the lack of a specific, standardized protocol for M-mode echocardiography, since we did not obtain data on inter-rater agreement for the two echocardiographers. In this regard, because this was a retrospective study, we sought not to use echocardiographic data for which accuracy is significantly decreased by the effects of obesity on the acoustic window, such as ejection fraction and Doppler echocardiography data.

We therefore conclude that the small airways in morbidly obese individuals have a correlation with cardiac hypertrophy, regardless of usual anthropometric variables, gender, or SAH. This study reveals that factors other than mechanical and/or hemodynamic limitations imposed by increased body mass may be important in the joint changes seen in the small airways and in cardiac hypertrophy. In addition, further studies are needed to examine the impact that lung function parameters have on predictive equations for LVM in obese individuals.

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Depression, anxiety, stress, and motivation over the course of smoking cessation treatment

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ABSTRACT

Objective: To evaluate changes in the levels of patient anxiety, depression, motivation, and stress over the course of smoking cessation treatment. **Methods:** This cohort study involved patients enrolled in a smoking cessation program in Cuiabá, Brazil. We selected patients who completed the program in six months or less (n = 142). Patient evaluations were conducted at enrollment (evaluation 1 [E1]); after 45 days of treatment with medication and cognitive-behavioral therapy (E2); and at the end of the six-month study period (E3). Patients were evaluated with a standardized questionnaire (to collect sociodemographic data and determine smoking status), as well as with the University of Rhode Island Change Assessment scale, Beck Anxiety Inventory, Beck Depression Inventory, and Lipp Inventory of Stress Symptoms for Adults. The data were analyzed with the nonparametric Wilcoxon test for paired comparisons. To compare treatment success (smoking cessation) with treatment failure, the test for two proportions was used. **Results:** Among the 142 patients evaluated, there were improvements, in terms of the levels of anxiety, depression, motivation, and stress, between E1 and E2, as well as between E1 and E3. In addition, treatment success correlated significantly with the levels of motivation and anxiety throughout the study period, whereas it correlated significantly with the level of depression only at E2 and E3. **Conclusions:** We conclude that there are in fact changes in the levels of patient anxiety, depression, motivation, and stress over the course of smoking cessation treatment. Those changes appear to be more pronounced in patients in whom the treatment succeeded.

Keywords: Anxiety; Depression; Motivation; Cognitive therapy; Smoking cessation.

INTRODUCTION

Smoking is now considered a chronic disease caused by nicotine dependence and is one of the main risk factors for various diseases. Exposure to tobacco smoke, either through the direct consumption of tobacco or its derivatives or in the environment (second-hand smoke), causes roughly 6 million deaths a year and is considered a worldwide health problem.[1] Despite the high prevalence of smoking in some countries, there has been an overall decrease in the number of smokers in recent decades, possibly due to public policies that have been implemented, together with increased access to smoking prevention and treatment. Annual reductions in smoking prevalence have been reported: 0.6% in Japan; 0.7% in the United States; and 0.8% in the United Kingdom. In Brazil, the prevalence of smoking declined from 32% in 1989 to 17.1% in 2008, representing a reduction of 0.78% per year.[2]

Despite the general advances in smoking control, the high rates of treatment failure in smoking cessation programs constitute a cause for concern.[3] Among the various complicating factors are high levels of anxiety, depression, and stress, as well as a low level of motivation for change, on the part of patients who seek treatment via smoking cessation programs.[3-5] Most of the currently available forms of smoking treatment have some weaknesses, and researchers have been seeking new approaches in order to improve the success rates of smoking cessation programs.

Consensuses and guidelines for smoking cessation interventions suggest that combining psychological support and the use of first-line pharmacotherapy (with nicotine replacement therapy, bupropion, or varenicline) increases the chances of treatment success.[3] Cognitive-behavioral therapy (CBT) is an important psychological intervention for the treatment of the nicotine dependence itself and plays a pivotal role in successfully treating and restructuring the lives of smokers.[6]

Smokers who decide to quit but are unable to do so on their own are the ones who seek out health care services for treatment. Among those, only 3% succeed in quitting without the aid of CBT and medication, and there is always a significant proportion of patients who relapse.[3] For smokers who seek treatment at specialized centers, the process of quitting is arduous, especially while coping with the ambivalence that nicotine dependence entails. They are aware of the harm that smoking causes but

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continue smoking because of their great dependence on the drug.[3]

Some patients are able to quit smoking with minimal suffering, whereas others try several times and are unable to quit. It is possible that certain individual characteristics, such as those related to the psychological state of the patient, are responsible for these different profiles. There could be changes in the levels of patient anxiety, depression, motivation for change, and stress during the process of smoking cessation. [5] Therefore, the present study was aimed at evaluating the influence of the interventions typically applied (medications and CBT) on factors believed to make smoking cessation more difficult.

METHODS

This was a cohort study in which the patients evaluated were over 18 years of age and spontaneously sought out the smoking cessation program at one of four health care facilities in the city of Cuiabá, Brazil: the Campo Velho Health Center; the Júlio Müller University Hospital; the Coxipó Multidisciplinary Clinic; and the Planalto Multidisciplinary Clinic. All smokers who enrolled in one of those programs between May and August of 2012 were invited to participate in this study.

There were 216 smokers who initially agreed to participate in the study. Of those, 74 (34.26%) abandoned the program before the end of the six-month study period and 142 (65.74%) completed the treatment within that period, the latter group therefore comprising the study population. As shown in Figure 1, the patients were evaluated at three different time points: at the initial evaluation (at enrollment), designated evaluation 1 (E1), at the mid-treatment evaluation (after 45 days of treatment with medication and CBT), designated evaluation 2 (E2), and at the end of the six-month study period, designated evaluation 3 (E3).

During the initial interview, the patients were evaluated by the physician responsible for the program and subsequently received the appropriate medication. They were also submitted to an initial psychological evaluation by the lead researcher (a psychologist), who applied the various psychometric instruments, counseled the patients in relation to the proposed treatment plan, and scheduled the first CBT session.

After data collection at E1, the patients were invited to attend four weekly 90-min group CBT sessions (10-15 patients each). As has been recommended,[7] they were also offered the option to attend five follow-up sessions, at 15, 30, 60, 90, and 180 days after the initial four-week treatment period.

The instruments employed were as follows:

- a standardized questionnaire, in two parts: Part I—sociodemographic profile; and Part II—smoking status, including data related to the smoking history, number of cigarettes smoked per day, and age at onset of the smoking habit
- the Fagerström Test for Nicotine Dependence (FTND),[8,9] patients scoring above the mean being considered highly dependent on nicotine
- the University of Rhode Island Change Assessment (URICA) scale,[10,11] which is used in order to assess the level of motivation for change (stage of change) in patients, who were thus categorized as being in the precontemplation/contemplation or preparation/action stages
- the Beck Anxiety Inventory (BAI),[12,13] which consists of a list of 21 common symptoms characteristic of anxiety, the level of anxiety in our patients thus being categorized as minimum/mild or moderate/severe
- the Beck Depression Inventory (BDI),[13,14] which comprises 21 items scored on a four-point scale, with scores of 0-3 corresponding to increasing degrees of severity of depression, which was thus categorized in our patients as minimum/mild or moderate/severe
- the *Inventário de Sintomas de Stress para Adultos de Lipp* (ISSL, Lipp Inventory of Stress Symptoms for Adults),[15] developed for use in Brazil, which (on the basis of physical and psychological symptoms) identifies stress and stratifies it by phase (alarm, resistance, near exhaustion, and exhaustion), our patients thus being dichotomized into a stress group and a no stress group

In the second and third evaluations (phases 2 and 3, respectively), the same psychometric instruments (URICA, BAI, BDI e ISSL) were again applied.

The FTND, URICA scale, BAI, and BDI have all been translated to Portuguese and validated for use in Brazil.[9,11,13] Although the URICA scale was validated in illicit drug users,[11] it can also be considered valid for smokers in Brazil.

The data were checked and were double entered into the EpiData program, version 3.1 (EpiData Association, Odense, Denmark), after which they were analyzed in the statistical programs STATA, version 13.0 (StataCorp LP, College Station, TX, USA) and the Statistical Package for the Social Sciences, version 17.0 (SPSS Inc., Chicago, IL, USA). The data were initially analyzed descriptively, with measurements of position and variation (mean, median, and standard deviation), as well as with box plots. Subsequently, an inferential analysis was carried out, and the data distribution was observed. For continuous variables without normal distribution, we used nonparametric tests (e.g., the Wilcoxon test) to make paired comparisons. The Wilcoxon test for paired samples was used in order to determine whether the measurements of the position of two samples were equal, if the samples were dependent.[16] In all comparisons, a level of significance of 0.05 ($p < 0.05$) was adopted. To compare treatment failure with treatment success (smoking cessation), we performed an inferential analysis of the data, comparing two proportions (when the distribution was normal) and calculating the respective 95% confidence intervals. To determine the magnitude of the difference between two proportions,

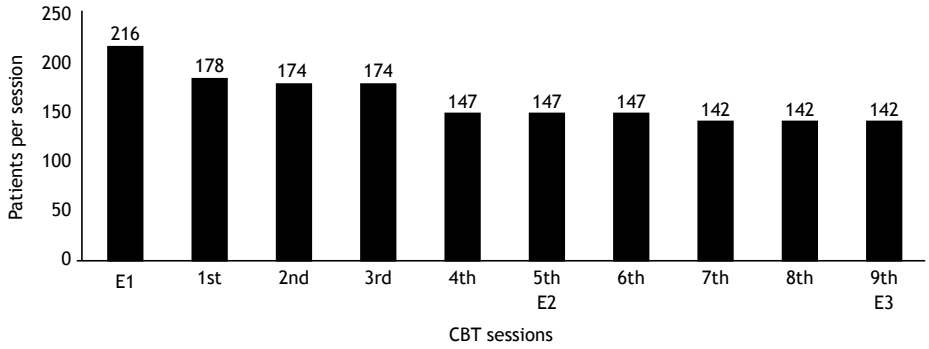

Figure 1. Number of patients attending cognitive behavioral therapy (CBT) sessions over the course of a six-month smoking cessation treatment program in the city of Cuiabá, Brazil, 2013. E1: initial (baseline) evaluation; E2: mid-treatment evaluation (after 45 days of treatment with medication and CBT; and E3: final evaluation (and at the end of the treatment period).

we used the test for two proportions, with a level of significance of 0.05 ($\alpha < 0.05$).[17,18]

This study was evaluated and approved by the Research Ethics Committee of the Júlio Müller University Hospital (Protocol nos. 0106612.6.0000.5541 and 19548). All participating patients gave written informed consent.

RESULTS

All of the participants were treated with the same protocol: nicotine replacement therapy, bupropion, and CBT. Among those who completed the six-month treatment protocol, the treatment success rate was 57.04%.

In the study sample, there was a predominance of females, who accounted for 100 (70.42%) of the 142 participants; 90 of the participants (63.38%) were between 40 and 59 years of age; 79 (55.63%) had no steady partner; 127 (89.44%) had children; 101 (71.13%) had had over 8 years of schooling; and 81 (57.04%) were currently employed. Regarding monthly family income, 66 (46.48%) of the participants earned less than three times the national monthly minimum wage, which was, in Brazilian reals (R$), R$ 622.00 at the time of the interview. Of the 142 patients evaluated, 114 (80.28%) had smoked for 20 years or more; 56 (39.44%) smoked 11-20 cigarettes/day; and 98 (69.01%) had a FTND score ≥ 6 (indicating high or very high nicotine dependence).

Of the 142 patients who completed the six-month treatment protocol, 81 (57.04%) were able to quit smoking. Of those 81 patients, 53 (65.4%) chose to quit abruptly ("cold turkey").

Figure 2 shows the distribution of the patients by stage of change category (based on the URICA scale scores) at the three time points evaluated. At E1, 20.42% of the sample (29 patients) were in the preparation/action stages, and that proportion rose to 82.39% (117 patients) by E3. In addition, the proportions of patients with URICA scale scores indicative of the precontemplation/contemplation stages were significantly lower at E2 and E3 than at E1 ($p < 0.001$ for both), although the difference between E2 and E3 was less than significant ($p = 0.499$).

As depicted in Figure 3, the mean BAI scores in phases 1, 2, and 3 were 17.58 ± 11.44 (median, 16.00), 13.02 ± 10.22 (median, 11.00), and 12.61 ± 10.75 (median, 10.00), respectively. In comparison with the BAI scores recorded at E1, those recorded at E2 and E3 were significantly lower ($p < 0.001$ for both), although no such difference was observed between E2 and E3.

Figure 4 shows the BDI scores at all three time points evaluated. The mean BDI scores at E1, E2, and E3 were 16.01 ± 9.99 (median, 14.00), 11.87 ± 9.13 (median, 10.00), and 10.55 ± 9.58 (median, 8.00), respectively. The scores were significantly lower at E2 and E3 than at E1 ($p < 0.001$ for both), as well as being significantly lower at E3 than at E2 ($p = 0.003$).

Figure 5 shows the distribution of the patients stratified by the level of stress (stress vs. no stress, based on the ISSL scores) at the three time points evaluated. In comparison with E1, the proportion of patients in the stress group was significantly lower at E2 and E3 ($p = 0.002$ and $p = 0.025$, respectively). However, the difference between E2 and E3 was less than significant ($p = 0.662$).

Table 1 details the differences between the patients who continued to smoke and those who did not, over the course of the treatment, stratified by whether or not the treatment was eventually successful, in terms of the level of motivation for change (URICA scale scores), level of anxiety (BAI scores), severity of depression (BDI scores), and level of stress (ISSL scores). As can be seen in the table, the treatment was more likely to fail if patients remained in the preparation/action stages of change until E3 ($p < 0.001$; ΔURICA, −40.98); continued to have minimum/mild anxiety until E3 ($p = 0.0007$; ΔBAI, −18.80); or exhibited minimum/mild symptoms of depression at E2 ($p = 0.0007$; ΔBDI, −19.61) or at E3 ($p = 0.0007$; ΔBDI, −17.99). However, the level of stress (ISSL score) did not have a statistically significant effect on

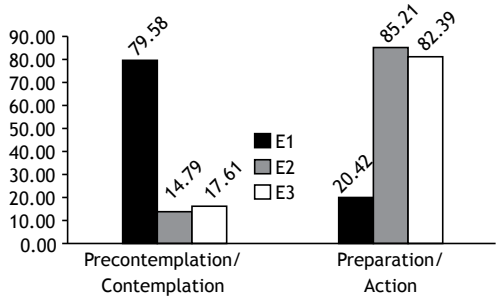

Figure 2. Distribution of patients by level of motivation (stage of change category, based on the University of Rhode Island Change Assessment scale scores) at the three time points evaluated during a six-month smoking cessation treatment program in the city of Cuiabá, Brazil, 2013.

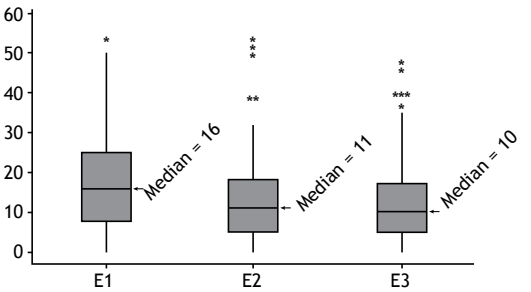

Figure 3. Distribution of patients by level of anxiety (based on the Beck Anxiety Inventory scores) at the three time points evaluated during a six-month smoking cessation treatment program in the city of Cuiabá, Brazil, 2013. *Outlier.

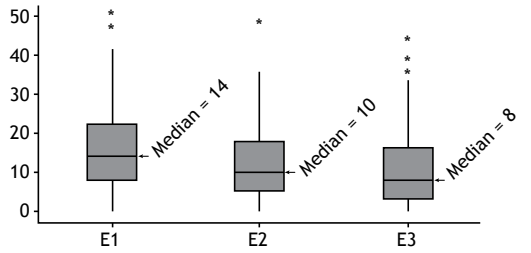

Figure 4. Distribution of patients by severity of depression (based on the Beck Depression Inventory scores) at the three time points evaluated during a six-month smoking cessation treatment program in the city of Cuiabá, Brazil, 2013. *Outlier.

the outcome of the treatment or on the propensity of smokers to relapse over the course of the treatment period. Although quitting smoking apparently contributed to the significant reductions in symptoms, the absolute increase in the differences between E1 and the subsequent evaluations indicates that the effects of the interventions were also significant.

DISCUSSION

In the present study, we observed that the number of patients who transitioned from the precontemplation/contemplation stages of change to the preparation/action stages was greatest between E1 and E2, the period in which the CBT portion of the intervention was most intense (weekly sessions). Therefore, it is possible that the CBT, rather than the bupropion, was responsible for that change. Other authors who evaluated the effectiveness of CBT in smoking cessation treatment have suggested the same.[19]

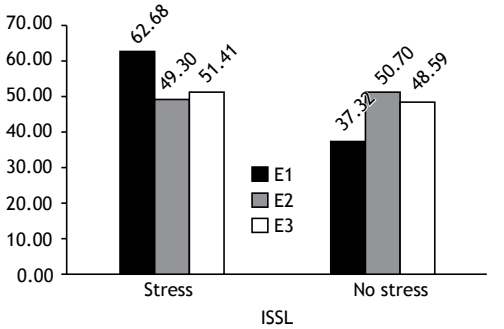

Figure 5. Distribution of patients by level of stress (stress category), based on the *Inventário de Sintomas de Stress para Adultos de Lipp* (ISSL, Lipp Inventory of Stress Symptoms for Adults) scores, at the three time points evaluated during a six-month smoking cessation treatment program in the city of Cuiabá, Brazil, 2013.

Our findings serve to alert health care professionals who enroll and treat patients in cessation programs to the need to focus on patient motivation, because the majority of smokers seeking help are not truly ready to quit smoking. Strengthening patient motivation is essential to encouraging behavioral changes, and it is fundamental to focus on the ambivalent behavior of smokers who want to quit smoking but simultaneously feel incapable of doing so.[20] Therefore, it is suggested that the health professionals involved in the dynamics of the cessation process conduct a motivational interview, using individualized therapeutic interventions for smokers who are unmotivated or unprepared and ambivalent, encouraging them to reflect upon and make changes in their behavior so that they can advance to the action stage.[21] Miller & Sanchez defined six motivational elements that are essential to making such changes: feedback (provide feedback); responsibility (emphasis on patient responsibility); advice (direct counseling to achieve changes); menu (alternatives, options, and choices); empathy; and self-efficacy (patients must believe in their own capacity to change).[22] This is in accordance with the transtheoretical model of behavior change, the main assumption of which is that successful self-initiated changes are related to the application of the right strategies (processes) at the right time (stages).[23]

Another important finding of the present study was the change in the BAI scores over the course of smoking cessation treatment (reductions from E1 to E2 and from E1 to E3). There have been few studies of changes in the level of anxiety among smokers during the cessation process, which makes it difficult

Table 1. Comparison between patients in whom smoking cessation treatment was ultimately successful and those in whom it was not, in terms of the levels of motivation, anxiety, depression, and stress, over the course of a six-month treatment period, in the city of Cuiabá, Brazil, 2013.

Variable	Time	Category	Treatment outcome				Δ[a]	p
			Failure		Success			
	(days)		n	%	n	%		
Motivation[b]	0	Precontemplation/contemplation	52	85.24	61	75.31	−9.94	0.132
		Preparation/action	9	14.75	20	24.69		
	45	Precontemplation/contemplation	17	27.87	4	4.94	−22.93	< 0.001*
		Preparation/action	44	72.13	77	95.06		
	180	Precontemplation/contemplation	25	40.98	0	0.00	−40.98	< 0.001*
		Preparation/action	36	59.02	81	100		
BAI	0	Moderate/severe	28	45.90	26	32.10	−13.80	0.093
		Minimum/mild	33	54.10	55	67.90		
	45	Moderate/severe	19	31.15	12	14.81	−16.34	0.022
		Minimum/mild	42	68.85	69	85.19		
	180	Moderate/severe	19	31.15	10	12.35	−18.80	0.007
		Minimum/mild	42	68.85	71	87.65		
BDI	0	Moderate/severe	22	36.07	21	25.92	−10.15	0.196
		Minimum/mild	39	63.93	60	74.08		
	45	Moderate/severe	21	34.42	12	14.81	−19.61	0.007
		Minimum/mild	40	65.58	69	85.19		
	180	Moderate/severe	17	27.87	8	9.88	−17.99	0.007
		Minimum/mild	44	72.13	73	90.12		
ISSL	0	Stress	42	68.85	51	62.96	−5.89	0.461
		No stress	19	31.15	30	37.04		
	45	Stress	36	59.02	39	48.15	−10.87	0.195
		No stress	25	40.98	42	51.85		
	180	Stress	38	62.30	38	46.91	−15.39	0.065
		No stress	23	37.70	43	53.09		

BAI: Beck Anxiety Inventory; BDI: Beck Depression Inventory; and ISSL: *Inventário de Sintomas de Stress para Adultos de Lipp* (ISSL, Lipp Inventory of Stress Symptoms for Adults). [a]Estimated difference between proportions. [b]Stage of change (level of motivation for change), as assessed with the University of Rhode Island Change Assessment scale. *Fisher's exact test.

to draw comparisons between our results and those of other authors. Although one study reported a similar reduction in patient anxiety during smoking cessation, that study involved only one patient.[24] In addition, we found that the difference between the patients who succeeded in quitting smoking and those who did not, in terms of the level of anxiety, was greater at E3 than at E1. Other studies involving patients in smoking cessation programs have shown that post-treatment anxiety levels are lower in those who were able to stop smoking than in those who continued to smoke.[25-27] In contrast, another study showed that smoking cessation results in an increase in the level of patient anxiety.[28] The relationship between smoking and anxiety is quite complex. In comparison with the general population, individuals with anxiety disorders are twice as likely to smoke, and these disorders are more common in smokers than in nonsmokers.[4,29] One of the reasons cited for this association is that smoking can be a way of self-medicating oneself to treat anxiety symptoms, because nicotine reduces negative emotions and is anxiolytic.[30,31] Furthermore, anxious smokers have greater difficulty in abandoning their dependence, thus showing high rates of relapse and treatment failure.[4,29,30] Anxiety can be defined as an emotional state, with psychological and physiological components, which is part of the normal spectrum of human experience and motivates performance. It can be pathological when it is disproportionate to the situation that triggers it or when it is directed at a subject that does not exist.[32] Therefore, it is important to remember the role that anxiety plays in smokers during the smoking cessation process and to attempt to help them overcome these symptoms.

As with anxiety, we found that the severity of patient depression, as quantified by the BDI score, was also lower after smoking cessation treatment. That outcome is likely attributable to the combined effects of the pharmacological treatment (with bupropion, which is an antidepressant) and the CBT. The pharmacological treatment functions as an adjuvant to the behavioral approach at the stage during which smokers show symptoms of withdrawal syndrome, because it facilitates the approach to the patients, who have been gradually encouraged and counseled to deal with their dependence and to try to break the conditioned

associations made with cigarettes. [5] Research has shown that quitting smoking does not increase the risk of developing a mental health problem,[25,27,33] which supports our finding that, over the course of treatment, BDI scores were lower among the patients in whom the treatment was ultimately successful. The broad category of depression includes a variety of disorders, such as major depressive disorder, dysthymia, and bipolar depression. Although comorbidity between smoking and depression has been documented, the mechanisms of that association are controversial, because biological, psychological, and social factors could be contributing factors.[34] However, there is strong evidence of comorbidity between smoking and depressive disorders, and many individuals who suffer from depression use nicotine to alleviate their symptoms.[30,34]

We found that, like those of anxiety and depression, the level of patient stress also decreased significantly over the course of smoking cessation treatment. It seems that, after the initial phase of the cessation process, when withdrawal symptoms are most pronounced, patient stress levels can be reduced. It is known that the prevalence of stress is higher in smokers than in nonsmokers. [35] Smokers claim that smoking is relaxing and alleviates stress. This is reported as one of the main reasons for smoking, which is considered a true anesthetic for feelings and emotional conflicts.[36] Paradoxically, although smokers report that smoking helps them relax, stress levels are higher in smokers than in nonsmokers. In addition, nicotine dependence increases stress, and the apparent relaxing effect of smoking is rapid and transient, reflecting only the circulating level of the drug. Soon after smoking (when the nicotine has been metabolized), tension and irritability return, making smokers feel the need to return to the consumption of the drug to become relaxed again.[35] However, despite the increased stress levels in the initial period of the cessation process, patients become less stressed after 14 days of abstinence.[37] Over the course of the present study, we observed an absolute increase in the differences between the patients in whom the treatment was ultimately successful and those in whom it was not, in terms of the level of stress, although the association was not statistically significant.

The most important limitation of our study is the lack of data on the proportional contributions of drug therapy and CBT to the results obtained. Further studies, involving control groups to determine the effects that the different forms of intervention have on the variables studied here, are warranted.

We can conjecture that CBT played an important role in our results, because the variables modified by the interventions applied were again measured after the end of the intervention, giving the impression that it was really behavioral change and not only the chemical effects of the drug, which disappear a few days after the end of the drug therapy regimen. In addition, the cessation of smoking, per se, can reduce levels of anxiety, depression, and stress,[26] making it a factor with an additive effect that could have contributed to the improvements observed in our study, in which there were reductions in the levels of anxiety, depression, and stress, as well as increased motivation, over the course of treatment, changes that were more pronounced among the patients in whom the treatment was ultimately successful (i.e., those who quit smoking).

Our findings indicate that the great majority of smokers begin the smoking cessation process with low motivation, and that this changes after the interventions have been applied within the cessation program. The effects of medications (diminishing withdrawal symptoms), combined with CBT and with the techniques applied in order to bring about change in the behavior of smokers, appear to be decisive for the success or failure of smoking cessation treatment.

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Factors predictive of obstructive sleep apnea in patients undergoing pre-operative evaluation for bariatric surgery and referred to a sleep laboratory for polysomnography

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Study carried out at the Sleep – Laboratório de Estudo dos Distúrbios do Sono, Centro Médico BarraShopping, and at the Instituto de Doenças do Tórax – IDT – Universidade Federal do Rio de Janeiro – UFRJ – Rio de Janeiro, Brasil.

ABSTRACT

Objective: To identify the main predictive factors for obtaining a diagnosis of obstructive sleep apnea (OSA) in patients awaiting bariatric surgery. **Methods:** Retrospective study of consecutive patients undergoing pre-operative evaluation for bariatric surgery and referred for in-laboratory polysomnography. Eight variables were evaluated: sex, age, neck circumference (NC), BMI, Epworth Sleepiness Scale (ESS) score, snoring, observed apnea, and hypertension. We employed ROC curve analysis to determine the best cut-off value for each variable and multiple linear regression to identify independent predictors of OSA severity. **Results:** We evaluated 1,089 patients, of whom 781 (71.7%) were female. The overall prevalence of OSA—defined as an apnea/hypopnea index (AHI) ≥ 5.0 events/h—was 74.8%. The best cut-off values for NC, BMI, age, and ESS score were 42 cm, 42 kg/m^2, 37 years, and 10 points, respectively. All eight variables were found to be independent predictors of a diagnosis of OSA in general, and all but one were found to be independent predictors of a diagnosis of moderate/severe OSA (AHI ≥ 15.0 events/h), the exception being hypertension. We devised a 6-item model, designated the NO-OSAS model (**N**C, **O**besity, **O**bserved apnea, **S**noring, **A**ge, and **S**ex), with a cut-off value of ≥ 3 for identifying high-risk patients. For a diagnosis of moderate/severe OSA, the model showed 70.8% accuracy, 82.8% sensitivity, and 57.9% specificity. **Conclusions:** In our sample of patients awaiting bariatric surgery, there was a high prevalence of OSA. At a cut-off value of ≥ 3, the proposed 6-item model showed good accuracy for a diagnosis of moderate/severe OSA.

Keywords: Polysomnography; Sleep apnea, obstructive; Bariatric surgery.

INTRODUCTION

Obstructive sleep apnea (OSA) is a major disease, affecting at least 2% of women and 4% of men, worldwide.[1] It is a sleep-related breathing disorder, characterized by recurrent upper-airway obstruction during sleep, resulting in a cycle of hypoxemia, increased respiratory effort, and frequent arousals, obesity being the most common known risk factor.[2] Recent data show that in the 2011-2012 period, the prevalence of obesity in the United States was 16.9% in juveniles and 34.9% in adults.[3] Obesity is a chronic disease that has become epidemic in the United States and worldwide; it is also a major risk factor for various disorders, including OSA.[4] In addition, over the last several decades, the criteria used in order to determine the prevalence of OSA have been redefined,[5] primarily because the prevalence of obesity continues to increase,[3] which in turn increases that of OSA.

In most cases, bariatric surgery results in dramatic weight loss and significant improvement in the indices of sleep-disordered breathing.[4] In addition, OSA is underdiagnosed in a significant proportion of obese patients undergoing bariatric surgery.[6-10] Most bariatric surgery programs now employ routine screening for OSA in all patients, regardless of whether or not they have sleep complaints, because most cases of OSA were previously not being diagnosed before the surgical procedure.[11] Bariatric surgery lowers body weight markedly and reduces the severity of comorbidities associated with obesity, as well as reducing that of OSA.[12,13] Worldwide, the accepted criteria for bariatric surgery include the following[14,15]: being 18-65 years of age and having a BMI ≥ 40 kg/m^2 or ≥ 35 kg/m^2 and having any obesity-related comorbidity (resistant hypertension, established heart disease, severe degenerative osteoarthritis, or respiratory failure). Although the exact pathophysiology of OSA in obese patients remains poorly understood, it is thought that the deposition of fatty tissue in the neck narrows the lumen of the upper airway, thereby inducing its collapse.[4,15]

The population of Brazil comprises a number of different ethnic, racial, and socioeconomic groups. Because of the considerable degree of miscegenation in the country, it is useful to identify the main clinical variables evaluated

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in making a diagnosis of OSA in patients belonging to those various groups. Although various studies have shown that OSA is quite prevalent among bariatric surgery patients, there is still a lack of data regarding the main clinical predictors of OSA in such patients, especially for those in Brazil.

METHODS

This was a retrospective analysis of a prospectively maintained database. We analyzed data related to consecutive outpatients undergoing pre-operative evaluation for bariatric surgery between January of 2010 and October of 2014, all of whom were referred to our sleep laboratory for polysomnography, regardless of whether or not they had complained of sleep-related respiratory disturbances. Patients were referred by their respective attending physicians. All demographic and polysomnographic data were collected at our sleep laboratory. The inclusion criteria were being 18-65 years of age, being obese (BMI ≥ 35.0 kg/m^2), and not having been previously diagnosed with OSA. Patients for whom clinical data were missing were excluded, as were those with a total sleep time (TST) of < 3 h and those in whom portable sleep studies had been used for the diagnosis of OSA. Additional informed consent was not obtained for this study, because there was no intervention. The study was approved by the Research Ethics Committee of the Federal University of Rio de Janeiro (Protocol no. 666.608/2014).

Data collection

All studies were conducted in the Sleep Laboratory of the BarraShopping Medical Center, located in the city of Rio de Janeiro, Brazil, a relatively large sleep laboratory with 18 beds, sleep technicians, and two board-certified sleep physicians. The variables evaluated included sex, age, BMI, neck circumference (NC), snoring, observed apnea, hypertension, and degree of daytime sleepiness, as determined by the Epworth Sleepiness Scale (ESS).[16,17] On the evening of the polysomnography, all demographic variables were collected by qualified skilled sleep laboratory technicians. The BMI was calculated as weight in kilograms divided by height in meters squared, and NC measurements were taken at the level of the cricoid membrane with the patients in the supine position. The study population was stratified into four categories, by BMI: 35.0-39.9 kg/m^2; 40.0-49.9 kg/m^2; 50.0-59.9 kg/m^2; and ≥ 60.0 kg/m^2. Subjects with an arterial blood pressure ≥ 140/90 mmHg were classified as having systemic arterial hypertension, as were those being treated with antihypertensive medication. Self-reported snoring and observed apnea were evaluated as dichotomous (yes/no) variables.

All patients underwent one-night, in-laboratory polysomnography, performed with a digital system (EMBLA® S7000; Embla Systems, Inc., Broomfield, CO, USA), consisting of continuous polygraphic recording from surface leads (for electroencephalography, electrooculography, electromyography of the chin/legs, and electrocardiography), thermistors (for nasal/oral airflow), thoracic/abdominal impedance belts (for respiratory effort), and position sensors (for sleep position), together with pulse oximetry (for SpO_2) and audio recording via a tracheal microphone (for snoring). Polysomnographic recordings were scored manually and were interpreted by an experienced sleep physician in accordance with established guidelines.[18-20] The data interpreted included TST, sleep efficiency, sleep stages, rapid eye movement (REM) latency, sleep latency, arousals, apnea/hypopnea index (AHI), and SpO_2.

Sleep stages were scored based on established criteria.[18] Arousals were defined as episodes lasting ≥ 3 s in which there was a return of alpha activity associated with an increase in electromyographic activity. An apnea event was defined as a ≥ 10 s cessation of oronasal airflow. A hypopnea event was defined as a ≥ 30% reduction in the nasal pressure signal accompanied by ≥ 4% desaturation that lasted for > 10 s.[18] The AHI was defined as the sum of the apnea and hypopnea events per hour of sleep. The diagnosis of OSA was based on an AHI ≥ 5.0 events/h, and OSA severity was categorized on the basis of the AHI[18]: mild (5.0-14.9 events/h); moderate (15.0-29.9 events/h); or severe (≥ 30.0 events/h).

Statistical analysis

Statistical analysis was performed with the Statistical Package for the Social Sciences, version 17.0 for Windows (SPSS Inc., Chicago, IL, USA). Continuous data are reported as mean ± standard deviation, whereas categorical data are reported as percentages of the total population. Comparisons between groups were performed with the chi-square test for dichotomous variables, Student's t-test for normally distributed continuous variables, and the Mann-Whitney U-test for non-normally distributed continuous variables. Correlations between continuous variables were evaluated by Spearman's rank correlation coefficient (r_s). For each continuous variable, we used a ROC curve, calculating the area under the curve (AUC) to obtain the cut-off value for use in the univariate and multivariate analyses. Univariate and multivariate tests were used in order to calculate the odds ratios and the corresponding 95% confidence intervals. Using 2 × 2 contingency tables, we calculated the following parameters for all variables: sensitivity, specificity, positive predictive value, negative predictive value, and accuracy. We constructed predictive models using the main independent variables obtained for an AHI ≥ 15.0 events/h, aiming to optimize the screening for moderate/severe OSA in bariatric surgery patients. The best predictive model was selected according to the ROC curves. All tests were two-sided, and values of $p < 0.05$ were considered statistically significant.

RESULTS

In a period of 58 months, 1,480 consecutive patients were referred for polysomnography. Of those

1,480 patients, 391 were subsequently excluded: 308 because of missing data; 30 because they had been the subjects of home sleep studies; 28 because they had a TST of < 3 h; and 25 because they had previously been diagnosed with OSA. Therefore, 1,089 patients, of whom 781 (71.7%) were female and 308 (28.3%) were male, were considered eligible for further analysis. Demographic and polysomnographic characteristics of those 1,089 subjects are listed in Table 1. The overall prevalence of OSA was 74.8%, and the prevalence of moderate/severe OSA was 52.0%. In comparison with the females, the males were younger ($p = 0.080$), had higher BMIs ($p < 0.001$), and had larger NCs ($p < 0.001$). In terms of the prevalence of excessive daytime sleepiness (ESS score ≥ 10), the difference between males and females did not reach statistical significance ($p = 0.122$). The severity of OSA was greater in males than in females, as was the prevalence of moderate/severe OSA (84.7% vs. 39.1%) and severe OSA (68.5% vs. 18.6%), the last two being statistically significant differences ($p < 0.001$ for both). The continuous variables (NC, BMI, age, and ESS score) were correlated with the AHI ($r_s = 0.500$, $r_s = 0.308$, $r_s = 0.247$, and $r_s = 0.156$, respectively; $p < 0.001$ for all).

Table 2 shows the differences among the various BMI categories, in relation to demographic, clinical, and polysomnographic variables. As BMI increased, there were statistically significant increases in the proportion of males, as well as in the proportions of subjects with hypertension, snoring, and observed apnea. In addition, NC and the ESS score increased in parallel with increases in BMI, although no such association was observed between age and BMI category ($p = 0.607$). Arousals and the AHI also increased progressively in parallel with increases in BMI, as did the numbers of apnea and hypopnea events per hour when calculated separately ($p < 0.001$ for all). Similarly, SpO_2 values worsened in parallel with increases in BMI ($p < 0.001$ for baseline, mean, and lowest SpO_2). As expected, there were linear increases in the prevalence of OSA, especially that of the severe form of the disease, corresponding to increases in the BMI: 253 (66.4%) of the 381 patients with a BMI 35.0-39.9 kg/m^2 were diagnosed with OSA, 81 (21.3%) of those patients being diagnosed with severe OSA; 460 (77.0%) of the 597 patients with a BMI 40.0-49.9 kg/m^2 were diagnosed with OSA, 200 (33.5%) of those patients being diagnosed with severe OSA; 88 (33,7%) of the 98 patients with a BMI 50.0-59.9 kg/m^2 were diagnosed with OSA, 65 (66.3%) of those patients being diagnosed with severe OSA; and all 13 of the patients with a BMI ≥ 60.0 kg/m^2 were diagnosed with OSA, 10 (76.9%) of those patients being diagnosed with severe OSA.

The ROC curve analyses of the relevant continuous variables yielded the following AUCs: 0.711 (95% CI: 0.679-0.744) for NC; 0.657 (95% CI: 0.620-0.694) for age; 0.625 (95% CI: 0.588-0.662) for BMI; and 0.557 (95% CI: 0.519-0.595) for ESS score. In addition, the ROC curves showed that the best cut-off values for NC, BMI, age, and ESS score (as diagnostic markers of OSA) were 42 cm, 42 kg/m^2, 37 years, and 10 points, respectively.

Table 3 shows the univariate and multivariate analyses of the eight variables evaluated in relation to three different AHI cut-off values (5.0 events/h, 15.0 events/h, and 30.0 events/h). All of those variables were thus found to be independent predictors of a diagnosis of OSA in general (AHI ≥ 5.0 events/h). All but one were found to be independent predictors of a diagnosis of moderate/severe OSA (AHI ≥ 15.0 events/h), the exception being hypertension ($p = 0.421$). All but two were found to be independent predictors of a diagnosis of severe OSA (AHI ≥ 30.0 events/h), the exceptions being hypertension ($p = 0.963$) and snoring ($p = 0.153$). The main predictor of a diagnosis of OSA in general was male sex, with an adjusted OR of 10.20 (95% CI: 5.07-20.83), followed by snoring, age ≥ 37 years, observed apnea, BMI ≥ 42 kg/m^2, ESS score ≥ 10, hypertension, and NC ≥ 42 cm. The main predictor of a diagnosis of moderate/severe OSA was also male sex, with an adjusted OR of 5.91 (95% CI: 3.92-8.92), followed by snoring, BMI ≥ 42 kg/m^2, age ≥ 37 years, observed apnea, NC ≥ 42 cm, ESS score ≥ 10, and hypertension. The main predictor of a diagnosis of severe OSA was again male sex, with an adjusted OR of 6.80 (95% CI: 4.62-10.00), followed by BMI ≥ 42 kg/m^2, age ≥ 37 years, observed apnea, snoring, NC ≥ 42 cm, ESS score ≥ 10, and hypertension.

As can be seen in Table 3, there were seven independent variables associated with a diagnosis of moderate/severe OSA: sex, snoring, BMI, age, observed apnea, NC, and ESS score. Among those variables, ESS score was seventh (i.e., last) in importance. That, together with the fact that the ESS comprises eight questions, prompted us to exclude ESS scores, thus simplifying the models. Therefore, we tested four models (Table 4): a 3-item model including male sex, snoring, and BMI ≥ 42 kg/m^2; a 4-item model encompassing the 3-item model plus age ≥ 37 years; a 5-item model encompassing the 4-item model plus observed apnea; and a 6-item model encompassing the 5-item model plus NC ≥ 42 cm. Of the four predictive models evaluated, the one found to be best at predicting OSA in general, moderate/severe OSA, and severe OSA was the 6-item model, which had AUCs of 0.777 (95% CI: 0.747-0.807), 0.784 (95% CI: 0.757-0.811), and 0.796 (95% CI: 0.769-0.824), respectively.

Table 5 shows the predictive parameters of the 6-item model, which was categorized into six possible cut-off values (to distinguish between high and low risk of OSA), in the three different situations: diagnosis of OSA in general, diagnosis of moderate/severe OSA, and diagnosis of severe OSA. Because the main objective of the model was to identify patients at high risk for moderate/severe OSA (AHI ≥ 15.0 events/h), we sought to determine the cut-off value that (within that category) achieved the best balance between

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

Characteristic	Total (N = 1,089)	Females (n = 781)	Males (n = 308)	p
Demographic variable				
Age, years	38.1 ± 10.0	38.4 ± 10.1	37.2 ± 9.7	0.080
Clinical variables				
BMI, kg/m^2	42.8 ± 5.4	42.1 ± 5.0	44.6 ± 5.8	< 0.001
BMI 35.0-39.9 kg/m^2, n (%)	381 (35.0)	310 (39.6)	71 (23.0)	< 0.001
BMI 40.0-49.9 kg/m^2, n (%)	597 (54.8)	416 (53.3)	181 (58.8)	< 0.001
BMI 50.0-59.9 kg/m^2, n (%)	98 (9.0)	49 (6.3)	49 (15.9)	< 0.001
BMI ≥ 60.0 kg/m^2, n (%)	13 (1.2)	6 (0.8)	7 (2.3)	< 0.001
NC, cm	42.3 ± 4.7	40.3 ± 3.3	47.5 ± 3.6	< 0.001
ESS score, points	8.9 ± 4.5	8.8 ± 4.5	9.2 ± 4.6	0.306
ESS score ≥ 10, n (%)	449 (41.2)	313 (40.1)	136 (44.2)	0.122
Hypertension, n (%)	445 (40.9)	296 (37.9)	149 (48.4)	< 0.001
Snoring, n (%)	1,010 (92.7)	704 (90.1)	306 (99.4)	< 0.001
Observed apnea, n (%)	369 (33.9)	228 (29.2)	141 (45.8)	< 0.001
Polysomnographic variables				
Total sleep time, min	337.7 ± 70.0	340.9 ± 69.3	329.5 ± 71.2	0.019
Sleep efficiency, %	77.4 ± 14.9	77.7 ± 14.8	76.6 ± 15.1	0.250
Sleep stage N1, %	4.8 ± 5.9	4.3 ± 4.7	6.3 ± 7.9	< 0.001
Sleep stage N2, %	66.3 ± 12.0	64.8 ± 11.6	70.2 ± 12.2	< 0.001
Sleep stage N3, %	12.7 ± 9.1	14.1 ± 9.0	9.2 ± 8.6	< 0.001
Sleep stage R, %	15.5 ± 7.8	16.1 ± 7.6	14.0 ± 8.0	< 0.001
Arousals, events/h	29.9 ± 27.7	21.8 ± 21.5	50.5 ± 30.9	< 0.001
Sleep latency, min	41.8 ± 40.4	43.0 ± 39.9	38.7 ± 41.4	0.112
REM latency, min	150.3 ± 81.3	147.7 ± 80.0	157.3 ± 84.5	0.095
AHI, events/h	27.2 ± 29.5	18.1 ± 22.6	50.4 ± 32.2	< 0.001
AI, events/h	12.1 ± 23.4	5.6 ± 14.9	28.6 ± 31.6	< 0.001
HI, events/h	15.1 ± 15.3	12.5 ± 14.1	21.8 ± 16.1	< 0.001
Baseline SpO_2, %	95.7 ± 2.1	96.1 ± 2.1	95.0 ± 2.0	< 0.001
Mean SpO_2, %	93.7 ± 3.1	94.2 ± 3.0	92.5 ± 3.2	< 0.001
Lowest SpO_2, %	81.8 ± 9.1	83.6 ± 8.3	77.3 ± 9.6	< 0.001
Prevalence of OSA[b]				
No OSA, n (%)	275 (25.2)	265 (33.9)	10 (3.3)	< 0.001
Mild OSA, n (%)	248 (22.8)	211 (27.0)	37 (12.0)	< 0.001
Moderate OSA, n (%)	210 (19.3)	160 (20.5)	50 (16.2)	< 0.001
Severe OSA, n (%)	356 (32.7)	145 (18.6)	211 (68.5)	< 0.001

NC: neck circumference; ESS: Epworth Sleepiness Scale; REM: rapid eye movement; AHI: apnea/hypopnea index; AI: apnea index; HI: hypopnea index; and OSA: obstructive sleep apnea. [a]Values expressed as mean ± SD, except where otherwise indicated. [b]No OSA: AHI < 5.0 events/h; mild OSA: AHI = 5.0-14.9 events/h; moderate OSA: AHI = 15.0-29.9 events/h; and severe OSA: AHI ≥ 30.0 events/h.

sensitivity and specificity. For moderate/severe OSA, the best diagnostic performance was obtained at the cut-off value of ≥ 3, which had an accuracy of 70.8%, a sensitivity of 82.8%, and a specificity of 57.9%. The use of the ≥ 3 cut-off value in the 6-item model showed an accuracy, sensitivity, and specificity, respectively, of 73.0%, 74.3%, and 69.4% for a diagnosis of OSA in general; 70.8%, 82.8%, and 57.9% for a diagnosis of moderate/severe OSA; and 62.9%, 90.1%, and 49.7% for a diagnosis of severe OSA. After choosing the 6-item model as the best model, we created a mnemonic device for it, designating it the **N**C ≥ 42 cm, **O**besity (BMI ≥ 42 kg/m^2), **O**bserved apnea, **S**noring, **A**ge ≥ 37 years, and male **S**ex (NO-OSAS) model. Therefore, this model consists of six yes/no questions (maximum possible total score, 6 points).

DISCUSSION

In this study, which involved a large sample of consecutive bariatric surgery patients, we showed that all of the variables evaluated (sex, NC, BMI, age, ESS score, snoring, observed apnea, and hypertension) were independent predictors of the AHI, regardless of the cut-off value used, the only exceptions being hypertension at two of the AHI cut-off values (≥ 15.0 events/h and ≥ 30.0 events/h), and snoring at the AHI cut-off value of ≥ 30.0 events/h. At three different cut-off values (AHI ≥ 5.0 events/h, ≥ 15.0 events/h,

Table 2. Demographic, clinical, and polysomnographic parameters, by BMI category, for the 1,089 patients evaluated.[a]

Parameter	BMI				p
	35.0-39.9 kg/m² (n = 381)	40.0-49.9 kg/m² (n = 597)	50.0-59.9 kg/m² (n = 98)	≥ 60.0 kg/m² (n = 13)	
Demographic variables					
Male sex, n (%)	71 (18.6)	181 (30.3)	49 (50.0)	7 (53.8)	< 0.001
Age, years	38.2 ± 9.9	38.0 ± 10.0	38.4 ± 10.5	34.5 ± 7.9	0.607
Clinical variables					
NC, cm	40.2 ± 3.7	42.9 ± 4.4	46.7 ± 5.0	47.6 ± 4.2	< 0.001
BMI, kg/m²	37.8 ± 1.3	43.9 ± 2.7	53.0 ± 2.4	63.4 ± 3.1	< 0.001
ESS score, points	8.7 ± 4.3	8.8 ± 4.6	10.4 ± 4.4	11.0 ± 5.5	0.004
ESS score ≥ 10, n (%)	149 (39.1)	236 (39.5)	57 (58.2)	7 (53.8)	0.003
Hypertension, n (%)	125 (32.8)	263 (44.1)	49 (50.0)	8 (61.5)	< 0.001
Snoring, n (%)	340 (89.2)	562 (94.1)	95 (96.9)	13 (100.0)	0.007
Observed apnea, n (%)	108 (28.3)	213 (35.7)	39 (39.8)	9 (69.2)	0.002
Polysomnographic variables					
Arousals, events/h	21.8 ± 20.1	30.8 ± 27.8	51.6 ± 33.8	66.3 ± 41.7	< 0.001
AHI, events/h	18.4 ± 21.5	28.1 ± 29.6	51.3 ± 35.6	67.1 ± 43.4	< 0.001
AI, events/h	6.5 ± 14.8	12.6 ± 24.3	27.4 ± 32.3	34.8 ± 39.6	< 0.001
HI, events/h	11.8 ± 12.6	15.4 ± 14.8	22.7 ± 20.2	32.2 ± 25.3	< 0.001
Baseline SpO_2, %	96.2 ± 1.7	95.6 ± 2.3	95.1 ± 2.0	94.9 ± 2.5	< 0.001
Mean SpO_2, %	94.5 ± 2.5	93.5 ± 3.2	91.9 ± 3.6	90.5 ± 5.1	< 0.001
Lowest SpO_2, %	84.6 ± 7.8	81.2 ± 8.9	76.1 ± 10.6	71.7 ± 13.0	< 0.001
Prevalence of OSA[b]					
No OSA, n (%)	128 (33.6)	137 (23.0)	10 (10.2)	-	< 0.001
Mild OSA, n (%)	111 (29.1)	125 (20.9)	10 (10.2)	2 (15.4)	< 0.001
Moderate OSA, n (%)	61 (16.0)	135 (22.6)	13 (13.3)	1 (7.7)	< 0.001
Severe OSA, n (%)	81 (21.3)	200 (33.5)	65 (66.3)	10 (76.9)	< 0.001

NC: neck circumference; ESS: Epworth Sleepiness Scale; AHI: apnea/hypopnea index; AI: apnea index; HI: hypopnea index; and OSA: obstructive sleep apnea. [a]Values expressed as mean ± SD, except where otherwise indicated. [b]No OSA: AHI < 5.0 events/h; mild OSA: AHI = 5.0-14.9 events/h; moderate OSA: AHI = 15.0-29.9 events/h; and severe OSA: AHI ≥ 30.0 events/h.

and ≥ 30.0 events/h), the main predictor of a diagnosis of OSA was male sex. The prevalence of moderate/severe and severe OSA was higher among the males than among the females ($p < 0.001$). The 6-item NO-OSAS model, at a cut-off value of ≥ 3, showed good diagnostic performance for distinguishing between high-risk patients and low-risk patients, in relation to a diagnosis of OSA, regardless of the degree of severity.

In our sample of patients awaiting bariatric surgery, with or without clinical features of suspicion of OSA, the overall prevalence of OSA was high (74.8%), as was the prevalence of severe OSA (32.7%). Our results are consistent with those of previous studies involving bariatric surgery patients, all of which have reported a high (69.9-93.6%) prevalence of OSA[10,11,15,21-27] and a high (21.0-48.0%) proportion of subjects classified as having the severe form of the disease.[9-11,15,21-25] Our findings indicate that this population differs from the general population of patients with OSA.[1,5] We found that, in comparison with the general population of OSA patients, that of bariatric surgery patients had a greater proportion of females and comprised younger patients. In addition, the prevalence of OSA was much higher in our sample of bariatric surgery patients than in the general population.

In accordance with the findings of previous studies,[11,24] we observed linear increases in the prevalence and severity of OSA in parallel with increases in BMI. In one previous study,[28] the authors identified 10 variables that were predictive of OSA in bariatric surgery patients: NC, systolic blood pressure, waist/hip ratio, waist, loud snoring, frequent snoring, weight, BMI, hypertension, and male sex. Using five or more of these variables it was possible to obtain a model with a sensitivity of 77% and a specificity of 77% in predicting an AHI ≥ 15.0 events/h.[28]

Using ROC curve analysis, we found the main cut-off values of the continuous variables in our sample to be age ≥ 37 years, BMI ≥ 42 kg/m², NC ≥ 42 cm, and ESS score ≥ 10. Dixon et al. showed that advanced age, male sex, observed apnea, and severe obesity (especially central obesity) increase the risk of a higher AHI.[29] Those authors also used ROC curve analysis for determining the appropriate cut-off values for continuous variables, which they found to be NC ≥ 43 cm, age ≥ 38 years, and BMI ≥ 45 kg/m², which are quite similar to the cut-off values identified in our study. However, those authors included only patients with clinical suspicion of OSA, whereas our sample

Table 3. Predictive parameters for a diagnosis of obstructive sleep apnea, by level of severity, in the patients evaluated.

OSA severity, by AHI[a]	Analysis		Sensitivity %	Specificity %	PPV %	NPV %	Accuracy %
Parameter	Univariate OR (95% CI)	Multivariate OR (95% CI)					
Mild/moderate/severe							
Sex							
Male vs. female	15.30 (8.01-29.23)	10.20 (5.07-20.83)	36.6	96.3	96.7	33.9	51.6
Snoring							
Yes vs. no	5.03 (3.14-8.08)	2.30 (1.38-3.86)	96.0	17.0	77.4	59.4	76.1
Age, years							
≥ 37 vs. < 37	2.55 (1.92-3.40)	2.25 (1.61-3.15)	56.2	66.5	83.2	33.9	58.8
Observed apnea							
Yes vs. no	3.17 (2.25-4.47)	1.85 (1.26-2.71)	39.5	82.9	87.2	31.6	50.5
BMI, kg/m^2							
≥ 42 vs. < 42	2.21 (1.66-2.94)	1.60 (1.14-2.23)	53.0	66.1	82.2	32.2	56.3
ESS score							
≥ 10 vs. < 10	1.69 (1.26-2.26)	1.56 (1.12-2.16)	44.3	68.0	80.4	29.2	50.3
Hypertension							
Yes vs. no	2.69 (1.97-3.66)	1.52 (1.06-2.17)	46.5	75.6	84.9	32.2	53.8
NC, cm							
≥ 42 vs. < 42	4.01 (2.97-5.41)	1.45 (1.01-2.09)	60.0	72.7	86.7	38.0	63.2
Moderate/severe							
Sex							
Male vs. female	8.66 (6.15-12.20)	5.91 (3.92-8.92)	46.1	91.0	84.7	60.9	67.6
Snoring							
Yes vs. no	5.59 (3.10-10.10)	2.41 (1.27-4.56)	97.5	12.4	54.6	82.2	56.6
BMI, kg/m^2							
≥ 42 vs. < 42	2.66 (2.08-3.40)	2.12 (1.58-2.84)	59.7	64.2	64.3	59.5	61.8
Age, years							
≥ 37 vs. < 37	1.98 (1.56-2.52)	2.09 (1.54-2.83)	58.6	58.3	60.3	56.5	58.4
Observed apnea							
Yes vs. no	2.78 (2.13-3.62)	1.84 (1.35-2.51)	44.5	77.6	68.2	56.3	60.4
NC, cm							
≥ 42 vs. < 42	4.44 (3.44-5.73)	1.63 (1.18-2.26)	68.9	66.7	69.1	66.4	67.8
ESS score							
≥ 10 vs. < 10	1.59 (1.25-2.03)	1.49 (1.11-2.00)	46.6	64.6	58.7	52.8	55.2
Hypertension							
Yes vs. no	1.96 (1.53-2.51)	1.13 (0.83-1.52)	48.5	67.4	61.7	54.8	57.6
Severe							
Sex							
Male vs. female	9.54 (7.06-12.88)	6.80 (4.62-10.00)	59.2	86.7	68.5	81.4	77.7
BMI, kg/m^2							
≥ 42 vs. < 42	2.70 (2.08-3.52)	2.14 (1.56-2.94)	64.6	59.7	43.8	77.6	61.3
Age, years							
≥ 37 vs. < 37	1.72 (1.33-2.22)	2.02 (1.45-2.81)	59.5	53.8	38.5	73.2	55.7
Observed apnea							
Yes vs. no	2.73 (2.09-3.56)	1.85 (1.34-2.55)	49.4	73.6	47.6	75.0	65.7
Snoring							
Yes vs. no	5.43 (2.47-11.92)	1.84 (0.79-4.29)	98.0	9.8	34.5	91.1	38.6
NC, cm							
≥ 42 vs. < 42	5.70 (4.16-7.45)	1.73 (1.18-2.52)	78.0	60.9	49.2	85.1	66.5
ESS score							
≥ 10 vs. < 10	1.64 (1.27-2.12)	1.54 (1.12-2.52)	49.4	62.7	39.1	71.8	58.4
Hypertension							
Yes vs. no	1.68 (1.30-2.17)	1.00 (0.72-1.36)	49.4	63.3	39.5	72.0	58.7

OSA: obstructive sleep apnea; AHI: apnea/hypopnea index; PPV: positive predictive value; NPV: negative predictive value; ESS: Epworth Sleepiness Scale; and NC: neck circumference. [a]Mild/moderate/severe = AHI ≥ 5.0 events/h; moderate/severe = AHI ≥ 15.0 events/h; and severe = AHI ≥ 30.0 events/h.

Table 4. ROC curves for the models evaluated, by the level of severity of obstructive sleep apnea.

Models	OSA severity, by AHI[a]		
	Mild/moderate/severe AUC (95% CI)	Moderate/severe AUC (95% CI)	Severe AUC (95% CI)
3-item Male sex Snoring BMI ≥ 42 kg/m^2	0.716 (0.683-0.748)	0.739 (0.710-0.769)	0.759 (0.729-0.790)
4-item Male sex Snoring BMI ≥ 42 kg/m^2 Age ≥ 37 years	0.752 (0.719-0.785)	0.756 (0.727-0.784)	0.765 (0.735-0.794)
5-item Male sex Snoring BMI ≥ 42 kg/m^2 Age ≥ 37 years Observed apnea	0.764 (0.733-0.796)	0.765 (0.738-0.793)	0.771 (0.742-0.800)
6-item Male sex Snoring BMI ≥ 42 kg/m^2 Age ≥ 37 years Observed apnea NC ≥ 42 cm	0.777 (0.747-0.807)	0.784 (0.757-0.811)	0.796 (0.769-0.824)

OSA: obstructive sleep apnea; AHI: apnea/hypopnea index; AUC: area under the curve; NC: neck circumference. [a]Mild/moderate/severe = AHI ≥ 5.0 events/h; moderate/severe = AHI ≥ 15.0 events/h; and severe = AHI ≥ 30.0 events/h.

included all patients awaiting bariatric surgery, with or without symptoms of OSA.

In the present study, there were significant differences between males and females: males had higher BMIs and higher NCs, as well as a higher prevalence of hypertension, snoring, and observed apnea. In addition, males had higher AHIs, lower nadir SpO_2 values, higher arousal indices, together with a higher prevalence of moderate/severe and severe OSA. These differences between sexes have also been reported in some other studies of bariatric surgery patients.[9-11,13,15,21-23,25,30]

Patients awaiting bariatric surgery should be screened for OSA to decrease the occurrence of peri-and post-operative complications. Bariatric surgery is the most effective weight loss therapy for morbidly obese patients; it improves OSA in most patients and has a relatively low mortality rate.[4] Due to the high prevalence of OSA, especially of the severe forms, previous studies[6,11,23,26] have underscored the need for polysomnography in all patients awaiting bariatric surgery, regardless of the presence or absence of symptoms of OSA.

Our study has some limitations. Patient selection occurred retrospectively in a sleep laboratory, which increased the possibility of selection bias. In addition, this was a single-center study, and the implications of our findings for the general population might therefore be limited. Furthermore, we did not evaluate comorbidities (other than hypertension) or other sleep complaints such as nocturia, nasal symptoms, morning headaches, and nocturnal choking or gasping. Moreover, data regarding regional obesity (waist circumference, hip circumference, neck-to-waist ratio, or waist-to-hip ratio) were not available. Conversely, our study has certain strengths. First, it involved a large sample of consecutive patients, all of whom were evaluated with full polysomnography at a sleep center, regardless of whether or not they had sleep complaints. In addition, the medical charts of the patients included in our final sample contained complete information about all eight of the variables of interest. Furthermore, the possibility of confounding was reduced in the analysis by the use of a multivariate logistic model including all variables with a p-value < 0.05. Therefore, we believe that the limitations of the study were outweighed by its strengths and did not affect the interpretation of the results.

In conclusion, our findings suggest that, among patients awaiting bariatric surgery, there is a high prevalence of OSA in general and of moderate/severe OSA. Our data also indicate that the variables sex, age, NC, BMI, ESS score, snoring, observed apnea, and hypertension can be used in order to confirm the suspicion of OSA and to assess its severity. The 6-item NO-OSAS model, at a cut-off value ≥ 3 to identify high-risk patients, showed good diagnostic accuracy for OSA in general, as well as for moderate/

Table 5. Predictive parameters of the 6-item model in relation to the level of severity of obstructive sleep apnea.

OSA severity, by AHI[a] Parameter	High risk n (%)	Low risk n (%)	Sensitivity %	Specificity %	PPV %	NPV %	Accuracy %	OR (95% CI)
Mild/moderate/severe								
≥ 1 vs. < 1	1,056 (97.0)	33 (3.0)	98.8	8.7	76.2	72.7	76.1	8.55 (3.92-18.64)
≥ 2 vs. < 2	915 (84.0)	174 (16.0)	91.0	36.7	80.9	58.0	77.3	5.89 (4.18-8.30)
≥ 3 vs. < 3	689 (63.3)	400 (36.7)	74.3	69.4	87.8	47.7	73.0	6.58 (4.87-8.89)
≥ 4 vs. < 4	431 (39.6)	658 (60.4)	48.7	87.6	92.1	36.6	58.5	6.74 (4.59-9.91)
≥ 5 vs. < 5	187 (17.2)	902 (82.8)	22.6	98.9	98.3	30.1	41.8	26.48 (8.38-83.59)
6 vs. < 6	52 (4.8)	1,037 (95.2)	6.3	100.0	100.0	26.5	30.0	-
Moderate/severe								
≥ 1 vs. < 1	1,056 (97.0)	33 (3.0)	99.4	5.7	53.3	90.9	54.4	11.42 (3.46-37.64)
≥ 2 vs. < 2	915 (84.0)	174 (16.0)	95.7	28.6	59.2	86.2	63.5	9.08 (5.78-14.25)
≥ 3 vs. < 3	689 (63.3)	400 (36.7)	82.8	57.9	68.0	75.7	70.8	6.65 (5.03-8.80)
≥ 4 vs. < 4	431 (39.6)	658 (60.4)	59.3	81.8	77.9	65.0	70.1	6.58 (4.98-8.69)
≥ 5 vs. < 5	187 (17.2)	902 (82.8)	29.8	96.5	90.3	55.9	61.8	11.94 (7.21-19.75)
6 vs. < 6	52 (4.8)	1,037 (95.2)	8.6	99.4	94.2	50.1	52.2	16.42 (5.08-53.04)
Severe								
≥ 1 vs. < 1	1,056 (97.0)	33 (3.0)	99.7	4.3	33.6	96.9	35.5	16.20 (2.20-119.07)
≥ 2 vs. < 2	915 (84.0)	174 (16.0)	97.4	22.5	37.9	94.8	47.0	11.20 (5.65-22.19)
≥ 3 vs. < 3	689 (63.3)	400 (36.7)	90.1	49.7	46.5	91.2	62.9	9.09 (6.23-13.27)
≥ 4 vs. < 4	431 (39.6)	658 (60.4)	69.9	75.1	57.7	83.7	73.4	7.04 (5.31-9.33)
≥ 5 vs. < 5	187 (17.2)	902 (82.8)	39.0	93.4	74.3	75.9	75.6	9.14 (6.36-13.12)
6 vs. < 6	52 (4.8)	1,037 (95.2)	12.6	99.0	86.5	70.0	70.2	15.00 (6.69-33.64)

OSA: obstructive sleep apnea; AHI: apnea/hypopnea index; PPV: positive predictive value; and NPV: negative predictive value. [a]Mild/moderate/severe = AHI ≥ 5.0 events/h; moderate/severe = AHI ≥ 15.0 events/h; and severe = AHI ≥ 30.0 events/h.

severe and severe OSA. Further studies, especially prospective ones, are necessary to validate the use of the NO-OSAS model as a means of screening for OSA in bariatric surgery patients.

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Control measures to trace ≤ 15-year-old contacts of index cases of active pulmonary tuberculosis

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ABSTRACT

This was descriptive study carried out in a medium-sized Brazilian city. In ≤ 15-year-old contacts of index cases of active pulmonary tuberculosis, we assessed compliance with the Brazilian national guidelines for tuberculosis control. We interviewed 43 contacts and their legal guardians. Approximately 80% of the contacts were not assessed by the municipal public health care system, and only 21% underwent tuberculin skin testing. The results obtained with the Chi-square Automatic Interaction Detector method suggest that health care teams have a biased attitude toward assessing such contacts and underscore the need for training health professionals regarding tuberculosis control programs.

Keywords: Tuberculosis, pulmonary\epidemiology, Tuberculosis, pulmonary\prevention and control; Contact tracing.

Assessment of contacts is one of the essential steps in tuberculosis control programs, and its purpose is to diagnose or rule out latent infection or active tuberculosis in such individuals.[1]

In Brazil, activities that health care facilities should employ to assess contacts are described in the Brazilian National Ministry of Health guidelines for tuberculosis control.[1] In those guidelines, this assessment involves five steps, namely invitation for contacts to come to the health care facility for assessment, interview by the health care team, tuberculin skin testing, chest X-ray, and, when necessary, prescription of treatment for latent tuberculosis infection (LTBI) or, if appropriate, for active tuberculosis.[1]

Despite the strategic importance of such measures, compliance rates are low (up to approximately 60%) in Brazil,[2,3] whereas, in developed countries, the aforementioned surveillance and control measures reach approximately 90% of individuals.[4]

The objective of the present study was to assess compliance with the steps applicable to ≤ 15-year-old contacts of index cases of active pulmonary tuberculosis.

This was a descriptive study carried out in a medium-sized city in the central-western portion of the Brazilian state of Minas Gerais. Minas Gerais is the second most populous Brazilian state, as well as being the third most important economically; the city under study serves as a regional hub for health care for 55 cities and had, between 2007 and 2010, an average resident population of 213,501.[5]

The inclusion criteria for contacts were as follows: being ≤ 15 years of age; living in the city under study; and being a contact of a case of active tuberculosis reported between January of 2007 and December of 2010, according to the Brazilian Case Registry Database. The index cases were located by means of the addresses available on the tuberculosis reporting and investigation forms that feed the database.

Data on contacts were collected in December of 2010 by administering a structured coding instrument, at a home visit; by determining, through a review of the municipal health information system, over a period of up to two years after the index cases had been reported, whether or not tuberculin skin testing and chest X-ray were performed; and by assessing prescription of and adherence to treatment for LTBI, through a review of dispensing records for isoniazid.

The statistical analysis included descriptive tests and bivariate and multivariate analyses in which the response variable was compliance or noncompliance with the steps in the assessment of contacts, as determined by the Chi-square Automatic Interaction Detector (CHAID) algorithm,[6] with cross-validation of results of 10 subsamples, a maximum of 10 nodes, and 5 cases in the child node. Pearson's chi-square test with Bonferroni's adjustment was used for between-node separation. Explanatory variables

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were degree of contact and family relationship between contacts and the index case, gender, number of rooms in the index case's house, and number of residents in the household. For the analysis of the second step (interview by the health care team), we included, in addition to the aforementioned variables, home visits (yes/no) and invitation for contacts to come to the health care facility.

The research project and its written informed consent form were submitted to and approved by the Human Research Ethics Committee of the *Hospital São João de Deus*—the only such committee in the city at the time the study was conducted— Protocol no. 63/2011.

Between January of 2007 and December of 2010, 135 cases of tuberculosis were reported, of which 54 (40%) consisted of patients with active pulmonary tuberculosis and who therefore were eligible for the study. We excluded 11 patients (20.4%) because there was no record of their addresses, 18 (34.2%) because they did not meet the inclusion criteria—13 (24.0%) because they had no ≤ 15-year-old contacts at the time of diagnosis and 5 (9.2%) because they lived in other cities—and 2 (3.7%) because they declined to participate in the study. There thus remained 21 index cases (38.9%), who were revisited between July of 2011 and February of 2013 and through whom 43 contacts who met the inclusion criteria were identified.

Table 1 presents the general characteristics of the study population.

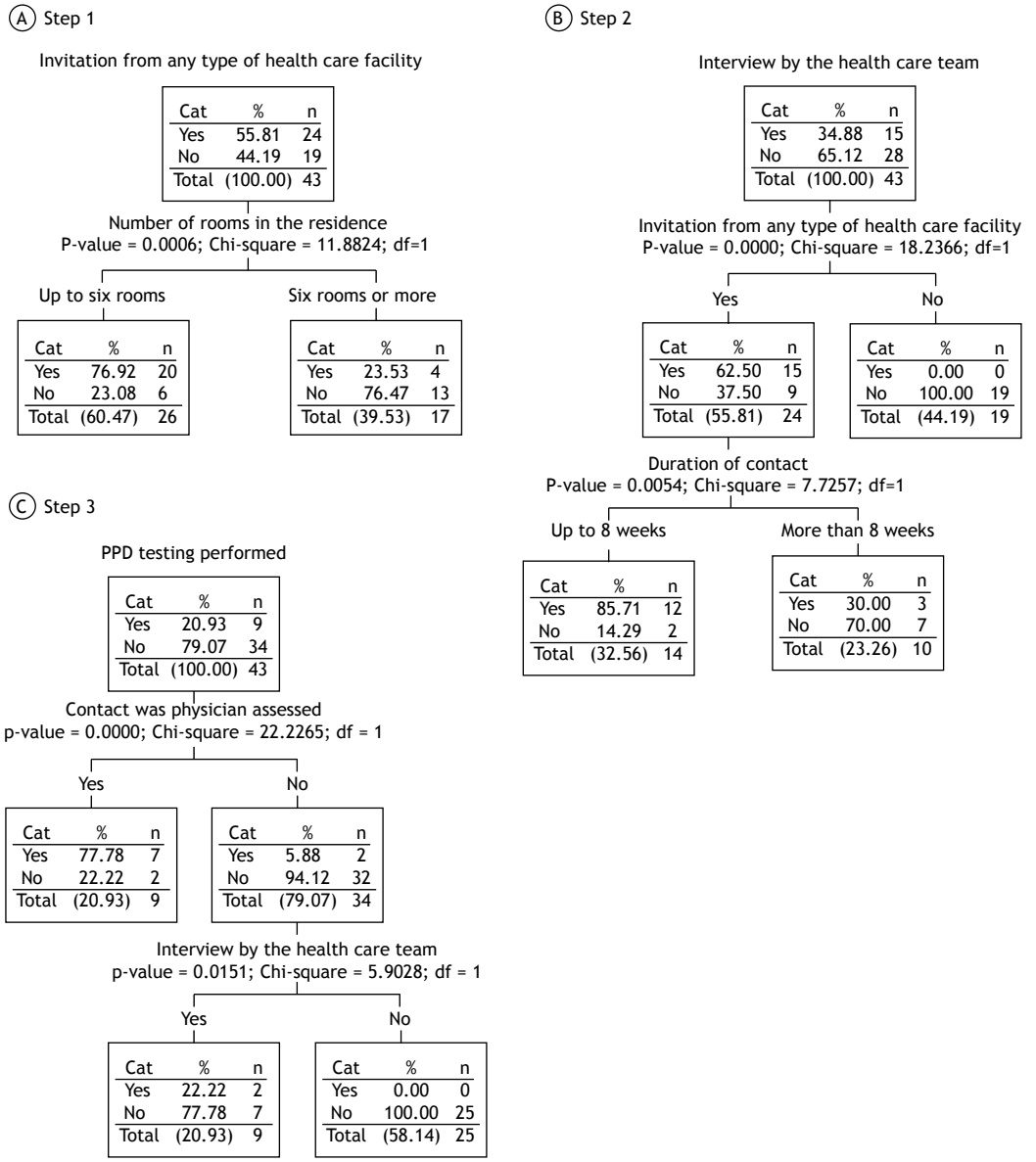

Figure 1. Multivariate analysis of factors influencing access to clinical and therapeutic resources by ≤ 15-year-old contacts of cases of active pulmonary tuberculosis between 2007 and 2010. Cat.: category; and df: degrees of freedom.

Table 1. Descriptive characteristics of ≤ 15-year-old contacts of index cases of active pulmonary tuberculosis.[a]

Characteristic	N = 43	Invitation from the PHC team to be assessed for health status		p*
		Invited (n = 24)	Not invited (n = 19)	
Sociodemographic				
Male gender	22 (51.2)	12 (50.0)	10 (52.6)	> 0.05
Age at interview[b]	10.2 (8.3-12.5)	10.5 (8.6-12.7)	10.0 (7.6-12.2)	> 0.05
Knowing how to read or write	35 (81.4)	20 (83.3)	15 (78.9)	> 0.05
Residence type				
Owned	32 (74.4)	17 (70.8)	15 (78.9)	
Rented	10 (23.3)	7 (29.2)	3 (15.8)	
Borrowed	1 (2.3)	-	1 (5.3)	
Number of rooms				0.01
Up to four	3 (7.0)	2 (8.3)	1 (5.3)	
Five	13 (30.2)	9 (37.5)	4 (21.1)	
Six	10 (23.3)	9 (37.5)	1 (5.3)	
Seven or more	17 (39.5)	4 (16.7)	13 (68.4)	
Number of residents in the household				< 0.01
Up to four	14 (32.6)	11 (45.8)	3 (15.8)	
Five or more	28 (65.1)	12 (40.0)	16 (85.2)	
No response	1 (2.3)	1 (4.2)	-	
Sanitation status				
Piped, treated water	43 (100.0)	24 (100.0)	19 (100.0)	> 0.05
Sewage collection system	38 (88.4)	20 (83.3)	18 (94.7)	> 0.05
Garbage collection	43 (100.0)	24 (100.0)	19 (100.0)	>0.05
Contact with the index case				
Frequency of contact				
Daily	25 (58.1)	15 (62.5)	10 (52.6)	> 0.05
Residence	20 (80.0)	13 (86.7)	7 (70.0)	
Same lot	5 (20.0)	2 (13.3)	3 (30.0)	
Infrequent	18 (41.9)	9 (37.5)	9 (47.4)	
Duration of contact				< 0.01
≤ 2 weeks	12 (27.9)	9 (37.5)	3 (15.8)	
3-10 weeks	14 (32.6)	9 (37.5)	5 (26.3)	
> 10 weeks	17 (39.5)	5 (24.0)	11 (57.9)	
Degree of family relationship with the index case				0.03
Grandchild	16 (37.2)	11 (45.8)	5 (26.3)	
Child	12 (27.9)	8 (33.8)	4 (21.1)	
Nephew/niece	12 (27.9)	2 (8.3)	10 (52.6)	
Other	2 (4.7)	2 (8.3)	-	
Sibling	1 (2.3)	1 (4.2)	-	
PHC received by contacts				> 0.05
Type of health care facility				
Family health care clinic	8 (18.6)	5 (20.8)	3 (15.8)	
Primary health care clinic	35 (81.4)	19 (79.2)	16 (84.2)	
Preventive activities				
BCG vaccination				> 0.05
First vaccination	42 (97.7)	23 (95.8)	19 (100.0)	
Revaccination	1 (2.3)	1 (4.2)	-	
Invitation from the PHC team to be assessed for health status	24 (55.8)	24 (100.0)	-	-
Invitation accepted	15 (62.5)	15 (62.5)	-	< 0.01
Home visit	7 (43.8)	7 (46.7)	-	0.01
Assessment by the physician[c]	9 (56.2)	8 (53.3)	1 (100.0)	0.03
Underwent tuberculin skin testing	9 (20.9)	8 (33.3)	1 (5.3)	0.03
Underwent chest X-ray	5 (11.6)	4 (16.7)	1 (5.3)	> 0.05
Underwent chemoprophylaxis	1 (14.3)	1 (4.2)	-	> 0.05

PHC: primary health care. [a]Values expressed as n (%), except where otherwise indicated.[b]Values expressed as median (interquartile range). [c]One contact who was not invited for assessment sought the physician by itself. Therefore, the total number of assessments performed by the PHC team was 16 rather than 15. *Pearson's chi-square test with Bonferroni's adjustment.

Of the 43 contacts, all had received BCG vaccination, 22 (51.2%) were male, 40 (93.0%) lived with five or more persons in the household, 25 (58.1%) had frequent contact with the index case, and 25 (58.1%) reported a family income of up to two times the national minimum wage.

Figure 1 contains the decision tree for the first three steps in the assessment of contacts. In it, the lack of invitation for contacts to come to the health care facility (in 44.2%; Figure 1A) is of note, as are the lack of interview by the health care team (in 65.1%; Figure 1B) and the lack of tuberculin skin testing (in 79.1%; Figure 1C). In addition, invitation for contacts to come to the health care facility was found to be associated only with number of rooms in the house (a proxy for socioeconomic status), the invitation being made mostly to those living in houses with fewer rooms (76.9%; Figure 1A). No statistical significance was found for either degree of contact or type of health care facility where care was provided.

Whether an interview would be conducted with contacts and their families was determined by contacts having been instructed to come to the health care facility and by duration of contact. Only 24 contacts (55.8%; Figure 1A) were invited to come to the health care facility, whereas, among these, the attendance rate was 62.5%.

The most significant variable ($p < 0.0001$) in determining whether a contact would undergo tuberculin skin testing was medical assessment, i.e., 77.8% of those who were assessed by a physician underwent such testing, which denotes that assessment of contacts was centered on only one professional. In cases in which the contact was not assessed by a physician, the second explanatory variable was interview by the health care team (Figure 1B).

The last two steps in the assessment of contacts were not included in the decision tree because they were not performed for all contacts; they are recommended based on the results obtained in the previous assessment step, i.e., whether a contact will undergo chest X-ray is dependent on tuberculin skin testing results, and whether a contact will receive treatment for LTBI or active tuberculosis is dependent both on chest X-ray findings and tuberculin skin testing results.

Treatment for LTBI should have been recommended to at least 2 of the contacts; however, only 1 of them (2.3%) received such treatment and for only about 30 days.

Our review of the literature found no studies on assessment of contacts in which the CHAID method was used, this method being a strategy for statistical analysis that allows the identification of critical points in each step in the investigation of such individuals.

As shown in the present study, assessment of contacts revealed that compliance rates were lower than desirable. A study conducted in the state of Mato Grosso, Brazil, reported that 60.5% of the contacts younger than 15 years were investigated, and that the proportion of contacts investigated was 40.0% higher among those exposed to active cases, being higher than that found in the present study.[3] In the city of São José do Rio Preto, Brazil, 63.1% of the contacts were assessed by the municipal health care system in 2002.[2] Nearly the reverse of this situation is found in developed countries; there, the proportion of contacts who are investigated ranges from 80% to 90%, as is the case in the USA and in the Netherlands.[4,7]

It is possible that biases occurred in the approach to contacts. One such bias is that only the low socioeconomic conditions of the contacts (perceived perhaps because of the size of the houses, given that approximately 60% had six rooms at most; Table 1) would favor the transmission of tuberculosis. However, in the present study, this was not observed, since only 11.6% of the contacts lived with more than five people in houses with up to six rooms. Another such bias is that the health professionals seem to have assumed that the risk of developing the disease would be higher among those 60% (Table 1) whose duration of exposure to the active source case had occurred within the first 10 weeks than would among those whose duration was greater than 10 weeks ($p < 0.01$). In other words, these professionals believed that, if contacts had not contracted tuberculosis up to that time, they would not develop the disease in the future. This perception is completely wrong. In addition, the present study found that assessment of contacts was physician-centered, contrary to the Brazilian National Tuberculosis Control Program guidelines, which strongly encourage the participation of all health professionals.[2]

In conclusion, the present study underscores the urgent need for training primary health care teams on how to approach contacts appropriately, especially those who are exposed to patients with active tuberculosis.

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REVIEW ARTICLE

Update on diagnosis and treatment of idiopathic pulmonary fibrosis

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ABSTRACT

Idiopathic pulmonary fibrosis is a type of chronic fibrosing interstitial pneumonia, of unknown etiology, which is associated with a progressive decrease in pulmonary function and with high mortality rates. Interest in and knowledge of this disorder have grown substantially in recent years. In this review article, we broadly discuss distinct aspects related to the diagnosis and treatment of idiopathic pulmonary fibrosis. We list the current diagnostic criteria and describe the therapeutic approaches currently available, symptomatic treatments, the action of new drugs that are effective in slowing the decline in pulmonary function, and indications for lung transplantation.

Keywords: Idiopathic pulmonary fibrosis/diagnosis; Idiopathic pulmonary fibrosis/therapy; Idiopathic pulmonary fibrosis/rehabilitation.

CONCEPT

Idiopathic pulmonary fibrosis (IPF) is a specific form of chronic, progressive fibrosing interstitial pneumonia of unknown cause. It occurs primarily in older adults, predominantly in the sixth and seventh decades of life, being limited to the lungs. It is associated with the histological/radiological pattern of usual interstitial pneumonia (UIP).[1-3] Prognosis is significantly worse in patients with the histologically confirmed UIP pattern of IPF than in those with other histological patterns of chronic interstitial pneumonia.[4] Therefore, there is a need to establish an accurate diagnosis of IPF, a process that is undoubtedly challenging.

Patients with IPF present with a median survival of 50% at 2.9 years after diagnosis.[1,4] However, given the varied natural history of the disease, it is difficult to determine an accurate prognosis for patients with newly diagnosed IPF.[5]

DIAGNOSTIC ASPECTS

For a definitive diagnosis of IPF, an integrated multidisciplinary approach involving pulmonologists, radiologists, and pathologists is required. The diagnosis of IPF is based on the absence of a known cause of pulmonary fibrosis and the presence of the UIP pattern, the former being a key factor in the diagnostic process. Even when a surgical lung biopsy (SLB) reveals a histological pattern of UIP, a definitive diagnosis requires the exclusion of other medical conditions that are associated with the UIP pattern, including connective tissue diseases, chronic hypersensitivity pneumonitis (CHP), drug-induced lung injury, asbestosis, familial pulmonary fibrosis, and Hermansky-Pudlak syndrome.[1,6,7]

The 2011 American Thoracic Society (ATS)/European Respiratory Society (ERS)/Japanese Respiratory Society (JRS)/*Asociación Latinoamericana del Tórax* (ALAT) guidelines for the diagnosis of IPF recommend a combination of criteria involving HRCT findings and histopathological features.[1] The ATS/ERS/JRS/ALAT guidelines reinforce previous conclusions that HRCT has a primary role in the diagnosis of IPF. In the appropriate clinical context, HRCT findings of UIP eliminate the need for SLB (Chart 1). However, SLB is recommended for patients in whom HRCT findings meet the criteria for "possible UIP" or "inconsistent with UIP" (Chart 2). Specific combinations of HRCT and histopathological patterns are also provided

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in the guidelines, the likelihood of IPF being defined as definite, probable, or possible (Chart 3).[1]

After the publication of the ATS/ERS/JRS/ALAT guidelines,[1] some questions were raised. The Brazilian Thoracic Association Guidelines for Interstitial Lung Diseases[6] raised the question of whether HRCT findings meeting the criteria for possible UIP plus SLB findings consistent with possible UIP or nonclassifiable fibrosis can really be considered indicative of "probable IPF". The question was whether the presence of homogeneous fibrosis with inflammation, as described for possible UIP, is really consistent with the histological pattern of UIP.[6] In addition, cases of nonclassifiable fibrosis might be secondary to sampling errors or clinical conditions

Chart 1. HRCT criteria for the diagnosis of usual interstitial pneumonia.[a]

UIP pattern (all four criteria)	Possible UIP pattern (all three criteria)	Inconsistent with UIP pattern (any of the seven criteria)
• Subpleural, basal predominance • Reticular abnormality • Honeycombing with or without traction bronchiectasis • Absence of findings listed as inconsistent with UIP (see third column)	• Subpleural, basal predominance • Reticular abnormality • Absence of findings listed as inconsistent with UIP (see third column)	• Upper or middle lung predominance • Peribronchovascular predominance • Extensive ground-glass abnormality (more extensive than reticular abnormality) • Diffuse micronodules (bilateral, predominantly in the upper lobes) • Discrete cysts (multiple, bilateral, away from areas of honeycombing) • Mosaic attenuation or air trapping (bilateral, in three or more lobes) • Peribronchial or lobar consolidation

UIP: usual interstitial pneumonia. [a]Based on Raghu et al.[1]

Chart 2. Histological criteria for the diagnosis of usual interstitial pneumonia.[a]

Pattern	Features
UIP (all four criteria)	• Evidence of marked fibrosis/architectural distortion with or without honeycombing in a predominantly subpleural/paraseptal distribution • Presence of patchy involvement of lung parenchyma by fibrosis • Presence of fibroblast foci • Absence of features against a diagnosis of UIP suggesting an alternate diagnosis
Probable UIP (all three criteria)	• Evidence of marked fibrosis/architectural distortion with or without honeycombing • Absence of either patchy involvement or fibroblastic foci, but not both • Absence of features against a diagnosis of UIP suggesting an alternate diagnosis or honeycomb changes only
Possible UIP (all three criteria)	• Patchy or diffuse involvement of lung parenchyma by fibrosis, with or without interstitial inflammation • Absence of other criteria for UIP • Absence of features against a diagnosis of UIP suggesting an alternate diagnosis
Not UIP (any of the six criteria)	• Hyaline membranes (unless the biopsy was performed during an AE) • Extensive areas of organizing pneumonia • Granulomas • Marked interstitial inflammatory cell infiltrate away from honeycombing • Predominant airway-centered changes • Other features suggestive of an alternate diagnosis
Nonclassifiable fibrosis	• Biopsy findings revealing a pattern of fibrosis that does not meet the criteria for UIP or other idiopathic interstitial pneumonias

UIP: usual interstitial pneumonia; and AE: acute exacerbation. [a]Based on Raghu et al.[1]

Chart 3. Combination of HRCT and lung biopsy findings for the diagnosis of idiopathic pulmonary fibrosis.

HRCT findings	Histological findings	Diagnosis
UIP	No biopsy required	IPF
Possible UIP	UIP or probable UIP	IPF
Possible UIP	Possible UIP or nonclassifiable fibrosis	Probable IPF
Inconsistent with UIP	UIP	Possible IPF

UIP: usual interstitial pneumonia; and IPF: idiopathic pulmonary fibrosis. [a]Based on Raghu et al.[1]

other than IPF. Another important point is the possibility of IPF despite HRCT findings inconsistent with UIP. In the appropriate context, ground-glass opacities at the lung bases and in the subpleural regions, which are most commonly found in patients with accelerated IPF, plus SLB findings consistent with definite or probable UIP can be indicative of IPF. Therefore, the diagnostic criteria in the Brazilian Thoracic Association Guidelines for Interstitial Lung Diseases[6] differ to some degree from those in the ATS/ERS/JRS/ALAT guidelines.[1] In Brazil, IPF is not classified as definite, probable, or possible (Chart 4). Despite being more practical, these criteria have yet to gain wide acceptance in the country.

In a case-control study conducted in Spain, 20 of 46 cases diagnosed with IPF on the basis of the 2011 ATS/ERS/JRS/ALAT guidelines[1] were reviewed at a center specializing in CHP, where they were found to meet diagnostic criteria for CHP.[8] Although the aforementioned findings raise concerns regarding the reliability of a UIP diagnosis based solely on HRCT findings, they were not sufficiently compelling to warrant changes in the 2011 ATS/ERS/JRS/ALAT diagnostic criteria for IPF.[1] Nevertheless, they underscore the importance of thoroughly investigating environmental exposure in patients with interstitial lung disease.[9]

DIFFERENTIAL DIAGNOSIS

In patients suspected of having IPF, other diagnoses should be carefully considered. Patients with HRCT findings consistent with probable or possible UIP are frequently encountered in clinical practice, and the differential diagnosis should include CHP and fibrotic nonspecific interstitial pneumonia. However, a proportion of such patients do not undergo SLB, either because of contraindications (comorbidities, advanced age, or disease severity) or because of their unwillingness to undergo a surgical procedure.

In this context, bronchoscopy with BAL can be useful in raising the suspicion of CHP, lymphocytosis in BAL fluid generally being above 30%.[1,6] It is of note that transbronchial biopsy is not useful in patients suspected of having UIP. However, recent data suggest that an emerging technique known as bronchoscopic cryobiopsy can be useful in this scenario.[10]

It is important to exclude pulmonary involvement by collagen vascular disease in patients with interstitial fibrosing diseases such as rheumatoid arthritis and systemic sclerosis, even in those in whom HRCT findings are consistent with UIP, especially in the presence of suggestive complaints or a family history of autoimmune disease.[7] It is also important to screen family members (including distant relatives) for pulmonary conditions, given that familial interstitial lung disease is common.

Early and accurate diagnosis of IPF is a challenge. Auscultation findings of late inspiratory crackles and pan-inspiratory crackles, particularly "Velcro" crackles, constitute an important warning sign of IPF.[11] Given that IPF is currently overdiagnosed on the basis of HRCT findings, there is an urgent need for standardizing diagnostic approaches. With regard to HRCT evaluation, it is still difficult to distinguish between honeycombing and traction bronchiectasis or between honeycombing and combined pulmonary fibrosis and emphysema, for example.[12] Although it is often helpful to compare HRCT and histological findings, not all patients benefit from that. Multidisciplinary meetings are essential for an accurate diagnosis in patients in whom it is difficult to use the proposed criteria.

PARADIGM SHIFTS AND TREATMENT FAILURE

The treatment of IPF initially focused on inflammation and fibrosis; that is, injury or damage triggers inflammation, and the onset of fibrosis leads to lung repair.[1] However, in patients with IPF, there is little or no inflammation, and fibrosis is progressive and massive. Paradigm shifts regarding the pathogenesis of IPF, which is now considered to be primarily a fibrosing, epithelial/mesenchymal disorder, led to studies investigating new therapeutic modalities.[13]

Until 2000, various terms were used in order to refer to IPF (including fibrosing alveolitis, chronic idiopathic pneumonia, and fibrosing pneumonitis), and various histological patterns were associated with it. In that year, an international consensus statement was published, standardizing the terminology and precisely defining the disease.[14] Therefore, all studies published before 2000 have serious limitations because they did not use the current criteria for defining IPF. It is also of note that small case series and single-center studies conducted earlier have been complemented by randomized studies in which the sample size has been effectively calculated, many of which have been multicenter in nature.

Recent studies investigating the treatment of IPF include numerous clinical trials showing negative results, some of which are summarized in Chart 5.

Chart 4. Combination of HRCT and lung biopsy findings for the diagnosis of idiopathic pulmonary fibrosis, in accordance with the 2012 Brazilian Thoracic Association Guidelines for Interstitial Lung Diseases.[a]

HRCT findings	Histological findings
UIP	No biopsy required
Possible UIP	UIP or probable UIP
UIP or possible UIP with ground-glass opacities at the lung bases	UIP or probable UIP

UIP: usual interstitial pneumonia. [a]Based on Baldi et al.[6]

The body of acquired knowledge on certain drugs is of particular interest.

For decades, corticosteroids have been the standard therapy for "pulmonary fibrosis", on the basis of retrospective studies including few patients and no clear definition of the lung disease being treated.[15] Although corticosteroids are quite useful in the treatment of interstitial lung diseases such as nonspecific interstitial pneumonia and cryptogenic organizing pneumonia, there is no evidence for the use of corticosteroids in the treatment of IPF. In addition to having many side effects and increasing the number of comorbidities, corticosteroids have been reported to be associated with an increased occurrence of acute exacerbations (AEs).[15]

The immunosuppressants azathioprine and cyclophosphamide, which are commonly used in the treatment of connective tissue disease-associated interstitial lung diseases, are not recommended for patients with IPF. In a randomized, double-blind, placebo-controlled study, hospitalization and mortality rates were significantly higher in the group of IPF patients receiving a combination of low-dose corticosteroids, N-acetylcysteine (NAC), and azathioprine than in the group of IPF patients receiving placebo.[16] The immunosuppression caused by the combination of low-dose prednisone and azathioprine is likely to have substantially influenced the results. Therefore, the use of immunosuppressants in patients with IPF is currently proscribed.

IFN-γ is an endogenous cytokine that has antifibrotic, immunomodulatory, and antiproliferative properties. Numerous animal model studies have suggested that IFN-γ has a therapeutic role in patients with fibrotic lung disease. A preliminary study published in 1999 suggested that IFN-γ provides some degree of clinical efficacy.[17] The aforementioned findings led to two multicenter, randomized, double-blind, placebo-controlled studies, the results of which were disappointing.[18,19] Those two studies were important because they showed that large, placebo-controlled clinical trials were feasible in patients with IPF, marking the beginning of a new era in IPF clinical research.

A precursor of glutathione, NAC is a major endogenous antioxidant present in the lungs. Oxidative stress in alveolar epithelial cells is considered to be one of the pathways involved in the pathogenesis of IPF, and glutathione levels appear to be decreased in patients with IPF. NAC replacement increases blood glutathione levels in such patients. In the Idiopathic Pulmonary Fibrosis International Group Exploring N-Acetylcysteine I Annual (IFIGENIA) trial, it was suggested that the addition of 1,800 mg of NAC to a therapeutic regimen of low-dose prednisone and azathioprine can slow the decline in pulmonary function in patients with IPF.[20] The methodological limitations of that study[20] led to a randomized clinical trial designated PANTHER-IPF, conducted by the Idiopathic Pulmonary Fibrosis Clinical Research Network, sponsored by the US National Heart, Lung, and Blood Institute, and comparing the effects of NAC alone with those of placebo in patients with IPF.[21] At 60 weeks, no statistically significant differences were found between the NAC group (in which there was a decline of 180 mL in FVC) and the placebo group (in which there was a decline of 190 mL in FVC).[21] In addition, mortality was similar between the two groups, as were AE rates. Therefore, there is currently no evidence to support the use of high-dose NAC in the routine treatment of patients with IPF.

Chart 5. A few randomized, double-blind, placebo-controlled clinical trials whose primary outcomes were not met.

Author	Medication
Idiopathic Pulmonary Fibrosis Clinical Research Network et al.[16]	NAC, prednisone, and azathioprine
Raghu et al.[18]	IFN-γ 1b
King Jr et al.[19]	IFN-γ 1b
Idiopathic Pulmonary Fibrosis Clinical Research Network et al.[55]	Sildenafil
Raghu et al.[66]	Etanercept
King TE Jr et al.[67]	Bosentan
Daniels et al.[68]	Imatinib
King Jr et al.[69]	Bosentan
Malouf et al.[70]	Everolimus
Noth et al.[71]	Warfarin
Raghu et al.[72]	Ambrisentan
Raghu et al.[73]	Macitentan
Shulgina et al.[74]	Co-trimoxazole
Idiopathic Pulmonary Fibrosis Clinical Research Network et al.[75]	NAC

NAC: N-acetylcysteine.

Albeit frustrating, the numerous clinical trials showing negative results were important because they provided a deeper understanding of the natural history of IPF and a better characterization of outcomes for future studies.

SPECIFIC TREATMENT OF LUNG DISEASE

Although several drugs have been investigated as potential treatments for IPF in randomized clinical trials, only two have been shown to be effective, namely pirfenidone and nintedanib.

For decades, the antifibrotic properties of pirfenidone have been investigated in various animal models.[22]

There is mounting evidence that pirfenidone inhibits collagen deposition and protects lung function in rodents treated with bleomycin administered intratracheally.

The mechanisms whereby pirfenidone acts seem to be pleomorphic but have yet to be fully elucidated. Experimental data indicate that the drug reduces procollagen, TGF-β, and PDGF gene expression and inhibits TNF-α production. In addition, pirfenidone appears to have antioxidant properties.[23]

The first clinical studies of pirfenidone involved small samples, were uncontrolled, or used outcomes of limited clinical utility.[24-26]

There were three major randomized, double-blind, placebo-controlled studies of pirfenidone.[27-29] In a multicenter study conducted by Taniguchi et al.,[27] 267 IPF patients were randomized to receive, over a 52-week period, placebo or pirfenidone at doses of 1,200 mg/day or 1,800 mg/day. At the end of the study, pirfenidone was found to have significantly reduced the rate of decline in FVC in comparison with placebo, regardless of the dose used (placebo: −0.16 L; low-dose pirfenidone: −0.08 L; and high-dose pirfenidone: −0.09 L). In addition, high-dose pirfenidone was associated with a significant increase in progression-free survival (time to loss of lung function or death) in comparison with placebo.

Under the auspices of a program designated Clinical Studies Assessing Pirfenidone in IPF: Research of Efficacy and Safety Outcomes (CAPACITY), two randomized, double-blind, placebo-controlled clinical trials were conducted simultaneously.[28] In study 004, patients were randomized to receive, over a 72-week period, placebo or pirfenidone at doses of 2,403 mg/day or 1,197 mg/day. At the end of the study, high-dose pirfenidone was found to have significantly reduced the rate of decline in FVC in comparison with placebo (−8.0% vs. −12.4%). The therapeutic effect of the drug was apparent from treatment week 24 onward. In addition, high-dose pirfenidone increased progression-free survival. In study 006, patients receiving pirfenidone at doses of 2,403 mg/day were compared with those receiving placebo. At the end of the study, no significant differences were found between the two groups of patients regarding the rate of decline in FVC, although the therapeutic effect of the drug on FVC was apparent from treatment week 12 to treatment week 48. A combined analysis of the two studies revealed that high-dose pirfenidone had a therapeutic effect on the rate of decline in FVC from treatment week 12 onward. At the end of the study, the rate of decline in FVC was significantly lower in the pirfenidone group than in the placebo group (−8.5% vs. −11.5%). In addition, progression-free survival was higher in the pirfenidone group.

The conflicting results of the two studies conducted under the auspices of the CAPACITY program regarding their primary outcome (i.e., the rate of decline in FVC) led to a clinical trial designated Assessment of Pirfenidone to Confirm Efficacy and Safety in Idiopathic Pulmonary Fibrosis (ASCEND).[29] In that study, 277 patients with IPF received placebo, whereas 278 were treated with pirfenidone at a dose of 2,403 mg/day for 52 weeks. Pirfenidone was associated with a lower rate of decline in FVC and higher progression-free survival. At the end of the study, mean decline in FVC was 428 mL in the placebo group and 235 mL in the pirfenidone group. A combined analysis of the results of the CAPACITY and ASCEND studies revealed that all-cause mortality and IPF mortality were significantly lower in the groups of patients receiving pirfenidone than in those of those receiving placebo.[28,29]

Pirfenidone capsules contain 267 mg of its salt, corresponding to 200 mg of the active ingredient. According to the manufacturer, pirfenidone should be taken orally at a dose of one 267-mg capsule every 8 h for 7 days. On day 8, the dose is increased to two 267-mg capsules (p.o.) every 8 h, and, from day 15 onward, patients should take three 267-mg capsules (p.o.) every 8 h. The medication should be taken with food in order to reduce the risk of nausea. Adjustments can be made if patients experience adverse effects, the most common of which are nausea, dyspeptic symptoms, rashes, photosensitivity, and liver enzyme abnormalities.[28,29]

Nintedanib was formerly known as BIBF 1120. An indolinone derivative, nintedanib was originally developed as an angiogenesis inhibitor to be used in the field of oncology.[30] The drug has been tested for the treatment of solid tumors of different lineages, and its clinical efficacy has been demonstrated, especially in the treatment of non-small cell lung cancer.[31]

In patients with IPF, the mechanisms whereby nintedanib acts involve inhibition of receptor tyrosine kinases.[32] The drug blocks the intracellular ATP-binding sites of specific tyrosine kinases. This results in inactivation of cellular receptors for mediators involved in the development of pulmonary fibrosis, particularly FGF and PDGF receptors. In addition, nintedanib inhibits the activity of VEGF receptors. As a result, fibroblast proliferation is inhibited and extracellular matrix deposition is reduced.

The first randomized clinical trial of nintedanib in patients with IPF was designated To imprOve pulMOnaRy fibROsis With BIBF1120 (TOMORROW) and lasted 12 months. In that study,[33] 432 patients were randomized to receive placebo or increasing doses of nintedanib, the maximum dose being 150 mg twice daily. The use of 150 mg of nintedanib twice daily resulted in a significant reduction in the number of AEs in comparison with placebo. At the end of the study, the rate of decline in FVC was lower in the nintedanib group than in the placebo group (−0.06 L vs. −0.19 L; p = 0.06).

Two phase III trials of nintedanib in patients with IPF were conducted simultaneously, being designated INPULSIS-1 and INPULSIS-2.[34] In both trials, the

drug was used at a dose of 150 mg twice daily. In INPULSIS-1, nintedanib led to a significant reduction in the annual rate of decline in FVC when compared with placebo (−114.7 mL vs. −239.9 mL). In INPULSIS-2, nintedanib also led to a significant reduction in the annual rate of decline in FVC when compared with placebo (−113.6 mL vs. −207.3 mL). In that study, nintedanib was associated with a significant increase in the time to the first AE.

According to the manufacturer, nintedanib should be taken orally at a dose of 150 mg twice daily. The dose can be temporarily reduced to 100 mg/day if adverse reactions occur. The drug should be taken with a full glass of water and food. The most common adverse effects of nintedanib are gastrointestinal adverse effects, particularly diarrhea and nausea. Diarrhea occurs in approximately 62% of patients using nintedanib, but it can be controlled with the use of loperamide.

Although pirfenidone had been approved for sale in Japan and Europe on the basis of previous studies, the US Food and Drug Administration approved it for use in the USA only after the results of the ASCEND trial. On the same date, nintedanib was also approved for use in the country. The approval of the two drugs by the US Food and Drug Administration was primarily based on their beneficial effect on the rate of decline in FVC.[35] Although FVC is a prognostic factor in IPF, the ideal would be to identify a positive effect of the new drugs on patient mortality. Unfortunately, long-term follow-up of a larger number of patients is required in order to characterize such an effect.

Long-term follow-up studies examining the aforementioned clinical trials have recently been published. Maintenance therapy with pirfenidone, even in patients showing a decline of at least 10% in FVC after 6 months of treatment, has been associated with a better outcome than has placebo. In addition, nintedanib use for up to 76 weeks and nintedanib use for 52 weeks have been shown to have the same efficacy and adverse effect profiles. Furthermore, it has been suggested that both drugs are effective in patients with early-stage IPF.

Because of the aforementioned data set, the 2015 ATS/ERS/JRS/ALAT guidelines for the treatment of IPF recommend the use of pirfenidone or nintedanib as treatment options for patients with the disease.[36]

It is of note that, at present, there is evidence that pirfenidone and nintedanib are effective in treating IPF, but there is no evidence that they are effective in treating other fibrosing interstitial lung diseases, such as CHP and collagen vascular disease-associated pulmonary impairment. In addition, the combined use of pirfenidone and nintedanib is not currently recommended, although an initial study has suggested that the combination is safe.[37] In this context, the decision to use pirfenidone or nintedanib should be made on a case-by-case basis, on the basis of commercial availability, comorbidities, treatment adherence, patient tolerance to adverse effects, and previous treatment failure.

The best timing for treatment initiation has yet to be determined. Most experts recommend that IPF treatment with either drug be initiated as soon as the diagnosis is established. This is due to the usually poor prognosis of IPF and the risk of AEs. Therefore, pharmacological treatment is warranted even in those few IPF patients with normal lung function. However, some experts disagree, arguing that it is difficult to establish an individual prognosis, and AEs are more common in the advanced phase of the disease. In this context, one possibility is to monitor lung function for some time and initiate pharmacological treatment as soon as lung function decline is detected. This is a controversial issue that has yet to be resolved, and clinicians and patients should make the decision together. Finally, because of the exclusion criteria used in the studies, the true efficacy of pirfenidone and nintedanib for patients with extremely advanced disease has yet to be determined.

SYMPTOMATIC TREATMENT

Cough

Cough is a very common symptom that can be difficult to control in patients with IPF, significantly contributing to impaired quality of life. Although it might be related to gastroesophageal reflux (GER), cough is in most cases secondary to IPF itself, being more common in patients with more advanced disease.[6]

Empirical treatment of GER can improve cough in some cases. Few options are available for the treatment of IPF-related cough when traditional antitussives, such as codeine, fail. Despite having no effect on disease progression, corticosteroids (prednisone, 20-30 mg/day) can provide relief of cough.[1,6] A randomized study showed that thalidomide (50-100 mg/day p.o.), a glutamic acid derivative, improves cough and quality of life in patients with IPF. However, thalidomide has yet to be approved for this use in Brazil.[38] It has been suggested that gabapentin (300-1,800 mg/day) is also useful for the treatment of cough.[39]

Dyspnea

Progressive dyspnea is quite common in patients with IPF, being associated with impaired quality of life and an increased risk of depression and death; in many cases, it is difficult to control.[40] In patients with IPF, dyspnea is due to disease progression and other factors, such as depression, anxiety, and muscle weakness. Although the available evidence is limited, morphine administered orally at low doses (of up to 20 mg/day) can be used in selected cases, the dose being adjusted on the basis of patient response and adverse effects, including somnolence and constipation.[6,41] For hypoxemic patients, oxygen supplementation at rest or during exercise can provide relief of dyspnea (Chart 6). Pulmonary rehabilitation can also contribute to reducing dyspnea.[42]

Depression and anxiety

Many IPF patients have symptoms of depression and anxiety, which should be routinely investigated in this population. The prevalence of depression in patients with IPF ranges from 25% to 50%, depression being associated with increased dyspnea and functional limitation.[42] Anxiety occurs in 30-40% of cases and is also associated with increased dyspnea.[42] In this context, despite the lack of robust evidence to support it, dyspnea management can improve anxiety and depression symptoms. Other strategies include psychological counseling and the use of anxiolytics and antidepressants.

RECOGNITION OF COMORBIDITIES

Certain comorbidities have been found to be common in patients with IPF. This is due, at least in part, to the fact that patients with IPF are at an advanced age and are usually former smokers. In this context, identification and treatment of comorbidities can contribute to improving quality of life and even survival.

GER

The existence of a relationship between IPF and microaspiration of gastric contents has been known for years and has been supported by biological and clinical data.[43] High levels of gastric substances, such as pepsin, have been found in the BAL fluid of patients with AE of IPF.[43] The presence of hiatal hernia on CT scans of the chest appears to be more common in patients with IPF than in those with other lung diseases, such as asthma and COPD. Acid GER as detected by pH monitoring was a common finding in two separate cohort studies. In one of the studies, 65 patients with IPF were compared with 133 patients with asthma, and acid GER was found to be significantly more common in the former, in whom the prevalence of acid GER was 87%.[44] In the other study, patients with IPF were compared with those with other interstitial lung diseases, and GER was found to be significantly more common in the former than in the latter (94% vs. 50%).[45] However, in the aforementioned studies,[44,45] only 47% and 25%, respectively, of the patients with IPF had classic GER symptoms. These data reinforce that GER symptoms should not be used as a screening tool.

To date, there have been no controlled clinical trials evaluating the effects of GER treatment on patients with IPF. In a case series of 4 IPF patients with GER treated with proton pump inhibitors (PPIs) or gastric fundoplication, stabilization of lung function was reported.[46] Similar results were reported in a study of IPF patients awaiting lung transplantation and undergoing fundoplication for the treatment of symptomatic GER.[47] An analysis of data from three randomized controlled trials revealed that, of the IPF patients who were assigned to the placebo groups of the trials, those who used PPIs or H_2 receptor antagonists for 30 weeks had a lower rate of decline in FVC and a lower frequency of AEs.[48] In a retrospective study of 204 patients followed at two medical centers in the USA, using GER medications and having undergone gastric fundoplication significantly increased survival.[49]

The use of PPIs, H_2 receptor antagonists, or a combination of the two appears to be beneficial for IPF patients, including those who are asymptomatic. However, well-designed controlled clinical trials are needed in order to confirm that. The same appears to be true for gastric fundoplication in selected cases. Therefore, the 2015 ATS/ERS/JRS/ALAT guidelines reaffirm the recommendation made in the 2011 ATS/ERS/JRS/ALAT guidelines, i.e., that patients with IPF should be routinely treated for GER.[36]

Lung cancer

The risk of lung cancer is higher in patients with IPF than in the general population. In a study of 890 patients diagnosed with IPF, the risk of lung cancer was reported to be 7.31 times higher in those patients than in the general population, regardless of smoking history.[50] The etiopathogenesis of the association between IPF and lung cancer has yet to be fully elucidated, and previously existing fibrotic abnormalities can hinder radiological detection. The coexistence of IPF and lung cancer interferes with the treatment of both entities, posing a risk of surgical complications, exacerbations, and pulmonary toxicity from drugs and radiation therapy.

Sleep disorders

Patients with IPF can have desaturation during sleep, regardless of the presence of obstructive sleep apnea (OSA). Sleep quality in IPF patients can be impaired by GER, nocturnal cough, use of medications, or even OSA.[51] Sleep quality is worse and OSA and nocturnal desaturation are more common in patients with IPF than in healthy individuals in the same age group.

In one study, a diagnosis of OSA was confirmed by polysomnography in 88% of patients with IPF, most of whom had moderate to severe disease.[52] In another study, nocturnal continuous positive airway pressure therapy was investigated in newly diagnosed IPF patients with moderate to severe OSA.[53] Patients were divided into two groups: the poor-adherence group and the high-adherence group. Although both groups showed improvements in quality of life and sleep quality, improvements were less marked in the poor-adherence group. In addition, during the study period, survival was higher in the high-adherence group. Therefore, OSA should be actively investigated, and treatment with continuous positive airway pressure should be prescribed when indicated.

Pulmonary hypertension

Pulmonary hypertension is a well-recognized complication in patients with IPF, particularly those in the advanced phases of the disease. In patients awaiting lung transplantation, the prevalence of pulmonary

hypertension is 46.1%.[54] In most cases, pulmonary hypertension is mild; however, in approximately 9% of cases, it can be severe (mean pulmonary artery pressure ≥ 35 mmHg or mean pulmonary artery pressure ≥ 25 mmHg and a cardiac index of < 2 L/min/m^2).

Severe pulmonary hypertension is associated with poor survival.[1,6] In two clinical trials in which medication was used in order to reduce pulmonary hypertension in patients with IPF, the primary outcomes were not met.[55,56] Nevertheless, in one of the studies, the use of sildenafil was associated with improved PaO_2, DLCO, dyspnea, and quality of life.[55] A post hoc analysis of the data from that study suggested that sildenafil is more likely to be effective in patients with echocardiographic evidence of right ventricular systolic dysfunction.[57] Although there is currently no strong evidence to support the routine use of medications to reduce pulmonary hypertension in patients with IPF, the issue has yet to be resolved.

Pulmonary emphysema

Smoking is a risk factor for IPF and pulmonary emphysema, and the prevalence of emphysema in patients with IPF ranges from 30% to 55%. Although combined pulmonary fibrosis and emphysema has previously been described, there is still debate as to whether it is a specific clinical entity that has a distinct genetic basis or a coincidence in smokers.[58] Most of the affected individuals are male and present with preserved lung volumes and markedly reduced DLCO. Prognosis is worse in patients with IPF and emphysema than in those with IPF alone. In the former, pulmonary hypertension is more severe and has a greater influence on survival than does reduced lung volumes.[12,59] Because of the paucity of data in the literature, the therapeutic approach to such patients remains unclear, being based on oxygen supplementation, smoking cessation, and general measures.

Cardiovascular diseases

Patients with IPF appear to be at an increased risk of cardiovascular disease.[1,6] In a study evaluating 920 patients with IPF, the risk of angina, deep vein thrombosis, and acute coronary syndrome was shown to be high in the period before the diagnosis of IPF.[60] After the diagnosis of IPF, the relative risks of deep vein thrombosis and acute coronary syndrome were found to be particularly high (3.39 and 3.14, respectively). Therefore, regular assessment of cardiovascular and thromboembolic events should be part of the management of IPF during the stable phase and during AEs.

NONPHARMACOLOGICAL TREATMENT

Education

It is essential that patients and their families remain informed of various aspects of the disease, including pathophysiology, symptoms, progression, and treatment (including palliative measures), in order to improve quality of life and prognosis. In addition, when relevant, questions regarding death should be addressed. In this context, for optimal management, patient preferences and beliefs should be valued and discussed by health care providers.

Vaccination

To date, there have been no studies evaluating the impact of vaccination on patients with IPF. However, IPF patients should receive influenza vaccination (annually) and pneumococcal vaccination.[6]

Oxygen supplementation

Hypoxemia is quite common in patients with IPF, and many IPF patients require supplemental oxygen during the course of the disease. All IPF patients should be periodically evaluated for hypoxemia at rest and during exercise.[1,6] Despite the lack of randomized studies evaluating the impact of oxygen supplementation on mortality in patients with IPF, oxygen supplementation should be used in the situations described in Chart 6.

The oxygen flow rate should be adjusted to maintain SpO_2 between 90% and 92%, resulting in improved exercise performance. The need for oxygen supplementation has been shown to be related to the prognosis of IPF patients, an increased required oxygen flow rate at rest translating to a decreased survival rate.[1,6] The need for supplemental oxygen during air travel should be evaluated.

Pulmonary rehabilitation

Exercise limitation of varying degrees is common in patients with IPF and has multiple causes, including changes in gas exchange, ventilatory limitation, pulmonary hypertension, and peripheral muscle dysfunction, which can act in isolation or in combination. A pulmonary rehabilitation program involves aerobic training, muscle strengthening exercises, educational lectures, nutritional counseling, and psychosocial support. Although there have been few robust studies evaluating the impact of pulmonary rehabilitation on IPF, pulmonary rehabilitation can improve dyspnea and quality of life, as well as increasing exercise duration and the six-minute walk distance in IPF patients.[61] A recent study demonstrated that the beneficial effects of pulmonary rehabilitation can be long-lasting, meaning that patients with IPF can undergo long-term pulmonary rehabilitation.[62] Therefore, IPF patients should undergo at least 12 weeks of pulmonary rehabilitation, unless there are any contraindications. Pulmonary rehabilitation is safe in such patients, the risk of adverse events being low.

In the absence of a formal pulmonary rehabilitation program, patients can walk for 20-30 min at least three times a week, supplemental oxygen being used when necessary.

Lung transplantation

Lung transplantation is a treatment option that increases survival in patients with IPF.[1,6] Among patients awaiting lung transplantation, mortality is highest in those with IPF because of rapid disease progression (in most patients), advanced age, and comorbidities. Therefore, IPF patients should be referred to a transplant center for evaluation in a timely manner, late referral being common in such patients. Ideally, patients should be referred for an initial evaluation at IPF diagnosis, regardless of the degree of dysfunction. The current indications and contraindications for lung transplantation in patients with IPF are shown in Chart 7.[6,63]

In IPF patients undergoing lung transplantation, 5-year survival is approximately 50% (median survival, 4.5 years), being worse than that in other patients undergoing lung transplantation.

Although lung transplantation improves the prognosis of patients with IPF, only a few procedures are performed in Brazil, meaning that the demand is not being met. This is due to the fact that there are only a few transplantation referral centers in the country and the fact that the number of available donor lungs is quite small.

ACUTE EXACERBATIONS

An AE of IPF is defined as an acute worsening of patient clinical status, lasting less than 30 days and being characterized by increased dyspnea and an increased need for oxygen supplementation, as well as by new chest HRCT findings (ground-glass opacities or bilateral pulmonary consolidation) superimposed on a background pattern consistent with UIP.[1,6,64] Clinical conditions such as heart failure, pulmonary thromboembolism, pneumothorax, and infection should be ruled out. In order to be characterized as AEs of IPF, these acute deteriorations should be of unidentifiable cause. AEs of IPF are associated with increased mortality and have been reported in up to 85% of cases.[1,6,64]

The incidence of AEs of IPF remains mostly unknown because there is no consensus regarding the definition of AE and because most studies evaluating AEs of IPF are retrospective in nature. The time to IPF diagnosis is possibly associated with an increased risk of AEs. The proportion of patients with AEs in the first year after IPF diagnosis has been reported to be lower than that of those with AEs in the third year after IPF diagnosis.

Risk factors for AEs of IPF are as follows: having an FVC of < 72% of predicted; having a DLCO of < 62%; never having smoked; and having pulmonary arterial hypertension.[60] The risk of 3-month mortality from an AE of IPF is higher in patients with more extensive disease on HRCT scans than in those with less extensive disease. In a systematic review, the risk of death from an AE of IPF was shown to be 60% at 1 month and 67% at 3 months. After an AE of IPF, mean survival is 2.2 months.

The etiology of AEs of IPF is unknown. They might be triggered by a sudden acceleration of the underlying

Chart 6. Indications for oxygen therapy in patients with idiopathic pulmonary fibrosis.

• PaO_2 ≤ 55 mmHg, resting SpO_2 ≤ 88%, or a combination of the two
• PaO_2 = 56-59 mmHg, resting SpO_2 = 89%, or a combination of the two if there is evidence of pulmonary hypertension, hematocrit > 55%, or a combination of the two
• During exertion or during sleep, in the presence of an SpO_2 ≤ 88%

Chart 7. Indications and contraindications for lung transplantation in patients with idiopathic pulmonary fibrosis.

Indications
• Being under 65 years of age
• DLCO below 40% of predicted
• Decline of at least 10% in FVC, decline of at least 15% in DLCO, decline of at least 50 m in the 6MWD, or any combination of the three after 6 months
• Decline in SpO_2 (to less than 88%), a 6MWD of less than 250 m, or a combination of the two
• Development of secondary pulmonary hypertension
Relative contraindications
• Being over 65 years of age
• Grade I obesity (BMI = 30-35 kg/m^2)
• Malnutrition (BMI of < 20 kg/m^2)
• Severe symptomatic osteoporosis
• Mechanical ventilation
• Colonization or infection with resistant microorganisms
• Infection with *Burkholderia cepacia*
• Comorbidities such as systemic arterial hypertension and diabetes mellitus (lung transplantation can be performed if they are controlled)
Absolute contraindications
• Neoplasms in the last 5 years
• Major organ dysfunction (kidney, liver, heart, or brain dysfunction)
• Uncorrectable coronary artery disease
• Active tuberculosis
• HIV infection
• Untreatable chronic pulmonary infection
• Severe spinal or chest wall deformity
• BMI ≥ 35 kg/m^2
• History of treatment noncompliance
• Uncontrolled psychiatric disorder
• Lack of social support
• Poor functional status with no potential for rehabilitation
• Substance abuse, including alcohol, tobacco, and drug abuse

6MWD: six-minute walk distance.

Chart 8. Contemporary treatment of idiopathic pulmonary fibrosis.

Lung disease treatment	Nintedanib (150 mg p.o. every 12 h) or pirfenidone (801 mg p.o. every 8 h)
Gastroesophageal reflux treatment	Patients should receive gastroesophageal reflux treatment even in the absence of digestive symptoms. Gastroesophageal reflux treatment includes proton pump inhibitors, H_2 receptor antagonists, and, in selected cases, gastric fundoplication.
Cough treatment	Traditional antitussives (including levodropropizine and codeine); thalidomide (50-100 mg/day p.o.); gabapentin (300-1,800 mg/day p.o.); corticosteroids (prednisone, 20-30 mg/day)
General measures	Education regarding the disease; smoking cessation; pulmonary rehabilitation; oxygen therapy (when indicated); and influenza and pneumococcal vaccination
Management of comorbidities	Anxiety and depression; lung cancer; obstructive sleep apnea; pulmonary hypertension; and cardiovascular disease
Palliative treatment for dyspnea	In advanced cases, morphine (p.o.)
Lung transplantation	In selected cases

fibrotic disease, infection of unknown etiology, viral infection, thoracic and extrathoracic surgical procedures, bronchoscopy, or microaspiration of gastroesophageal refluxate.

The most common HRCT finding is that of new ground-glass opacities superimposed on a preexisting reticular or honeycomb pattern. The pattern of distribution of opacities appears to be associated with prognosis, small, peripheral opacities being associated with better outcomes and diffuse, multifocal opacities being associated with worse outcomes. Histology shows diffuse alveolar damage superimposed on a pattern consistent with UIP. A pattern of cryptogenic organizing pneumonia and nonspecific acute lung injury without hyaline membrane formation has also been described.

The treatment of AEs of IPF has yet to be established. To date, there have been no randomized, double-blind, placebo-controlled studies on the topic. Guidelines established by respiratory/thoracic societies recommend the use of corticosteroids and intensive clinical care. This is a weak recommendation based on low-quality evidence, with no specific dose, duration of treatment, or route of administration.[1,6,64]

Other therapeutic approaches have been studied, including direct hemoperfusion with a polymyxin B-immobilized fiber column, rituximab, thrombomodulin, and control of GER.[65]

Despite the lack of clear clinical evidence, the use of corticosteroids is based on the type of lung injury that occurs during an AE. The most common option is methylprednisolone pulse therapy at a dose of 1.0 g for 3 consecutive days. However, clinical experience suggests that, in some situations, lower doses are equally effective. When bronchoscopy cannot be performed or when infection cannot be completely ruled out, most clinicians tend to administer broad-spectrum antibiotic therapy before or simultaneously with corticosteroids.

FUTURE DIRECTIONS

There have been substantial advances in the field of IPF in recent decades. For the first time, there is a developing body of knowledge regarding IPF and there are molecules that can positively influence the natural history of the disease (Chart 8). In addition, several pharmaceutical companies are currently working on new treatment options for patients with IPF, which until recently was considered an orphan disease. Furthermore, several phase II and III studies involving new molecules, including immunobiological agents, are in progress, and this is good news.

It can therefore be assumed that, in the coming decades, survival will increase significantly in patients with IPF, meaning that the number of IPF patients being followed at specialized medical centers will also increase.

Despite the aforementioned advances, a substantial number of challenges remain to be met: (i) increasing patient and physician knowledge of IPF; (ii) developing diagnostic methods for early-stage IPF; (iii) gaining a better understanding of the genetic basis of IPF and of how it interacts with environmental agents; (iv) determining the worldwide incidence, prevalence, and distribution of IPF; (v) expediting the approval process for drugs whose efficacy has been confirmed; and (vi) ensuring universal access to pharmacological and nonpharmacological treatments for IPF.

The fight against IPF can only be won through the combined efforts of basic scientists, clinical researchers, physicians, pharmaceutical companies, associations representing patients and families, and, in many countries, the government.

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REVIEW ARTICLE

Inhalation therapy in mechanical ventilation

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Study carried out at the Unidade de Terapia Intensiva Adulto of the Hospital Moinhos de Vento; and under the auspices of the Programa de Pós-Graduação em Ciências Pneumológicas, Universidade Federal do Rio Grande do Sul, Porto Alegre (RS) Brasil.

ABSTRACT

Patients with obstructive lung disease often require ventilatory support via invasive or noninvasive mechanical ventilation, depending on the severity of the exacerbation. The use of inhaled bronchodilators can significantly reduce airway resistance, contributing to the improvement of respiratory mechanics and patient-ventilator synchrony. Although various studies have been published on this topic, little is known about the effectiveness of the bronchodilators routinely prescribed for patients on mechanical ventilation or about the deposition of those drugs throughout the lungs. The inhaled bronchodilators most commonly used in ICUs are beta adrenergic agonists and anticholinergics. Various factors might influence the effect of bronchodilators, including ventilation mode, position of the spacer in the circuit, tube size, formulation, drug dose, severity of the disease, and patient-ventilator synchrony. Knowledge of the pharmacological properties of bronchodilators and the appropriate techniques for their administration is fundamental to optimizing the treatment of these patients.

Keywords: Bronchial hyperreactivity; Drug delivery systems; Respiration, artificial.

INTRODUCTION

Patients with obstructive lung disease, such as COPD and bronchial asthma, often require ventilatory support via invasive mechanical ventilation (MV) or noninvasive MV (NIMV), depending on the severity of the exacerbation. Many such patients have increased airway resistance and, consequently, airway obstruction, which results in increased positive end-expiratory pressure (PEEP) and, consequently, auto-PEEP (also known as dynamic hyperinflation). Auto-PEEP results in increased respiratory effort, contributing to muscle fatigue in such patients.[1] Therefore, the use of positive pressure MV can improve respiratory function, improving the outcomes of decompensated patients.[2] The use of inhaled bronchodilators can significantly reduce airway resistance, contributing to the improvement of respiratory mechanics and patient-ventilator synchrony.

The major advantages of using inhalation therapy in such patients are selective treatment of the lungs and high drug concentrations in the airways. In addition, inhaled drugs have a more rapid onset of action and fewer systemic adverse effects than do drugs administered by other routes. However, correct inhaler technique and regular medication use are needed in order to improve drug efficacy, given that inhaled drugs have shorter half-lives.

In a recently published study, physician practices regarding the prescription of inhaled drugs were analyzed in 70 countries.[2] Of the 854 intensivists whose responses were analyzed, 99% reported prescribing aerosol therapy to patients on MV, including those on NIMV, and 43% exclusively used nebulizers. During nebulization, ventilator settings were never changed by 77% of the respondents; in addition, 87% stated that ultrasonic nebulizers were superior to jet nebulizers. The aforementioned study provides evidence of the heterogeneity in prescribing inhaled drugs, showing that current scientific knowledge is poorly applied.

Although various studies have been published on this topic, little is known about the efficacy of the bronchodilators routinely prescribed for patients on MV or about the deposition of those drugs throughout the lungs. The use of inhaled drugs in patients requiring NIMV poses an even greater challenge.

INHALATION THERAPY DURING MV

The use of inhaled drugs has the advantage of allowing selective treatment of the lungs by delivering high drug concentrations to the airways, having a rapid onset of action and few systemic adverse effects. It is believed that the beneficial effects of inhaled drugs are smaller in patients on MV than in those breathing spontaneously. In an early study, only 2.9% of the administered dose reached the distal airway (vs. 11.9% when the dose was administered without an artificial airway)[3]; this might be due to a substantial drug loss caused by the turbulent flow produced by the respiratory prosthesis. However, precautions observed at the time of drug

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administration can improve lung drug deposition,[4] as shown in Chart 1.

With regard to aerosol delivery devices, it was initially believed that lung drug deposition was better with the use of metered dose inhalers (MDIs) than with the use of conventional nebulizers.[5] However, when the two types of devices are used correctly, the results are similar.[6,7] In general, MDIs are more economical and pose a lower risk of nosocomial pneumonia.[4,7] Clinical studies have shown that nebulizers and MDIs have similar effects on lung function, both types of devices resulting in equivalent changes in FEV_1.[6]

Bronchodilators, corticosteroids, antibiotics, prostaglandins, nitric oxide, anticoagulants, and heliox can be administered via inhalation. However, inhalation is most commonly used for bronchodilator administration, improving ventilatory parameters and patient-ventilator synchrony in cases of airway constriction.[8] Bronchodilators relax airway smooth muscles, reversing airway obstruction and preventing bronchoconstriction.[6] Ventilator-dependent patients, COPD patients, and asthma patients routinely receive treatment with inhaled bronchodilators.

PHARMACOLOGICAL AGENTS

The inhaled bronchodilators that are most commonly used in the ICU are beta adrenergic agonists and anticholinergics.[8] Beta adrenergic agonists can also be administered intravenously, subcutaneously, or orally; however, inhalation is the preferred route of administration because of direct lung delivery, need for a lower dose, rapid onset of action, and reduced systemic absorption, thus reducing adverse effects.[6,8,9] One study evaluated the emergency room treatment of patients with asthma and showed that there is no evidence to support the use of intravenous β_2 agonists, even in patients refractory to inhaled β_2 agonists.[10] Chart 2 shows the inhaled bronchodilators that are most commonly used in the ICU, including doses and pharmacological characteristics such as onset of action, time to peak effect, and duration of action.

CLINICAL USE OF BRONCHODILATORS

In patients with COPD, long-acting β_2 agonists and inhaled corticosteroids are used in order to relieve symptoms, improve quality of life, improve lung function, and prevent decompensation.[8] In patients with exacerbation of COPD or severe asthma, emergency bronchodilator treatment is required. The drug of choice is a short-acting β_2 agonist (e.g., albuterol), because short-acting β_2 agonists have a more rapid onset of action and a greater bronchodilator effect and because they can be repeated at short intervals during bronchospasm attacks.[6] The need for high doses in critically ill patients has led to studies of continuous nebulization in selected patients. However, the results are conflicting, showing no evidence that this strategy is beneficial.[6,11]

In general, the severity of asthma or COPD exacerbation can be best evaluated by the severity of the attack and the bronchodilator response than by previous lung function.

FACTORS THAT INFLUENCE INHALED DRUG DELIVERY DURING MV

In patients on MV, bronchodilators can be delivered by jet nebulizers, ultrasonic nebulizers, or MDIs. In the case of jet nebulizers, compressed gas generates aerosol particles that are delivered with tidal volume. This necessarily increases the tidal volume delivered in each inspiratory cycle. Ultrasonic nebulizers are available for certain ventilators. They deliver medicine by using high-frequency vibrations to convert the liquid into an aerosol and do not increase patient tidal volume during inhalation.

To date, no clinical differences have been found between jet and ultrasonic nebulizers.[6] The disadvantages of conventional nebulizers include the need for an external flow source independent of the ventilator, the need to install the equipment, and the need for thorough cleaning. Ultrasonic nebulizers can provide a higher nebulization rate in a shorter period of time; however, their availability is limited by high cost.[6]

Studies investigating clinical differences between nebulizers and MDIs have yielded inconsistent results. The efficacy of MDI-delivered drugs depends particularly on the position of the tube in the ventilator circuit. In the case of MDI-delivered bronchodilators, a spacer is essential and can increase aerosol deposition in the airways by four to six times.[12-14] A variety of spacers are available. It is currently believed that an MDI with a spacer is as effective as a nebulizer, being more practical and quicker to administer and requiring no disconnection from the ventilator circuit after each dose.

Many other factors influence aerosol deposition in the lower airways, as shown in Chart 3. Such factors include drug-related properties (including physical and chemical properties), the characteristics of the aerosol generator, the position of the aerosol generator in the ventilator circuit, ventilator settings, ventilation modes, heating and humidification of the inhaled air, the characteristics of the endotracheal tube, the anatomy of the airways, and the presence of respiratory secretions.[15-17]

Even in ventilator-dependent patients, bronchodilators should preferentially be administered with the head of the bed elevated, given that the sitting position improves drug delivery.[16] Heating and humidification of the inhaled air are required during ventilatory support in order to reduce the risk of ventilator-associated pneumonia. However, they increase particle impaction in the ventilator circuit, reducing aerosol deposition in the more distal airways by as much as 40%.[12,13]

The aerosol generator should be placed at a distance of 20-30 cm from the endotracheal tube, between the tube and the Y-piece of the ventilator circuit,[16,18,19] as shown in Figure 1. This is due to the fact that the

Chart 1. Strategies to improve lung drug deposition during mechanical ventilation.

Ventilator-related strategies
Deliver a tidal volume > 500 mL[a]
Maintain an inspiratory flow of 30-50 L/min
Avoid delays between actuation and inhalation
Circuit-related strategies
Remove the filter or deliver the drug at a location more proximal to the filter
Turn the humidifier off 10 min before aerosol delivery
Install the aerosol generator 15 cm proximal to the Y-piece
Device-related strategies
Metered dose inhaler
Heat it and shake it before actuation
Use an appropriate connector
Use a spacer
Coordinate actuation with inhalation
Nebulizer
Use an intermittent-flow nebulizer system only if the gas source is > 15 psi
If an external flow source is used, use a flow rate of 6-8 L/min
Complete the volume by adding 2.5 mL of saline solution

psi: pound-force per square inch. [a]In patients with obstructive lung disease, a tidal volume > 500 mL can result in auto-PEEP (dynamic hyperinflation). In such cases, respiratory mechanics should be monitored, tidal volume being controlled in order to avoid barotrauma.

Chart 2. Doses and duration of action of the inhaled bronchodilators most commonly administered to patients on mechanical ventilation.

Drug	Formulation	Dose	Onset of action, min	Time to peak effect, min	Frequency of use, number of times/day
		β_2 agonist			
Fenoterol hydrobromide	Solution: 5 mg/mL	5-8 drops	5-10	15	3-6
	Aerosol: 100 µg/jet	1 jet every 5 min			
Albuterol	Aerosol: 100 µg/jet	2 jets	5-15	30-60	4-6
		Anticholinergic agent			
Ipratropium bromide	Solution: 0.25 mg/mL	20-40 drops	15	90-120	4-6
	Aerosol: 20 µg/jet	4 jets			

inspiratory limb of the ventilator circuit acts as an aerosol reservoir during exhalation.[19] Synchronization of actuation with the beginning of inhalation increases lung drug deposition by as much as 30% when compared with failure to synchronize actuations with inhalation. A delay of 1-1.5 s between actuation and inhalation can reduce the efficacy of drug delivery.[13]

Ventilator settings also play an important role in inhaled drug delivery. A tidal volume of at least 500 mL,[20] increased inspiratory time, and low inspiratory flow (30-50 L/min) are recommended in order to optimize lung drug deposition.[16,18,20] Attention should be paid to the adverse effects of high (> 500 mL) tidal volume in patients with obstructive lung disease, given that it can worsen dynamic hyperinflation or cause barotrauma. According to the authors of an in vitro study, drug delivery by nebulizers can vary depending on the ventilation mode (i.e., pressure-controlled ventilation or volume-controlled ventilation).[21] However, there have been no clinical studies showing the beneficial effects of any particular ventilation mode on inhaled drug delivery.[6]

High and turbulent flows can increase particle impaction, increasing particle deposition in the proximal airways.[17] The density of the inhaled gas also influences drug delivery. Inhalation of a less dense gas, such as a 70/30 mixture of helium and oxygen, makes airflow less turbulent and more laminar, facilitating inhaled drug delivery.[22,23]

BRONCHODILATOR RESPONSE DURING MV

Given that it is impossible to assess FEV_1 and FVC in patients on MV, treatment response is evaluated on the basis of respiratory mechanics parameters. Treatment is aimed at reducing inspiratory airway resistance. Reduced inspiratory airway resistance can be confirmed by a reduction in peak pressure or in the difference between peak and plateau pressures during an inspiratory pause. A reduction of more than 10% in the variation in resistance indicates a significant bronchodilator response.[6] It is important to analyze pre- and post-bronchodilator flow curves, which can

Chart 3. Factors influencing aerosol deposition in the airways during mechanical ventilation.

Factors	Parameters	Influence on aerosol deposition
Ventilator-related	Ventilation mode Tidal volume Respiratory rate Inspiratory/expiratory time ratio Inspiratory flow Inspiratory trigger	In vitro studies have shown that aerosol deposition varies depending on the ventilation mode. A longer inspiratory time translates to better drug delivery.
Circuit-related	Endotracheal tube size Inhaled gas humidity Inhaled gas density	A larger tube translates to a more turbulent flow and worse drug delivery.
Nebulizer-related	Nebulizer type Inhaled volume Gas flow Nebulization cycling: inspiratory vs. continuous Duration of nebulization Position in the ventilator circuit	High, turbulent flows increase drug deposition in the proximal airways, thus reducing drug efficacy.
Metered dose inhaler-related	Type of spacer and connector Position of the spacer Coordination of actuation with inhalation Type of metered dose inhaler	Failure to coordinate actuation with inhalation results in lower lung drug deposition.
Drug-related	Dose Formulation Aerosol particle size Duration of action	During mechanical ventilation, higher doses of inhaled bronchodilators are required.
Patient-related	Severity of airway obstruction Mechanism of airway obstruction Dynamic hyperinflation Patient-ventilator synchrony	Severe airway obstruction and auto-PEEP reduce deposition of bronchodilators in the more distal airways, thus reducing drug efficacy.

Adapted from Dhand.[15]

show a reduction in intrinsic PEEP, i.e., a reduction in auto-PEEP.[6]

BRONCHODILATOR THERAPY DURING NIMV

Given the scientific evidence for the use of NIMV in patients with COPD or asthma, it is necessary to study bronchodilator administration during NIMV. Currently, in daily practice, for bronchodilator administration in patients on NIMV, the mask is removed and the drug is delivered as usual (i.e., by a nebulizer or MDI), or the device is connected to the mask or the ventilator circuit. There is currently no commercially available system designed specifically for inhalation therapy during NIMV.[24]

As is the case with invasive MV, the effect of the inhaled drug during NIMV depends on the pharmacological properties of the drug and on lung drug deposition. For better drug delivery, aerosol particles must be small enough to penetrate through the upper airways but large enough to avoid being eliminated by the expiratory flow. Devices that produce aerosols with mass of less than 2 μm are more efficient for pulmonary deposition during NIMV.[17]

In NIMV-dependent patients, an MDI with a spacer was found to be four to six times more efficient for bronchodilator administration than an MDI without a spacer.[17] Nava et al.[25] evaluated MDI-delivered albuterol in clinically stable COPD patients who were on NIMV and in those who were not. The authors found a significant increase in FEV_1 after albuterol administration, regardless of the method used.[25]

Aerosol deposition in the mask and nasal cavity significantly reduces lung drug deposition,[17,26-28] possibly reducing drug efficacy. However, a mask is required for ventilatory support in some patients with bronchospasm, in whom it can avoid intubation.[29-32] For increased efficacy, the mask must be well secured. Leaks can significantly reduce drug delivery.[33]

Ventilators specifically designed for NIMV have a single-limb circuit, and exhalation valve position can influence the efficiency of aerosol delivery; this does not occur when an MDI is used.[17] Branconnier & Hess[34] used an experimental model in which the leak port was incorporated either into the circuit or into the mask in order to determine whether albuterol delivered during NIMV was affected by the use of a nebulizer or an MDI. The authors found that, with the nebulizer, significantly more albuterol was delivered when the leak port was in the circuit than when it was in the mask.[34] Calvert et al.[35] reported that albuterol delivery was more efficient when the nebulizer was placed between

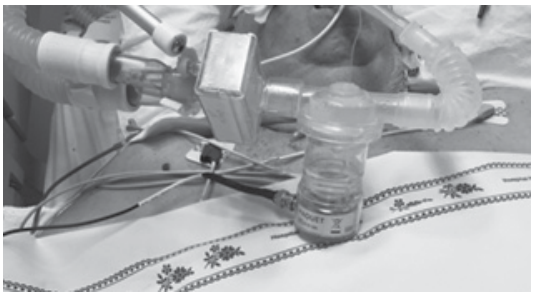

Figure 1. The aerosol generator should be placed at a distance of 20-30 cm from the endotracheal tube, between the tube and the Y-piece of the ventilator circuit.

the exhalation port and the ventilator for NIMV than when the nebulizer was placed between the exhalation port and the mask. In contrast, Abdelrahim et al.[36] observed higher aerosol deposition when the nebulizer was placed between the exhalation port and the mask. The divergent results show that this is a controversial issue and indicate the need for further studies.

The position of the nebulizer in relation to the mask also plays an important role in aerosol deposition, front-loaded nebulizers being more efficient than bottom-loaded nebulizers in delivering drug to the patient.[37] An in vitro study investigating the effect of ventilator settings and nebulizer position on albuterol delivery during NIMV showed that albuterol delivery varied significantly depending on nebulizer position in the ventilator circuit, inspiratory/expiratory pressure levels, and respiratory rate. Albuterol delivery was greatest (with as much as 25% of the nominal dose being delivered) when the nebulizer was placed between the mask and the circuit, when inspiratory pressure was highest (20 cmH_2O), and when expiratory pressure was lowest (5 cmH_2O).[38]

The extent of lung disease and the ability of patients to tolerate the mask also play a decisive role in the success of treatment with NIMV and inhalation therapy. Patient-ventilator synchrony improves lung drug deposition. A delay of 1-1.5 s between device actuation and the beginning of inhalation can significantly reduce the efficiency of drug delivery.[13,17]

FINAL CONSIDERATIONS

Many patients with COPD require ventilatory support via invasive MV or NIMV. Inhaled drug delivery is complex in this context. Multiple factors influence the efficacy of inhaled bronchodilators administered during MV. For improved drug efficacy, the appropriate dose and formulation should be prescribed. Measures that can improve the efficacy of bronchodilators include the use of a spacer, patient-ventilator synchrony, an appropriate interval between doses, and adjustment of the ventilator settings during administration.

Despite the recommendations for inhaled drug delivery, few such interventions are implemented in daily clinical practice. Knowledge of the factors influencing lung drug deposition is fundamental to optimizing the treatment of these patients.

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Acute invasive pulmonary aspergillosis, shortly after occupational exposure to polluted muddy water, in a previously healthy subject

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ABSTRACT

Invasive pulmonary aspergillosis (IPA) predominantly occurs in severely neutropenic immunocompromised subjects. The occurrence of acute IPA after brief but massive exposure to *Aspergillus* conidia in previously healthy subjects has been documented, although only six such cases have been reported. The diagnosis was delayed in all six of the affected patients, five of whom died. We report the case of a 50-year-old HIV-negative male, a water pipeline maintenance worker, who presented with acute-onset dyspnea and fever one day after working for 2 h in a deep pit containing polluted, muddy water. Over a one-month period, his general condition deteriorated markedly, despite antibiotic therapy. Imaging showed bilateral diffuse nodules with cavitation, some of which were surrounded by ground-glass opacity suggestive of a halo sign (a hallmark of IPA). Cultures (of sputum/bronchial aspirate samples) and serology were positive for *Aspergillus fumigatus*. After being started on itraconazole, the patient improved. We conclude that massive exposure to *Aspergillus* conidia can lead to acute IPA in immunocompetent subjects.

Keywords: Environmental exposure; Azoles; Water pollution; Immunocompetence; Invasive pulmonary aspergillosis.

INTRODUCTION

Fungi of the genus *Aspergillus* can cause a wide variety of respiratory disorders, depending on the immune status of the patient. Such disorders can range from simple allergic reactions and saprophytic colonization to invasive destruction of lung tissue with systemic dissemination, designated invasive pulmonary aspergillosis (IPA), which can be fatal. Typically, IPA occurs in immunocompromised patients, with or without neutropenia. It is now also being seen in critically ill patients, without apparent immunosuppression, in intensive care units. Other predisposing risk factors include chemotherapy (in patients with acute hematological malignancy), alcoholism, diabetes mellitus, immunosuppression therapy (in recipients of organ transplants), and high doses of systemic corticosteroids.[1,2]

There have been few reports of acute IPA caused by brief but massive exposure to *Aspergillus* sp. A search of the literature revealed four reports of six cases occurring in immunocompetent subjects.[3-6] There have also been a few reports of acute IPA in immunocompetent subjects after near-drowning in contaminated water.[7] The rarity of such scenarios prompted us to report the case of a previously healthy 50-year-old male who developed acute IPA after working for 2 h in a pit containing polluted muddy water.

CASE REPORT

A 50-year-old, HIV-negative male former smoker who was a water pipeline maintenance worker with the water supply organization of the state of Delhi, India, was referred to our institute for evaluation of dyspnea and fever that had developed acutely and had peaked over a period of three days. He presented to us one month later, and his clinical course was characterized by progressive exertional dyspnea, together with cough and scant mucoid sputum, accompanied by low grade, intermittent fever with chills and rigors. There was no wheezing, chest pain, palpitations, or hemoptysis.

When questioned, the patient reported having been exposed to polluted muddy water for 2 h while working in a deep pit, to repair a water pipeline, one day prior to the onset of the symptoms. However, the patient emphatically denied having aspirated any of the water. The patient was completely healthy prior to this event and had no history of using corticosteroids or any other medication. He had a 10 pack-year smoking history: before quitting smoking 10 years prior, he had smoked 10 cigarettes per day for 20 years. The type of cigarette he smoked is known as a bidi (or beedi), which is manufactured in India and consists of finely ground, sun-dried tobacco rolled in a brown leaf of one of two broadleaf plants native to India—*Diospyros melanoxylon* or *Diospyros ebenum*.[8]

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Physical examination revealed that the patient was a middle-aged man in respiratory distress. There was no pallor, digital clubbing, or cyanosis. He was tachypneic, with a respiratory rate of 25 breaths/min, and febrile. Diaphragmatic excursion, though rapid, was comparable on both sides. Breath sounds of equal intensity were audible bilaterally, together with coarse bibasilar crackles.

While breathing room air, the patient had an SpO_2 of 90%, with a pH of 7.37, $PaCO_2$ of 41.2 mmHg, and a PaO_2 of 46 mmHg. The total leukocyte count was 28.6 $\times$ 10^3 cells/μL, neutrophils accounting for 86%. The results of an electrocardiogram, urinalysis, and blood glucose testing, as well as of tests of renal and hepatic function, were all within normal limits. A chest X-ray obtained after the onset of symptoms showed bilateral multifocal consolidations with cavitation in some of the lesions (Figure 1A). A contrast-enhanced HRCT scan of the chest obtained one week after the onset of symptoms revealed multiple areas of consolidation as well as nodular lesions of varying sizes with ill-defined margins. Some of those lesions showed cavitation, whereas others were surrounded by ground-glass opacity, suggestive of a halo sign (Figure 1B). An abdominal ultrasound revealed hepatomegaly with grade II fatty infiltration. Sputum smear microscopy and cultures revealed no growth of *Mycobacterium tuberculosis* or other aerobic organisms. However, sputum cultures showed pure growth of *Aspergillus fumigatus*.

Spirometry showed that the patient had an FVC of 3.01 L (82% of predicted), an FEV_1 of 1.88 L (62% of predicted), and an FEV_1/FVC ratio of 0.62. These results are indicative of moderate obstructive lung disease with no bronchodilator response. Fiberoptic bronchoscopy revealed hyperemic mucosa with whitish patches and foci of mucosal bleeding in the right upper lobe. Cultures of post-bronchoscopy sputum and bronchial aspirate showed heavy growth of *A. fumigatus*. On skin prick testing, the patient also showed immediate reactivity to *A. fumigatus* and *A. niger*. Total serum IgE was 114 kilo units of allergen per liter (kUA/L; reference: < 64 kUA/L), and a fluorescence enzyme immunoassay (ImmunoCAP 100*E*; Phadia, Uppsala, Sweden) identified specific IgE and IgG antibodies against *A. fumigatus*. Multiple endobronchial and transbronchial biopsies from both lungs demonstrated chronic nonspecific inflammation. The bronchial aspirate did not yield *M. tuberculosis* or any other aerobic organism.

The patient was diagnosed with acute IPA. The diagnosis was substantiated by the heavy growth of *A. fumigatus* seen in the post-bronchoscopy sputum cultures, as well as in those of the bronchial aspirate. The patient was started on itraconazole (200 mg twice daily for two months), together with treatment for obstructive lung disease in the form of an inhaled long-acting β_2 agonist and an inhaled muscarinic antagonist. The patient showed remarkable clinical improvement, and chest imaging showed marked resolution of the lesions, with residual fibrosis (Figures 2A and 2B). At this writing, the patient is on regular therapy for obstructive lung disease, the severity of which has been reduced considerably, and is largely asymptomatic.

DISCUSSION

Seen predominantly in immunocompromised subjects, IPA is a life-threatening form of pneumonia caused by *Aspergillus* spp., most commonly *A. fumigatus*. It is increasingly being seen in critically ill patients admitted to intensive care units and in recipients of organ transplants.[1,2]

The occurrence of acute IPA in a previously healthy subject is rather uncommon, and IPA due to massive but brief environmental exposure to *Aspergillus* sp. is quite rare; in the literature, we identified four reports describing a collective total of six cases.[3-6]

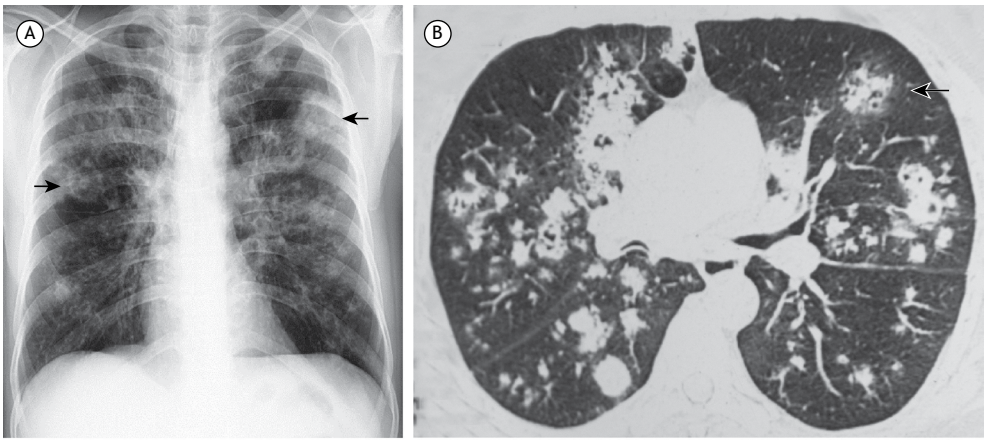

Figure 1. A) Chest X-ray, obtained after the onset of symptoms, showing bilateral multifocal consolidations with cavitation in some of the lesions (arrows); B) HRCT scan of the chest, obtained one week after the onset of symptoms, showed multiple areas of consolidation as well as nodular lesions of varying sizes, some showing cavitation and others surrounded by ground-glass opacity consistent with a halo sign (arrow).

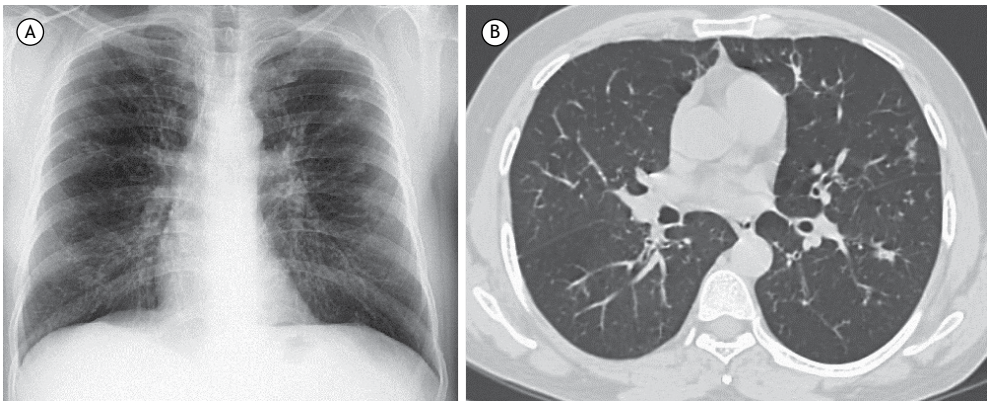

Figure 2. Chest X-ray (A) and HRCT scan of the chest (B), both obtained after two months of treatment, showing marked resolution of the lesions, with residual fibrosis.

The clinical descriptions of those six patients and of our patient are summarized in Table 1.[3-6] All six patients had a history of exposure to damp material likely to harbor *Aspergillus* sp., potentially resulting in massive inhalation of conidia. There was a considerable diagnostic delay in all six cases. Of the six patients, five died,[3-6] and the diagnosis was established only at autopsy in four.[3,5,6] Cultures of sputum or bronchial aspirate were positive for *A. fumigatus* in three of the six patients.[4-6] In our patient, *A. fumigatus* was also cultured from sputum collected at admission. Chest X-rays showed patchy/homogeneous infiltrate in five patients,[3-6] with right upper lobe cavitation in one.[6] Our patient also showed bilateral diffuse cavitary nodules with ill-defined margins. An HRCT scan of the chest revealed bilateral interstitial infiltrates in only one of the six patients,[6] none of the other five patients having undergone HRCT. In our patient, HRCT demonstrated multiple nodules of varying sizes with ill-defined margins, some of which showed cavitation, whereas others were surrounded by ground-glass opacity suggestive of a halo sign, which is a hallmark of IPA and therefore facilitated the diagnosis. Four of the six patients underwent biopsy[3,4,6]: needle biopsy in one; open lung biopsy in one; and bronchial biopsy in two. *Aspergillus* hyphae were identified in only two of the six patients[4,6]: from an open lung biopsy sample in one and from a bronchial biopsy sample in the other.

Fungi are known to occur in polluted water. A study conducted in Malaysia identified fungi in wastewater from a sewage treatment plant,[9] *Aspergillus* spp. being the second most common isolates. Another study, conducted in Denmark, highlighted the dangers of the inhalation of aerosols, including the conidia of *Aspergillus* spp., by wastewater workers.[10] Putrid sludge from wastewater provides warm, humid conditions, which are ideal for the growth of molds.[10] Our patient was exposed to polluted muddy water for 2 h while working in a deep pit. Given that his symptoms commenced the very next day, that water was most probably the source of his exposure to *Aspergillus* conidia.

Near-drowning episodes, especially in polluted water, can also result in acute IPA in immunocompetent individuals.[7] *Aspergillus* spp. are often recovered from water bodies and are a potential cause of invasive disease in near-drowning victims, because the lung tissue can be damaged due to immersion and the large inoculum of *Aspergillus* that can be deposited therein under such circumstances.[7]

Our patient showed immediate skin reactivity to *Aspergillus* antigens, as well as testing positive for specific IgE and IgG antibodies against *A. fumigatus*, which suggests prior sensitization. Because his profession entailed working in such environments on a regular basis, it is likely that he had previously been exposed to *Aspergillus* antigens. Serological investigation plays a supporting role in the diagnosis of IPA. Although the disease typically occurs in immunocompromised subjects, IgG antibodies against *Aspergillus* antigens are detected in 29-100% of IPA patients, such sensitization being proportionally highest in non-neutropenic patients. However, the fact that it takes a mean of 10.8 days for antibodies to appear during the acute phase of the disease reduces their diagnostic utility.[11]

A halo sign is defined as a nodule or mass surrounded by ground-glass opacity on HRCT and is the earliest manifestation of IPA. This sign is transient, mainly seen during the early stages, and tends to disappear with time.[12] It is thus imperative to obtain HRCT scans in the early stages of IPA, because this key radiological marker might not be visible thereafter. In our patient, the halo sign raised the suspicion of IPA and enabled rapid introduction of an antifungal agent, which likely helped our patient survive. Although most commonly seen in IPA, halo signs can also be seen in other fungal, viral, or bacterial infections and even in some systemic or neoplastic diseases.[12]

Because IPA usually occurs in immunocompromised hosts, it rarely comes to mind in the diagnosis of those who are immunocompetent. This frequently leads to considerable diagnostic delays and consequently to poor outcomes. Our report highlights the importance

Table 1. Clinical descriptions of cases of acute invasive pulmonary aspergillosis, after massive exposure to *Aspergillus* conidia, in immunocompetent individuals.

Reference	Case	History of acute exposure	Smoking status	Other comorbidities	Respiratory symptoms	Imaging	Cultures	Diagnostic confirmation	Serological markers	Treatment	Outcome
Strelling et al.,[3] conducted in the UK in 1966	1	Sisters who played long hours in a barn during the months preceding the disease, thus being exposed to natural and artificial manure; linseed oil; cattle cake; and grain.	Not stated	None	Dyspnea, fever, and cough	Chest X-ray showed bilateral patchy infiltrates, more in the middle lobes	Sputum, negative for fungus	Lung needle biopsy, no organism identified	Not stated	Not stated	Death (in both cases); positive staining for fungus was observed at autopsy
	2				Dyspnea and fever	Chest X-ray showed bilateral homogeneous infiltrates		Not stated			
Meeker et al.,[4] conducted in the USA in 1991	3	Exposure to old damp hay two weeks prior to presentation	Not stated	None	Low-grade fever, chills, and dry cough	Chest X-ray showed diffuse nodular and interstitial infiltrates	Sputum and BAL, negative for fungus; lung tissue, positive for *Aspergillus fumigatus*	Open lung biopsy, hyphae of *Aspergillus* sp.	Total IgE, 6,630 kUA/L (reference: < 260 kUA/L); immunodiffusion, positive for *Aspergillus* antibodies	Amphotericin B	Death; no autopsy performed
Batard E et al.,[5] conducted in France in 2003	4	Exposed to vegetal dust one day prior to presentation	Current (10 cigarette-a-day) smoker		Fever, headache, myalgia, and dry cough	Chest X-ray showed bilateral interstitial miliary infiltrates	Bronchial aspirate, positive for *A. fumigatus*	Not stated	Serology, negative for *Aspergillus*	Amphotericin B	Death; postmortem lung biopsy culture positive for *A. fumigatus*
Arendrup et al.,[6] conducted in Denmark in 2006	5	Both exposed to bark chippings on the day symptoms started	Not stated	Heart disease	Fever and dry cough	Chest X-ray and HRCT scan showed bilateral interstitial infiltrates	BAL, positive for *A. fumigatus*	Bronchial biopsy, hyphae	Positive *Aspergillus* antibody titer	Amphotericin B	Death; postmortem histopathology suggestive of *Aspergillus* pneumonia
	6		Current (20-cigarette-a-day) smoker	Mild COPD and Barrett's esophagus	Dry cough, pleuritic chest pain, and sweating	Chest X-ray showed cavitating pneumonia in the right upper lobe	BAL, negative for fungus	Bronchial biopsy, not suggestive of *Aspergillus*	Positive Aspergillosis precipitin test	Itraconazole	Improvement
Present study	7	Worked for 2 h in a deep pit containing polluted muddy water, 1 day prior to symptom onset	Former smoker who quit 10 years prior (smoking history, 10 pack-years)	Undiagnosed moderate obstructive lung disease	Dyspnea, cough, and fever	Chest X-ray showed bilateral diffuse patchy infiltrates with bilateral cavitation; chest HRCT showed multiple ill-defined nodular lesions affecting both lungs, with cavitation, some surrounded by ground-glass opacity (halo sign)	Sputum and bronchial aspirate, positive for *A. fumigatus*	Chronic nonspecific inflammation	Total IgE, 114 kUA/L (reference: < 64 kUA/L); skin prick test reactivity to *A. fumigatus* and *A. niger*; positivity for specific IgE and IgG antibodies against *A. fumigatus*	Itraconazole (200 mg twice a day for 2 months)	Clinical and radiological improvement

kUA: kilo units of allergen.

of suspecting IPA in immunocompetent patients who, in comparable scenarios, might have suffered brief but massive exposure to *Aspergillus* conidia, leading to acute IPA.

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Idiopathic pleuroparenchymal fibroelastosis: incidental findings in a patient with suspected pneumonia

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TO THE EDITOR:

Idiopathic pleuroparenchymal fibroelastosis (IPPFE) is an uncommon disease of the pleura and lungs. In 2013, IPPFE was classified as a rare interstitial lung disease (ILD) in a joint American Thoracic Society/European Respiratory Society statement on the classification of the idiopathic interstitial pneumonias.[1] Characterized by fibrosis, together with thickening of the pleural and subpleural tissue (subpleural fibroelastosis), IPPFE predominantly affects the periphery of the upper lung lobes, with volume loss, as first described by Frankel et al. in 2004.[2] To date, no more than forty cases of IPPFE have been described in the literature in English. There is currently no consensus regarding the diagnostic criteria used in order to classify IPPFE, as well as regarding whether or not it represents a real, new, specific entity. Although the etiology is unknown, conditions associated with the disease include infections, bone marrow transplantation, autoimmunity, and possibly genetic predisposition. Clinically, patients with IPPFE usually present with chronic respiratory symptoms such as dyspnea and dry cough. The diagnosis of IPPFE is established on the basis of clinical, radiological, and histopathological findings. Chest HRCT scans show marked subpleural consolidations with irregular thickening; distortion, usually located in upper lung lobes ("pleural cap"); subpleural bronchiolectasis; reticular opacities; and, in some cases, mild honeycombing. These features are similar to those of other forms of idiopathic pulmonary fibrosis. However, in IPPFE, they are seen mainly in upper lobes, being rare or absent in the lower lobes.[3,4] The histological characteristics of IPPFE are homogeneous subpleural fibrosis and abundant elastic fibers on elastic fiber stains.[5]

A 55-year-old nonsmoking female presented to her pulmonologist with fever (38°C for six days), worsening of dyspnea under stress, and a productive cough. The patient stated that she had not been previously exposed to environmental allergens or asbestos. She further stated that she had not used any drugs and had not been previously exposed to environmental allergens, as well as that she had not been under treatment with chemotherapy or radiotherapy. She tested positive only for autoantibodies against endomysium; other serological tests were negative. Physical examination showed that, over a period of six months, she had lost weight (5 kg) and muscle mass. There was also a reduction in oxygen saturation (SaO_2 of 81% on room air). On auscultation, there were reduced breath sounds and mild bilateral rales in the upper lung fields. Heart rate and rhythm were normal. Her extremities were also normal, without digital clubbing. Pulmonary function tests showed normal FVC (96%) and normal FEV_1 (91%), although the DLCO was reduced (61%). An initial chest X-ray (not shown) revealed marked, irregular opacities in the subpleural region of the upper fields, with mild upper hilar retraction. Fiberoptic bronchoscopy with BAL was carried out, and neutrophils were found to account for 72% of the inflammatory cells (normal value, 1-2%). Microbiology tests were negative. To elucidate the chest X-ray and BAL findings, we performed chest HRCT. The HRCT scans showed peripheral foci of lung consolidation, with distortion and irregular pleuroparenchymal thickening, that was most evident in the subpleural regions of the upper lobes, accompanied by bronchiolectasis, mild interlobular septal thickening, and (in rare cases) microcystic subpleural changes (Figure 1A). Scans of the lower lung fields (middle lobe and lingula) showed considerably fewer fibrotic changes, no distortion or other interstitial disease being observed in the apical and basal segments of the lower lobes (Figures 1B and 1C, respectively). These HRCT characteristics pose a diagnostic dilemma for the radiologist, who must make the differential diagnosis among IPPFE, sarcoidosis, and (albeit less likely) chronic hypersensitivity pneumonia. Therefore, we also performed a pleuroparenchymal frozen section biopsy in the upper lobes. Histopathological findings from elastic fiber staining revealed distortion and marked pleural thickening, with evidence of dense fibroelastotic tissue in the pleura and alveolar walls, together with sparse fibroblastic foci near the transition from the lung to the pleura (Figure 1D). On the basis of the clinical and radiological data, a diagnosis of IPPFE was made. In conclusion, although there are specific HRCT features that are suggestive of IPPFE, the disease continues to be underdiagnosed, probably because there is still a significant lack of knowledge and awareness of this entity. A diagnosis of IPPFE should be considered in cases of pulmonary fibrosis that is located predominantly in the upper lobes. The differential diagnosis includes advanced hypersensitivity pneumonia, advanced sarcoidosis, advanced smoking-related ILD, asbestosis, connective tissue disease, radiation pneumonia, and drug-induced lung disease. The possibility of IPPFE should

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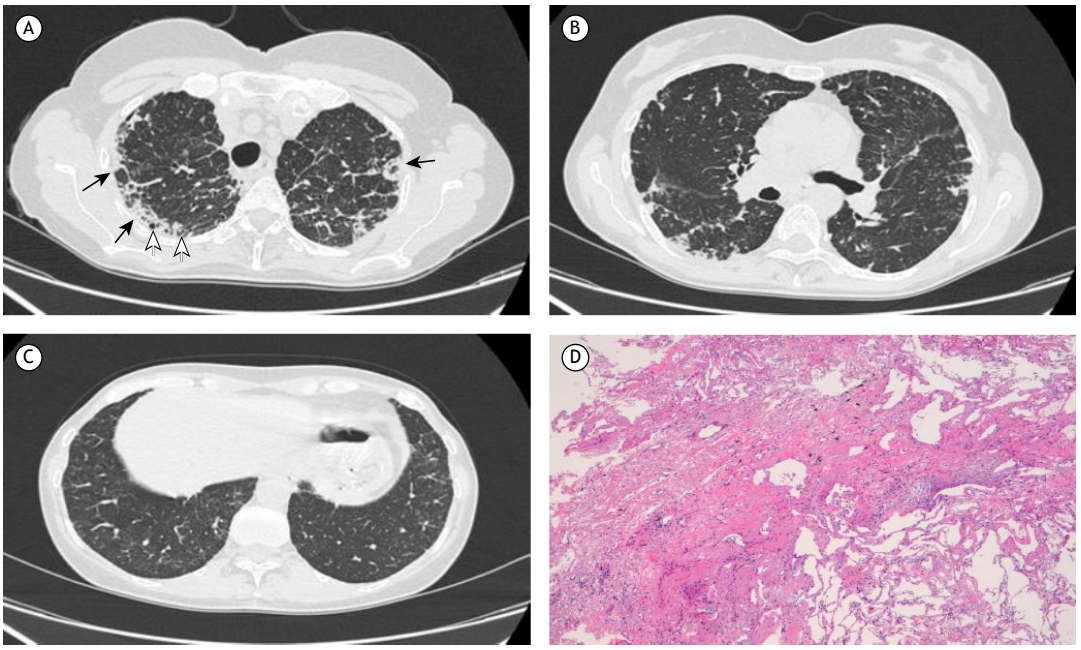

Figure 1. Chest HRCT and histology: A) HRCT scan showing marked subpleural thickening and irregular consolidations (black arrows), reticular opacities in the lung parenchyma at upper lobes, microcystic subpleural changes (white arrows), and bronchiolectasis; B) HRCT scan showing sparse fibrotic subpleural changes in the apical segments of the lower lung lobes, most pronounced on the right; C) HRCT scan showing near absence of fibrotic changes in the basal segments of the lower lung lobes; and D) histological section showing dense subpleural fibroelastotic tissue with an abrupt transition from pathological to normal lung parenchyma, containing a fibroblastic focus.

therefore be borne in mind when the radiological evidence is not consistent with other, more well-defined ILDs. It is recommended that surgical biopsy (using video-assisted thoracoscopic surgery)—or better yet frozen section biopsy—be performed in the affected area. A greater understanding of the etiology, risk factors, prognosis, and therapy related to IPPFE is needed in order to manage this disease in the future.

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BCGitis: A rare complication after intravesical BCG therapy

Maria João Oliveira[1], Daniel Vaz[1], Aurora Carvalho[1,2], Rosário Braga[3], Raquel Duarte[1,2,4,5]

DEAR EDITOR:

In most cases, bladder carcinoma is located superficially, and the therapeutic approach is usually transurethral resection followed by intravesical therapy (chemotherapy or immunotherapy).[1,2] Initially produced as a vaccine against tuberculosis, BCG—an attenuated strain of *Mycobacterium bovis*—has been widely used in immunotherapy over the last decades.[1,3] Although BCG, used as immunotherapy, has not produced the best results in many cancers, it has been clinically successful in the intravesical treatment of superficial bladder carcinomas.[4] Immunotherapy with intravesical BCG eradicates the residual tumor, slows the progression of the disease, reduces the need for cystectomy, and prolongs survival.[4] Treatment with BCG is well tolerated by over 95% of patients. The most common side effects are local (inflammation, fever, and pelvic adenopathy). However, although rare, systemic complications have been described.[1,3-6] Systemic dissemination of the attenuated *M. bovis* bacillus is known as BCGitis. It is more common in individuals with underlying primary or secondary immunodeficiency but can occur in immunocompetent patients.[1,6] There have been only a few reports of cases of respiratory BCGitis.[1,2,6] Here, we report the case of a patient who was treated with local BCG immunotherapy for urothelial bladder carcinoma and developed a severe *M. bovis* respiratory infection.

In March of 2013, a 72-year-old male presented with hematuria. The patient also had hypertension, dyslipidemia, cerebrovascular disease (previous stroke), chronic renal failure, and depression. He was being treated with perindopril, indapamide, atorvastatin, acetylsalicylic acid, furosemide, and escitalopram. He had no known drug allergies. Ultrasound revealed a 2.5-cm polyp in the bladder. The patient underwent transurethral resection of the bladder tumor. Histological examination revealed urothelial cell carcinoma (grade 2), without vascular or muscle invasion. Chemotherapy and immunotherapy with intravesical instillation of BCG were started and continued until December of 2013. In February of 2014, the patient presented to the emergency department with a one-week history of dyspnea and productive cough (mucopurulent sputum). He reported no fever, chest pain, hemoptysis, sweating, or other symptoms. On physical examination, he was afebrile, with an increased respiratory rate, hemodynamic stability, and an SpO_2 of 89% on room air. Auscultation revealed bilateral breath sounds, with crackles in both lung bases. There were no other significant changes. Ancillary tests showed a C-reactive protein level of 10 mg/dL, without leukocytosis, together with normal liver and kidney function, overlapping with previous studies of the patient. Blood gas analysis (at a FiO_2 of 24%) showed a pH of 7.43, a PaO_2 of 66 mmHg, a $PaCO_2$ of 45 mmHg, and an HCO_3 of 29.9 mEq/L. In addition, a chest X-ray showed bilateral diffuse reticulonodular infiltrates. A CT scan of the chest revealed randomly distributed micronodules in the lungs, together with enlargement of the hilar and mediastinal lymph nodes (Figure 1). After having collected sputum for analysis, we started empirical antibiotic treatment with amoxicillin and clavulanic acid. Due to respiratory failure and suspected miliary tuberculosis or diffuse pulmonary metastasis, the patient was admitted to the respiratory ward of the hospital.

During hospitalization, microbiological and mycobacteriological cultures of sputum samples were negative. Bronchoscopy revealed bilateral mucopurulent secretions, edema, and diffuse mucosal congestion. Microbiological cultures of bronchial lavage and BAL fluid (BALF) samples were negative. Although the BALF was negative for *M. tuberculosis* on smear microscopy, it tested positive for *M. tuberculosis* complex DNA and for *M. bovis* in cultures. Cytology of the BALF was negative for malignant cells; the patient also tested negative for the viral markers

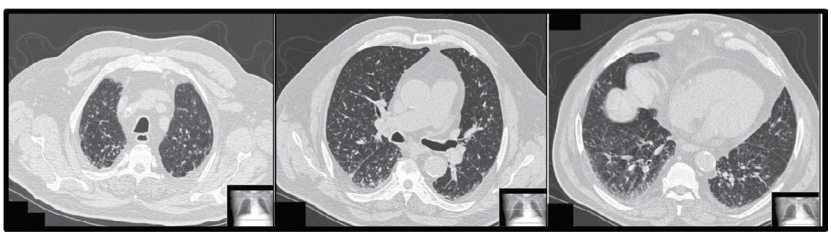

Figure 1. Chest CT scan showing randomly distributed micronodules in the lungs, together with enlargement of the hilar and mediastinal lymph nodes.

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of infection with HIV, HCV, and HBV. Because of the positive result on the nucleic acid amplification test of the BALF, we started tuberculosis treatment with isoniazid, rifampin, pyrazinamide, and ethambutol. Despite improvements in his test results and clinical resolution of the respiratory failure, the patient showed a slight increase in liver enzymes (to less than double the normal values). He underwent upper abdominal ultrasound, which revealed hepatic steatosis with no other abnormalities. In view of the BALF culture positivity for *M. bovis* (which is naturally pyrazinamide-resistant), we suspended the pyrazinamide, and the liver enzyme values normalized thereafter.

The patient was discharged and continued treatment on an outpatient basis. Future scheduled BCG instillations were suspended. In the initial phase of treatment, the regimen was the isoniazid-rifampin-ethambutol combination, whereas the isoniazid-rifampin combination was used in the maintenance phase. After a total of 6 months of treatment, the patient showed a good response. At this writing, the patient remains under follow-up monitoring of his bladder, without signs of recurrence. The patient gave written informed consent for the reporting of his case.

Various recent studies have analyzed the outcomes of patients with bladder carcinoma who underwent therapeutic intravesical instillation of BCG. The study conducted by Lamm et al. showed that disseminated BCGitis was extremely rare.[2] Some studies have reported that, among patients with bladder cancer, there is a relationship between the complications of BCG instillation and a prior diagnosis of tuberculosis, such complications not occurring in patients without a history of tuberculosis and with no evidence of sequelae on chest X-rays.[1]

In this report, we have presented the case of a male patient without a history of tuberculosis who developed a respiratory infection soon after treatment with intravesical instillation of BCG. The initial diagnostic hypotheses included malignancy. However, after careful investigation, the patient was diagnosed with BCGitis, with no remaining doubt that the lung disease was due to the spread of the BCG used in the treatment of his bladder carcinoma. Despite the rarity of this complication, our case report underscores the need for vigilance and awareness of the possibility of BCG dissemination, given the widespread use of BCG in patients with bladder carcinoma.

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Bronchiectasis caused by common variable immunodeficiency

Paulo Henrique do Amor Divino[1], José Henrique de Carvalho Basilio[1], Renato Moraes Alves Fabbri[1], Igor Polônio Bastos[1], Wilma Carvalho Neves Forte[2]

TO THE EDITOR:

Primary immunodeficiencies (PIDs) are characterized by impairment of one or more arms of the immune response, resulting in decreased defense, an increased number of infections, and, in certain cases, a higher incidence of autoimmune diseases and cancers.[1] Although PIDs are considered rare diseases, many of them are more common than are those currently diagnosed with the "heel prick" test. The manifestations of PIDs are heterogeneous and are usually caused by genetic defects of the immune system and its development.

Common variable immunodeficiency (CVI) is the most prevalent of the severe PIDs. A diagnosis of CVI is based on reduced levels of IgG, IgA, and (in some cases) IgM, together with reduced levels of specific antibodies, after other causes of hypogammaglobulinemia have been excluded.[2] The incidence of CVI is similar in both genders, with either sporadic or familial distribution. Although it can manifest at any time in life, it is especially common in adolescence and young adulthood. The most striking characteristics of this disease include hypogammaglobulinemia associated with frequent infections, especially with encapsulated bacteria, as well as a poor response to immunization protocols.[3]

A 27-year-old Black female, who worked as a maid, was admitted to the ER of a tertiary hospital with a 7-day history of productive cough, fever, and dyspnea. The patient reported a history of asthma, recurrent pneumonia, and some episodes of furunculosis. In addition, she reported that, one month prior, she had been hospitalized for five days because of pneumonia and that the frequency of such infections had increased in the last five years.

The initial examination revealed fever, an SpO_2 of 84% on room air (digital pulse oximetry), a heart rate of 120 bpm, and an arterial pressure of 90/60 mmHg. A chest X-ray of the chest showed right pleural effusion as well as pneumonic infiltrates in the middle third and lower lobe of the left lung (Figure 1). The patient was started on antibiotic therapy to treat the pulmonary focus and underwent thoracentesis followed by chest tube drainage, on the right side, because of empyema.

The patient was found to be antinuclear factor-negative. Serology for HIV, HTLV, hepatitis A, hepatitis B, hepatitis C, Epstein-Barr virus, rubella, toxoplasmosis, and cytomegalovirus was negative, as was the venereal disease research laboratory test (for syphilis). In addition, sputum smear microscopy and sputum cultures were negative for tuberculosis and fungi. No bacteria were isolated from blood or pleural fluid culture. The results of thyroid function testing, anti-thyroglobulin testing, and anti-thyroid peroxidase testing were normal, ruling out the possibility of autoimmune thyroiditis. Quantification of serum immunoglobulins revealed a persistent decrease in IgA, IgM, and IgG. Serology was negative for antibody to hepatitis B surface antigen (anti-HBs), although the patient had received three doses of the hepatitis B vaccine. Additional immunological assessment, which included determination of total complement activity (CH50), photoreduction of nitroblue tetrazolium, and measurement of phagocytosis by neutrophils and mononuclear phagocytes, yielded normal results.

On the basis of the clinical picture, findings from history taking, and laboratory test results, a diagnosis of CVI was made and the patient was started on human immunoglobulin replacement therapy (600 mg/kg), which resulted in rapid clinical and radiological improvement. Two months after admission, the patient was discharged to follow-up in the pulmonology and allergy/immunodeficiency outpatient clinics for continuation of her immunoglobulin replacement therapy (monthly administration).

Recurrent pneumonia can result in bronchiectasis and forms part of the core clinical picture of CVI. Among PIDs, CVI is the second most common, although it is believed to be underdiagnosed. Its incidence is reported as 1:10,000 among individuals of European descent, being rare among Asians, with a reported incidence of 1:2,000,000 individuals in Japan.[4] To date, there have been no studies investigating its incidence in the Black population.

Encapsulated bacteria, such as *Streptococcus pneumoniae* and *Haemophilus influenzae*, are combated by IgG2 subclass antibodies to polysaccharide antigens. In the absence of such immunoglobulins, as in cases of CVI, patients experience sinopulmonary infections, especially pneumonia, bronchitis, sinusitis, and otitis.[1,2] Infections with atypical bacteria, such as some species of the genus *Mycoplasma*, have also been reported.[5] Often, patients experience tonsillitis, otitis, and giardiasis in childhood, all of which are facilitated by IgA deficiency, and, in adolescence or young adulthood, develop recurrent pneumonia, which is characteristic of IgG deficiency, suggesting that CVI is the result of progression of IgA deficiency.[6]

The patient in question had been immunized against hepatitis B, as recommended, having received all three doses of the vaccine. Nevertheless, she tested negative for anti-HBs, i.e., she had deficient production of specific protein antibodies, which also occurs in CVI.[2] In this

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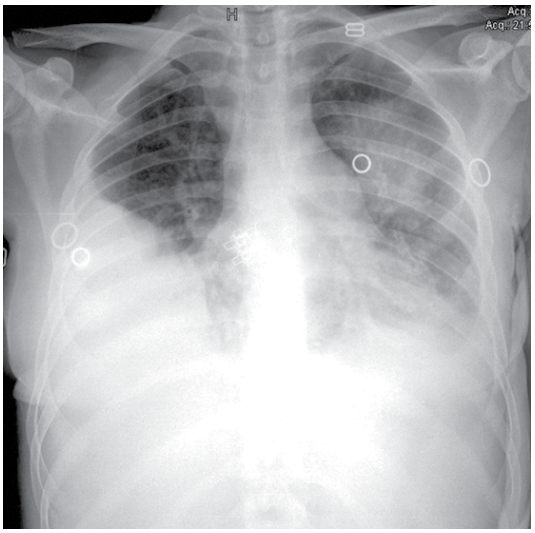

Figure 1. Chest X-ray showing right pleural effusion as well as pneumonic infiltrates in the middle third and lower lobe of the left lung.

PID, there can be deficient production of other specific antibodies, especially those to polysaccharide antigens, and the pneumococcal vaccination status of the patient must therefore be taken into account.

Patients with CVI have normal or slightly reduced B lymphocyte counts. However, because of problems intrinsic to B lymphocytes, they can lack the ability to differentiate into antibody-producing plasma cells, might not function properly as antigen-presenting cells to T helper lymphocytes, or might not receive sufficient assistance from T helper lymphocytes, all of which can impair the response to immunizations and infections.[3-7] Such problems are probably due to disturbances in the expression of surface molecules on B lymphocytes or T helper lymphocytes, intracellular enzyme activity disturbances, or increased apoptosis.[8]

The prevalence of chronic pulmonary complications at CVI diagnosis is high (27.0-34.2%).[9] The most common such complication is bronchiectasis. Extensive pneumonia and the chronicity of infectious pulmonary episodes are responsible for the poor prognosis in CVI patients.[10] Bronchiectasis can accompany diseases and conditions other than CVI, including tuberculosis, aspergillosis, cystic fibrosis,alpha-1 antitrypsin deficiency, AIDS, cancer, systemic lupus erythematosus, and rheumatoid arthritis. Therefore, it is necessary to make the differential diagnosis, whether it is based on findings from history taking or on ancillary test results.

The treatment for patients with CVI includes administering human immunoglobulin replacement therapy and combating infections. Immunoglobulin preparations contain neutralizing antibodies against a wide variety of bacteria and viruses, reflecting the immunological memory of the donors, and should be administered every three or four weeks.

We believe that CVI should be borne in mind by health professionals who treat patients with recurrent pneumonia. Typically manifesting in adulthood, CVI is a PID that must be diagnosed early so that prompt treatment can be instituted, thereby lowering morbidity, improving quality of life, and, in many cases, making survival possible for these patients.

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Diffuse lung cysts

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

A 57-year-old woman presented with an abdominal mass requiring investigation. She was asymptomatic from a respiratory standpoint. Laboratory test results were unremarkable. A CT scan of the abdomen showed bilateral, fat-containing renal masses and cysts in the lung bases. An HRCT scan showed scattered lung cysts (Figure 1).

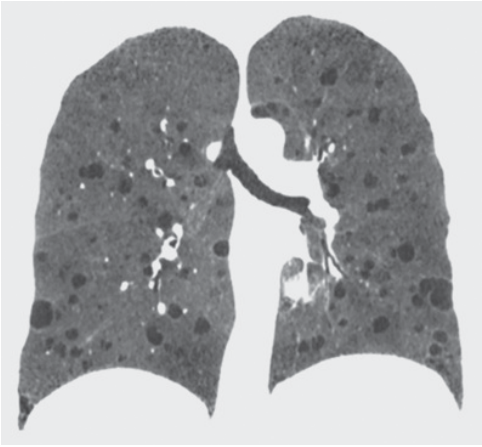

Figure 1. HRCT scan showing multiple, round, thin-walled cysts distributed homogeneously throughout the lungs. The remainder of the lung parenchyma is unremarkable. Note that some of the cysts are located in the lung bases.

The patient basically had diffuse lung cysts on HRCT examination. Cysts are characterized by rounded areas of low attenuation in the lung parenchyma and a well-defined interface with the normal adjacent lung. They are distinguishable from pulmonary emphysema because they have no arterioles at their center and usually have an identifiable wall. The cyst wall is usually thin, but it can vary in thickness. Cysts usually contain air but occasionally contain fluid. A cystic pattern is encountered in a number of diseases, the most common being lymphangioleiomyomatosis (LAM), Langerhans cell histiocytosis, lymphocytic interstitial pneumonia (LIP), and Birt-Hogg-Dubé syndrome (BHDS). Clinically, cysts are usually asymptomatic or accompanied by dyspnea and are often discovered in routine tests or when complications, such as pneumothorax, occur.

Some clinical and tomographic criteria can be useful for the differential diagnosis. In LIP, cysts are less numerous and can be associated with ground-glass opacities. Frequently, LIP occurs in patients with immunological diseases, especially Sjögren's syndrome. In Langerhans cell histiocytosis, cyst shapes can be more bizarre and, more importantly, cysts predominate in the upper lung fields, sparing the lung bases, especially the costophrenic sulci.

Two syndromic conditions can present with lung cysts and renal masses: tuberous sclerosis and BHDS. In BHDS, cysts are less numerous, are larger, and predominate in the lower lobes. Renal masses, as a rule, correspond to malignant tumors. In tuberous sclerosis, cysts correspond to LAM, are more numerous and diffuse, and also affect the lung bases. Renal masses are benign in nature and are angiomyolipomas.

Tuberous sclerosis is a genetic syndrome, caused by mutations in the *TSC1* or *TSC2* gene, and is characterized by formation of hamartomas in multiple organs or organ systems. Despite the recent advent of genetic testing for *TSC* gene mutations, diagnosis continues to be based on clinical criteria. A definitive diagnosis can be made when patients have at least two of the following findings: cardiac rhabdomyomas; cortical tubers; facial angiofibromas; hypermelanotic macules; LAM; renal angiomyolipomas, retinal hamartomas; Shagreen patches; subependymal giant cell astrocytomas; subependymal nodules; or ungual fibromas.

In the case of this patient, taking into account the presence of numerous diffuse cysts in the lung bases, as well as of fat-containing renal masses (angiomyolipomas), the final diagnosis was tuberous sclerosis-associated LAM.

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What does the p value really mean?

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

WHY CALCULATE A P VALUE?

Consider an experiment in which 10 subjects receive a placebo, and another 10 receive an experimental diuretic. After 8 h, the average urine output in the placebo group is 769 mL, versus 814 mL in the diuretic group—a difference of 45 mL (Figure 1). How do we know if that difference means the drug works and is not just a result of chance?

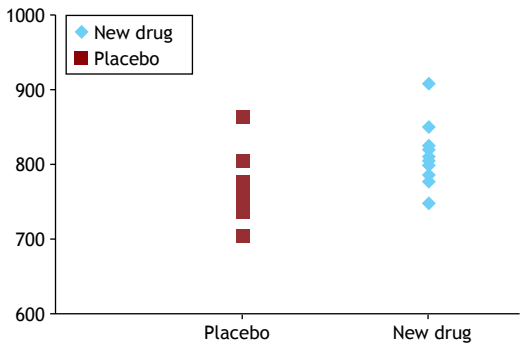

Figure 1. Urine output (mL) for each subject in the placebo (squares) and new drug groups (diamonds).

The most common way to approach this problem is to use statistical hypothesis testing. First, we state the null hypothesis of no statistical difference between the groups and the alternative hypothesis of a statistical difference. Then we select a statistical test to compute a test statistic, which is a standardized numerical measure of the between-group difference. Under the null hypothesis, we expect the test statistic value to be small, but there is a small probability that it is large, just by chance. Once we calculate the test statistic, we use it to calculate the p-value.

The p value is defined as the probability of observing the given value of the test statistic, or greater, under the null hypothesis. Traditionally, the cut-off value to reject the null hypothesis is 0.05, which means that when no difference exists, such an extreme value for the test statistic is expected less than 5% of the time.

Now let us go back to our case: we are comparing means and assuming that the data is normally distributed, so we use a t-test and compute a t-statistic of 2.34, with a p value of 0.031. Because we use a 0.05 cutoff for the p value, we reject the null hypothesis and conclude that there is a statistically significant difference between groups. So what does "p = 0.031" mean? It means that there is only a 3% probability of observing a difference of 45 mL in the average urine output between groups under the null hypothesis. Because this is a very small probability, we reject the null hypothesis. It does **not** mean that the drug is a diuretic, nor that there is 97% chance of the drug being a diuretic.

MISCONCEPTIONS ABOUT THE P VALUE

Clinical versus statistical significance of the effect size

There is a misconception that a very small p value means the difference between groups is highly relevant. Looking at the p value alone deviates our attention from the effect size. In our example, the p value is significant but a drug that increases urine output by 45 mL has no clinical relevance.

Nonsignificant p values

Another misconception is that if the p value is greater than 5%, the new treatment has no effect. The p value indicates the probability of observing a difference **as large or larger** than what was observed, under the null hypothesis. But if the new treatment has an effect of smaller size, a study with a small sample may be underpowered to detect it.

Overinterpreting a nonsignificant p value that is close to 5%

Yet another misconception is that if the p value is close to 5%, there is a trend towards a group difference. It is inappropriate to interpret a p value of, say, 0.06, as **a trend towards a difference**. A p value of 0.06 means that there is a probability of 6% of obtaining that result by chance when the treatment has no real effect. Because we set the significance level at 5%, the null hypothesis should not be rejected.

Effect sizes versus p values

Many researchers believe that the p value is the most important number to report. However, we should focus on the effect size. Avoid reporting the p value alone and preferably report the mean values for each group, the difference, and the 95% confidence interval—then the p value.

RECOMMENDED LITERATURE

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Right lung exclusion in massive pulmonary thromboembolism

Rodrigo Abensur Athanazio[1], Samia Zahi Rached[1]

A 37-year-old female patient presented to the emergency department with a 3-week history of dyspnea, hypoxemia, pleuritic chest pain, and lower limb edema. She had no history of comorbidities and had had two normal pregnancies. There was no family history of thrombosis. An electrocardiogram showed right axis deviation, and blood tests revealed elevated D-dimer levels. A routine chest X-ray showed oligemia in the right hemithorax and engorgement of the left pulmonary artery (Figure 1). Chest CT angiography confirmed the presence of a thrombus in the pulmonary artery trunk and full occlusion of the right segment (Figure 2). The coronal reconstruction shown in Figure 3 elegantly demonstrates the complete lack of pulmonary perfusion in the right lung, together with ipsilateral oligemia. Echocardiography confirmed pulmonary hypertension (systolic pulmonary artery pressure, 80 mmHg) and right ventricular dysfunction. Because of hemodynamic instability, the patient was submitted to thrombolysis with alteplase and started on anticoagulation therapy. Her dyspnea persisted, and she was categorized as New York Heart Association functional class III. After 6 months, she evolved to chronic pulmonary thromboembolic disease. Positron emission tomography and nuclear magnetic resonance imaging were performed to exclude angiosarcoma. At this writing, the patient is under evaluation for thromboendarterectomy.

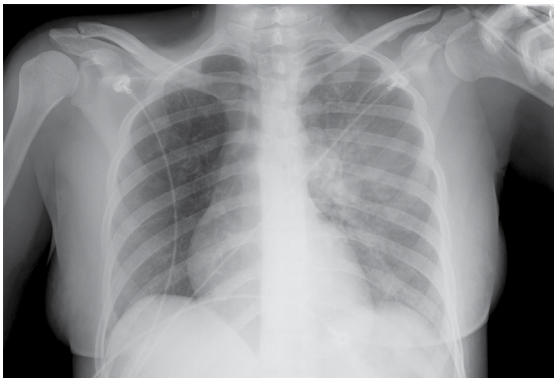

Figure 1. Thoracic X-ray revealing oligemia in the right hemithorax and engorgement of the left pulmonary artery.

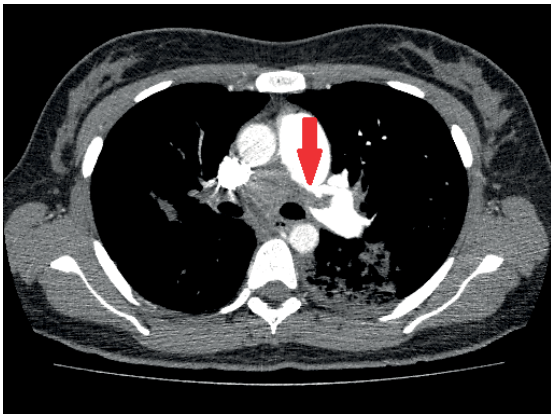

Figure 2. CT scan confirming a thrombus in the pulmonary artery trunk and full occlusion of the right segment (arrow).

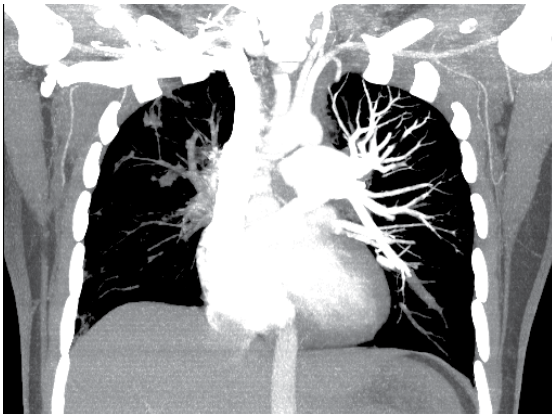

Figure 3. Coronal reconstruction demonstrating the complete lack of pulmonary perfusion in the right lung, together with ipsilateral oligemia.

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Case Reports: Case Reports should not exceed 1500 words, excluding title page, abstract, references and illustrations. The text should be composed of: Introduction, Case Report, Discussion and References. It is recommended that any and all information that might identify the patient be withheld, and that only those laboratory exams that are important for the diagnosis and discussion be presented. The total number of illustrations (figures or tables) should not exceed three, and the number of references should be limited to 20. When the number of cases presented exceeds three, the manuscript will be classified as a Case Series, and the same rules applicable to an original article will be applied.

Brief Communications: Brief communications should not exceed 1500 words, excluding references and tables. The total number of tables and figures should not exceed two, and the references should be limited to 20. The text should be unstructured.

Letters to the Editor: Letters to the Editor should be succinct original contributions, not exceeding 800 words and containing a maximum of 6 references. Comments and suggestions related to previously published materials or to any medical theme of interest will be considered for publication.

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

Abstracts

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

Chapter in a Book

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

Official Publications

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

Theses

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

Electronic publications

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

Homepages/URLs

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

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50 anos[1] da marca Fluimucil

Há 50 anos na Itália, nascia a marca Fluimucil e junto com ela uma nova classe terapêutica, a dos mucolíticos.

Alguns anos após o seu lançamento, Fluimucil tornou-se o principal produto da Zambon no mundo, permitindo-lhe expandir o seu mercado e tornar-se uma das maiores empresas farmacêuticas na Itália. Foram muitos sonhos realizados, muitos projetos patrocinados com a força que Fluimucil traz para a companhia até hoje.

A importância de Fluimucil ao longo do tempo é comprovada pela quantidade de pacientes tratados a cada ano, pela quantidade de prescrições médicas e, acima de tudo, pelas publicações médicas recentes envolvendo o produto. Todos estes fatores levaram Fluimucil à liderança mercadológica que contribuiu para o desenvolvimento contínuo de novos estudos. Isso mesmo! **Em 2014, foram dois novos estudos em DPOC com desfechos muito relevantes, que resultaram na inclusão do produto no principal guideline de tratamento da doença, o GOLD, em 2015.**

É por estas razões que temos aqui no Brasil um selo comemorativo com o símbolo do infinito. O que é infinito é para sempre, não tem fim. Pois para nós 50 anos representa apenas o começo e nós queremos muito mais!

Obrigado por fazer parte da construção desta marca!

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acetilcisteína

FLUIMUCIL® ACETILCISTEÍNA É UM MEDICAMENTO. SEU USO PODE TRAZER RISCOS. PROCURE O MÉDICO E O FARMACEUTICO. LEIA A BULA.

Fluimucil®, acetilcisteína. **Uso oral - Uso adulto:** Comprimido efervescente 200 mg e 600 mg com 16 comprimidos efervescentes. **Indicações:** Dificuldade para expectorar e existência de muita secreção densa e viscosa, tais como: bronquite crônica e suas exacerbações, enfisema pulmonar, bronquite aguda, pneumonia, colapsos/atelectasias pulmonares, mucoviscidose/fibrose cística. Também é indicado como antídoto na intoxicação acidental ou voluntária por paracetamol. **Contraindicações:** Hipersensibilidade conhecida à acetilcisteína e/ou demais componentes de suas formulações. Fluimucil® comprimido efervescente: "Atenção fenilcetonúricos: contém fenilalanina". Estas substâncias podem causar reações alérgicas (possivelmente tardias). Registro MS.: 1.0084.0075

REFERÊNCIAS: 1. Documento interno: registro do produto Fluimucil na Itália, datado de 1965. **2.** Bula do produto Fluimucil® Oral. **3.** IMS PMB – produtos com a molécula acetilcisteína isolada na forma farmacêutica comprimidos efervescentes de 200mg e 600mg. Consulta em Janeiro de 2015. **4.** Global Strategy for Diagnosis, Management, and Prevention of COPD. Updated January 2015. Pág. 36 Management Stable COPD

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

Clenil® HFA

dipropionato de beclometasona

O tratamento da asma ao alcance de todos[1]

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

COMODIDADE POSOLÓGICA:[5]

ADULTOS:

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

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

250 mcg Jet® - 2 doses, 2-4 X ao dia

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AQUI TEM FARMÁCIA POPULAR

Custo Zero para seu paciente[1]

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

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

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- **Prolonga significativamente o tempo até a primeira exacerbação; reduz a taxa de exacerbações em 34% e reduz em 61% o risco de exacerbações graves que levam a hospitalizações[6]**
- **Melhora significativamente a tolerância ao exercício aumentando o tempo, diminuindo a dispneia e o desconforto das pernas[7]**
- **Perfil de segurança documentado e comparável a placebo[2,4,6]**
- **Vem com Breezhaler®, dispositivo desenvolvido especialmente para DPOC e com feedback sensorial: OUVE, SENTE E VÊ[8]**

SEEBRI™ brometo de glicopirrônio. **Forma farmacêutica e apresentações:** Cápsulas com pó para inalação contendo 63 mcg de brometo de glicopirrônio equivalente a 50 mcg de glicopirrônio. Caixas com 12 cápsulas + 1 inalador ou 30 cápsulas + 1 inalador. **Indicações:** Seebri™ é indicado para tratamento broncodilatador de manutenção para o alívio de sintomas dos pacientes com doença pulmonar obstrutiva crônica (DPOC). **Posologia:** Adultos – A dose recomendada é de uma inalação uma vez ao dia do conteúdo de uma cápsula de Seebri™ 50 mcg usando o inalador de Seebri™. Crianças (menores de 18 anos) – Não deve ser utilizado em pacientes abaixo de 18 anos de idade. População especial – Nenhum ajuste de dose é necessário para pacientes idosos, pacientes com doenças hepáticas ou com insuficiência renal leve e moderada. Deve-se ter cautela em pacientes com insuficiência renal grave, incluindo estágio final de doença renal que requeiram diálise. **Método de administração:** As cápsulas de Seebri™ devem ser administradas apenas por via inalatória oral e apenas usando o inalador de Seebri™. As cápsulas não devem ser engolidas. Seebri™ deve ser administrado no mesmo horário todos os dias. Se uma dose for esquecida, a próxima dose deve ser tomada o mais rápido possível. Os pacientes devem ser instruídos a não administrar mais que uma dose por dia. As cápsulas devem sempre ser armazenadas no blíster, e apenas removidas imediatamente antes do uso. Os pacientes devem ser instruídos em como administrar o medicamento corretamente. Os pacientes que não apresentarem melhora na respiração, devem ser questionados se estão engolindo o medicamento ao invés de inalando. **Contraindicações:** Hipersensibilidade ao glicopirrônio, que é o princípio ativo de Seebri™ ou a qualquer um dos excipientes. **Advertências e Precauções:** Uso Agudo – Não deve ser usado como medicamento de resgate. Hipersensibilidade – Se ocorrer reação de hipersensibilidade, Seebri™ deve ser descontinuado imediatamente e uma terapia alternativa deve ser instituída. Broncoespasmo paradoxal – Assim como com outras terapias inalatórias, a administração pode resultar em broncoespasmo paradoxal que pode ocasionar risco à vida. Se ocorrer broncoespasmo paradoxal, Seebri™ deve ser descontinuado imediatamente e um tratamento alternativo deve ser instituído. Efeito Anticolinérgico – utilizar com cautela em pacientes com glaucoma de ângulo fechado e retenção urinária. Insuficiência renal grave – utilizar somente se o benefício esperado for maior que o potencial de risco em pacientes com insuficiencia renal grave incluindo aqueles no estágio final de doença renal que requeiram diálise. Gravidez –deve ser utilizado durante a gravidez apenas se os benefícios esperados justificarem o risco potencial ao feto. Lactação –deve ser considerado apenas se o benefício esperado para a mulher for maior que qualquer possível risco ao bebê. **Interações medicamentosas:** A co-administração com outros medicamentos anticolinérgicos inalatórios não foi estudada e, portanto, não é recomendada. Foi usado concomitantemente com broncodilatadores simpaticomiméticos, metilxantinas, esteróides orais e inalatórios, os quais são comumente utilizados no tratamento da DPOC, sem evidência clínica de interacções medicamentosas. **Reações adversas:** Comuns (1 a 10%): boca seca, insônia, gastroenterite; Incomuns (0,1 a 1%): dispneia, cárie dental, dor nas extremidades, dor torácica musculoesquelética, erupção cutânea (rash), fadiga, astenia, congestão nasal, tosse produtiva, irritação na garganta, epistaxe, rinite, cistite, hiperglicemia, disúria, retenção urinária, fibrilação atrial, palpitações, hiposestesia. Não conhecido: Angioedema, broncoespasmo paradoxal, hipersensibilidade, prurido. Outras reações adversas: nasofaringite, vômito, dor musculoesquelética, dor no pescoço, diabetes mellitus. Em pacientes idosos: Dor de cabeça, infecção no trato urinário. VENDA SOB PRESCRIÇÃO MÉDICA. MS – 1.0068.1117. Informações completas para prescrição disponíveis mediante solicitação ao Departamento Médico da Novartis BBSS 10.03.15 2014-PSB/GLC-0726-s.

Contraindicações: Hipersensibilidade ao glicopirrônio, que é o princípio ativo de Seebri™ ou a qualquer um dos excipientes. **Interações medicamentosas:** A co-administração com outros medicamentos anticolinérgicos inalatórios não foi estudada e, portanto, não é recomendada. Foi usado concomitantemente com broncodilatadores simpaticomiméticos, metilxantinas, esteróides orais e inalatórios, os quais são comumente utilizados no tratamento da DPOC, sem evidência clínica de interacções medicamentosas.

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6338790 BM LAMINA ANUNCIO 0815 BR. Material dirigido unicamente a profissionais da saúde habilitados a prescrever e/ou dispensar medicamentos. Data de Produção: agosto/2015. 2015 -

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