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HIGHLIGHT

Exercise and sleep apnea

Pulmonary function and sickle cell disease

Indwelling pleural catheter

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Consolidating in the present, with an eye to the future

Rogerio Souza

The scientific literature has changed substantially over the last few decades. There has been a progressive migration to a model based on exclusive online platforms, even by traditional periodicals. In addition to reducing costs, the use of such platforms also increases the speed at which accepted articles gain exposure. In parallel with that, the appearance of an increasing number of journals has increased the portfolio of options for the publication of a given manuscript. However, the absolute majority of these new journals employ a paid submission model, which creates another type of barrier to publishing, particularly for novice researchers, whose sources of funding are more limited.

Within the context of the scenario described above but respecting the fundamental objectives of the JBP,[1] various editorial decisions have been made, the work of the associated editors having been of fundamental importance. Their work gave greater representation to areas that previously were not well covered in the JBP. For example, among the most often cited JBP articles in the last two years, there are two articles on the physiology of the respiratory muscles,[2,3] one on the pulmonary circulation,[4] and two related to smoking.[5,6] These have been added to the already established topics covered in the JBP, such as that of obstructive lung diseases and even the study of tuberculosis. There has also been a significant increase in the number of JBP articles related to invasive procedures,[7,8] as well as to the field of thoracic surgery,[9] clearly indicating an expansion of the representativeness of the Journal. In parallel, JBP review articles have sought to illuminate subjects of more general interest to our readership, such as sleep,[10] idiopathic pulmonary fibrosis,[11] and imaging,[12] together with special sections on continuing education in scientific methodology and imaging, with the goal of making the JBP an accessible tool for keeping everyone with an interest in respiratory medicine up to date.

We have been able to reduce the average time between submission and the final decision on the manuscripts. Here, we must offer our sincere thanks to all of the reviewers who contribute to making our evaluation and publication process more agile, while it continues to be free. It was the direct participation of the reviewers that allowed such advancement. It must be acknowledged, however, that there is still much room for improvement. A number of steps in the decision-making process still need to be further streamlined. Thus, the JBP can become even more attractive to researchers as a means of broadly and rapidly bringing their results to light.

The changes described above would be illogical were they not accompanied by greater international recognition of the content published in the JBP. We are pleased to report that that is what has occurred. The JBP impact factor, as published in Thomson Reuters Journal Citation Reports has stabilized and has actually risen slightly, currently standing at 1.019. That indicates that the journal has begun to overcome the effects of the temporary suspension of 2014.[13] Supporting that impression is the fact that the two-year Scimago Jornal Rank citation index is now 1.282, corresponding to a 15% increase in relation to the previous cycle. These figures, while indicating substantial room for growth, make the JBP the leading journal in the field of respiratory medicine in Latin America. In addition, the JBP continues to be an important journal for the dissemination of postgraduate studies conducted in Brazil, receiving a good grade in the journal ranking system of the Brazilian Office for the Advancement of Higher Education, a system known as Qualis.

There is a need for further consolidation of the JBP processes. There are several highly relevant research groups in our country that do not yet participate significantly in the publication of the JBP and that could greatly enrich the representativeness of the journal. There is also an opportunity to update several of the Brazilian Thoracic Association guidelines, which also play a fundamental role in the visibility of any scientific journal. These opportunities will be explored in upcoming years.

The JBP can also become a platform for the discussion of pathways and alternatives in respiratory medicine. There is room to open a debate on several aspects, from the education of pulmonologists to the future of research in the area of respiratory medicine. Relevant themes for the future of respiratory medicine, which could be exposed in the JBP in the form of debates between exponents of each of the respective areas include the ideal curriculum, funding sources, the minimum structure of a postgraduate program in the pulmonology, incentives for young researchers, retention of professionals in the university environment, and professional defense.

If there is still a great need to improve the processes and solidify the continued growth of the JBP, we must not lose sight of the opportunities to give the JBP an even more comprehensive role in leading the reader to reflection, not only on science, a fundamental principle of the existence of the journal, but also on health policies, vocational training, and medical education. We invite our readers to take this next step with us.

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REFERENCES

1. Souza R. The next 40 years. J Bras Pneumol. 2015;41(5):404. https://doi.org/10.1590/S1806-37132015000500008
2. Caruso P, Albuquerque AL, Santana PV, Cardenas LZ, Ferreira JG, Prina E, et al. Diagnostic methods to assess inspiratory and expiratory muscle strength. J Bras Pneumol. 2015;41(2):110-23. https://doi.org/10.1590/S1806-37132015000004474
3. Marques TB, Neves Jde C, Portes LA, Salge JM, Zanoteli E, Reed UC. Air stacking: effects on pulmonary function in patients with spinal muscular atrophy and in patients with congenital muscular dystrophy. J Bras Pneumol. 2014;40(5):528-34. https://doi.org/10.1590/S1806-37132014000500009
4. Gavilanes F, Alves Jr JL, Fernandes C, Prada LF, Jardim CV, Morinaga LT, et al. Left ventricular dysfunction in patients with suspected pulmonary arterial hypertension. J Bras Pneumol. 2014;40(6):609-16. https://doi.org/10.1590/S1806-37132014000600004
5. Knorst MM, Benedetto IG, Hoffmeister MC, Gazzana MB. The electronic cigarette: the new cigarette of the 21st century? J Bras Pneumol. 2014;40(5):564-72. https://doi.org/10.1590/S1806-37132014000500013
6. Stelmach R, Fernandes FL, Carvalho-Pinto RM, Athanazio RA, Rached SZ, Prado GF, et al. Comparison between objective measures of smoking and self-reported smoking status in patients with asthma or COPD: are our patients telling us the truth? J Bras Pneumol. 2015;41(2):124-32. https://doi.org/10.1590/S1806-37132015000004526
7. Perazzo A, Gatto P, Barlascini C, Ferrari-Bravo M, Nicolini A. Can ultrasound guidance reduce the risk of pneumothorax following thoracentesis? J Bras Pneumol. 2014;40(1):6-12. https://doi.org/10.1590/S1806-37132014000100002
8. Ortakoylu MG, Iliaz S, Bahadir A, Aslan A, Iliaz R, Ozgul MA, et al. Diagnostic value of endobronchial ultrasound-guided transbronchial needle aspiration in various lung diseases J Bras Pneumol. 2015;41(5):410-4. https://doi.org/10.1590/S1806-37132015000004493
9. Marchetti-Filho MA, Leão LE, Costa-Junior Ada S. The role of intercostal nerve preservation in acute pain control after thoracotomy. J Bras Pneumol. 2014;40(2):164-70. https://doi.org/10.1590/S1806-37132014000200010
10. Beltrami FG, Nguyen XL, Pichereau C, Maury E, Fleury B, Fagondes S. Sleep in the intensive care unit. J Bras Pneumol. 2015;41(6):539-46. https://doi.org/10.1590/S1806-37562015000000056
11. Baddini-Martinez J, Baldi BG, Costa CH, Jezler S, Lima MS, Rufino R. Update on diagnosis and treatment of idiopathic pulmonary fibrosis. J Bras Pneumol. 2015;41(5):454-66. https://doi.org/10.1590/S1806-37132015000000152
12. Hochhegger B, Alves GR, Irion KL, Fritscher CC, Fritscher LG, Concatto NH, et al. PET/CT imaging in lung cancer: indications and findings. J Bras Pneumol. 2015;41(3):264-74. https://doi.org/10.1590/S1806-37132015000004479
13. Souza R. 2015–another step along the road in a 40-year journey. J Bras Pneumol. 2015;41(1):1-2. https://doi.org/10.1590/S1806-37132015000100001

J Bras Pneumol. 2016;42(6):401-401
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The JBP and sleep medicine

Pedro Rodrigues Genta[1]

Sleep medicine is a relatively new discipline that has begun to consolidate as an important area of activity for pulmonologists, in Brazil as well as in the rest of the world. The JBP has been a part of this transformation, as evidenced by the increasing number of submissions and publications related to the field of sleep medicine. Although we are still a month away from the end of the year, the number of submissions to the JBP in 2016 has already hit a record, growing by 18% in comparison with 2013. Even more significant was the increase in the number of submissions related to sleep medicine, which increased from 8 in 2013 to 16 (to date) in 2016. The increasing interest in the JBP, together with an increase in the quality of the articles submitted, demonstrates the maturing of the sleep medicine community in Brazil.[1,2]

It also shows the evolution of the JBP, which has increased its visibility on various fronts. As a matter of fact, there have also been submissions on the topic from outside Brazil.[2,3]

All of this has made the JBP stand out among the Brazilian journals indexed for the *Index Medicus* (Medline/PubMed) as one of the journals that publishes the most articles on the topic of sleep.

In this edition of the JBP, Andrade and Pedrosa[4] review a current theme: the role of physical exercise in obstructive sleep apnea. Exercise has a broad range of effects. In sleep apnea, exercise can reduce the frequency of respiratory events and relieve symptoms. The treatment of sleep apnea with strategies other than the use of continuous positive airway pressure is relevant because of the difficulty that some patients have in adhering to the treatment, as well as because of the high cost of the equipment. Although the efficacy of physical exercise is limited, studies in which physical exercise is combined with other strategies, such as myofunctional speech therapy, weight loss, and positional therapy, have shown promise.

I would therefore like to thank everyone who has been contributing to the sleep medicine section of the JBP, either by submitting their scientific production or by dedicating themselves to reviewing the manuscripts submitted. In addition, I appeal to the entire scientific community that is interested in sleep medicine to contribute with new submissions and to volunteer to act as a JBP reviewer. The dedication of all involved will increase the international visibility of the JBP, with an emphasis on sleep medicine, which will benefit the Brazilian Thoracic Association and the scientific community at large.

REFERENCES

1. Fonseca LB, Silveira EA, Lima NM, Rabahi MF. STOP-Bang questionnaire: translation to Portuguese and cross-cultural adaptation for use in Brazil. J Bras Pneumol. 2016:42(4):266-272. https://doi.org/10.1590/S1806-37562015000000243
2. Sunnetcioglu A, Sertogullarindan B, Ozbay B, Gunbatar H, Ekin S. Obstructive sleep apnea related to rapid-eye-movement or non-rapid-eye-movement sleep: comparison of demographic, anthropometric, and polysomnographic features. J Bras Pneumol. 2016:42(1):48-54. https://doi.org/10.1590/S1806-37562016000000012
3. Salvaggio A, Lo Bue A, Isidoro SI, Romano S, Marrone O, Insalaco G. Gel pillow designed specifically for obstructive sleep apnea treatment with continuous positive airway pressure. J Bras Pneumol. 2016:42(5):362-366. https://doi.org/10.1590/S1806-37562016000000015
4. Andrade FM, Pedrosa RP. The role of physical exercise in obstructive sleep apnea. J Bras Pneumol. 2016:42(6):457-464.

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

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Clusters of small nodules with no confluence

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

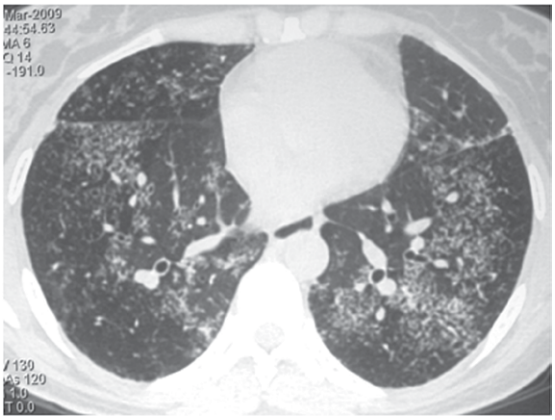

Figure 1. HRCT scan showing clusters of small nodules with no confluence in the lower lobes of both lungs.

CLINICAL HISTORY

A 36-year-old man presented with a two-month history of dry cough, fever, and weight loss (8 kg). Laboratory test results were normal. HRCT of the chest showed clusters of interstitial nodules with no confluence (Figure 1). BAL specimens were negative for tuberculosis and fungi. Open lung biopsy showed necrotic granulomas. Culture of lung tissue was positive for *Mycobacterium tuberculosis*.

DISCUSSION

This patient had multiple small interstitial nodules on HRCT. Small pulmonary nodules (or micronodules) are round opacities of soft tissue density and less than 1 cm in diameter. On the basis of their distribution in the lung parenchyma, they can be classified as perilymphatic, centrilobular, or random micronodules.

A perilymphatic distribution occurs when the small nodules are located predominantly along the lung lymphatic system (peribronchovascular interstitium, interlobular septa, and subpleural regions). A centrilobular distribution is characterized by nodules that are located within a few millimeters of the pleural surface and fissures but do not touch them. A random pattern corresponds to small nodules randomly distributed in the secondary lobule and scattered uniformly throughout the lungs.

Some other patterns of distribution of small interstitial nodules have been described more recently. They include the sarcoid galaxy sign, the sarcoid cluster sign, and the nodular reversed halo sign. The reversed halo sign is defined as a round area of ground-glass attenuation surrounded by a ring of consolidation. The designation of nodular reversed halo sign is used when the walls of the dense peripheral ring are formed by nodules, instead of exhibiting the usual smooth appearance. Nodules are also frequently seen within the halo. Findings of this pattern are highly suggestive of active granulomatous disease, particularly tuberculosis or sarcoidosis.

The sarcoid galaxy sign corresponds to a large parenchymal nodule that is formed by the coalescence of small nodules and is surrounded by satellite nodules. The sarcoid cluster sign corresponds to a generally round or elongated group of small nodules with no confluence, as in the case presented here. The nodules are close to each other but do not group. These two signs were initially reported in patients with sarcoidosis, hence their names. However, they were subsequently described in patients with tuberculosis, thus requiring to be renamed. The names currently proposed for these new signs are "cluster of nodules with confluence" and "cluster of nodules without confluence", respectively. From an anatomical and pathological standpoint, in the cases of both signs, the nodules correspond to granulomas, and the two major diagnoses that should be considered in the presence of these findings are active tuberculosis and sarcoidosis.

RECOMMENDED READING

1. Marchiori E, Zanetti G, Barreto MM, de Andrade FT, Rodrigues RS. Atypical distribution of small nodules on high resolution CT studies: patterns and differentials. Respir Med. 2011;105(9):1263-7. http://dx.doi.org/0.1016/j.rmed.2011.02.010

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Developing research questions that make a difference

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

BACKGROUND

A clinical research question is defined as an ***uncertainty*** about a health problem that points to the need for meaningful understanding and deliberate investigation. [1] For clinicians interested in conducting high-quality clinical research, it is essential to recognize the fact that the research process starts with developing a question about a specific health-related area of interest. This is important because once the research question is defined, it has an impact on every remaining component of the research process, including generating the hypothesis and defining the appropriate study design, as well as the study population, study variables, and statistical approach. However, conceiving a sound research question is not an easy task; it requires having a particular set of personal skills and utilizing structured approaches.

DEVELOPING AND WRITING A RESEARCH QUESTION

Developing a research question starts by identifying a clinical problem that is important to patients, being related to managing and ultimately improving their health. The process requires clinician scientists to be curious about and attentive to day-to-day practice outcomes, as well as to be avid readers of the scientific literature, to participate in scientific activities (e.g., journal clubs), and to have access to a scientific mentor or collaborators interested in clinical research.

The research question itself should meet certain criteria, as summarized by the acronym FINGER, which stands for Feasible, Interesting, Novel, Good (for your career), Ethical, and Relevant (Chart 1).[1] We recommend going through the FINGER criteria systematically and discussing all issues with a mentor or colleague before writing the study protocol and conducting a study that will answer the proposed research question.

Once the research question has been defined, it should be written out in such a way that the answer can be expressed as either a number, typical of descriptive research questions (e.g., a prevalence related to disease burden, such as "What is the prevalence of asthma among favela residents in Brazil?"), or as a yes or no, typical of studies about associations between exposures and outcomes (e.g., "Is living in a *favela* in Brazil associated with increased mortality among adults with asthma?"). In addition, if the researcher has a hypothesis about the answer to the research question,[1] it is important that it be written out using a comprehensive approach, as summarized by the acronym PICOT, which stands for **P**opulation (the population to be included in the study), **I**ntervention (treatment applied to participants in the treatment arm), **C**omparison (treatment applied to the control group), **O**utcome (the primary outcome variable), and **T**ime (follow-up time to measure the outcome).[2]

INVESTING THE TIME AND EFFORT TO COME UP WITH A HIGH-QUALITY, WELL-WRITTEN RESEARCH QUESTION IS WORTH IT!

As clinician scientists who train clinicians to become successful researchers, we cannot emphasize enough the importance of investing one's time wisely to develop a high-quality research question. Researchers who conceive and clearly state a research question about an important health-related problem are at an advantage because they are more likely to convince key individuals to provide them with the necessary resources and support to carry out the study, as well as to increase the reporting quality of the paper to be published.[3]

Chart 1. Expanded descriptions of the recommended criteria for developing a good research question.

FINGER Criteria	
Feasible	
	Access to an adequate number of participants
	Research team has technical expertise to conduct the study
	Affordable: costs are reasonable and funding is available
	Can be completed in a reasonable time period
Interesting	
	Results of the study will be of interest to the research community
Novel	
	Provides new findings, extends or refutes previous findings
Good	
	For your career: fits into your career development plan
Ethical	
	Risk to participants is low/acceptable, considered ethical by peers and the Institutional Review Board
Relevant	
	To improve scientific knowledge, inform clinicians and health policy, and to impact future research

REFERENCES

1. Hulley SB, Cummings SR, Browner WS, Grady DG, Newman TB. Designing clinical research. 4th ed. Philadelphia (PA): Lippincott Williams and Wilkins; 2013.
2. Haynes R. Forming research questions In: Haynes R, Sackett D, Guyatt GH, Tugwell P, editors. Clinical Epidemiology: How to do Clinical Practice Research. Philadelphia, PA: Lippincott Williams & Wilkins; 2006. p. 3-14.
3. Rios LP, Ye C, Thabane L. Association between framing of the research question using the PICOT format and reporting quality of randomized controlled trials. BMC Med Res Methodol. 2010;10:11. http://dx.doi.org/10.1186/1471-2288-10-11

1. Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA.
2. Methods in Epidemiologic, Clinical and Operations Research (MECOR) Program, American Thoracic Society, New York, NY, USA, and Asociación Latinoamericana de Tórax, Montevideo, Uruguay.
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Effects of positive expiratory pressure on pulmonary clearance of aerosolized technetium-99m-labeled diethylenetriaminepentaacetic acid in healthy individuals

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ABSTRACT

Objective: To evaluate the effects of positive expiratory pressure (PEP) on pulmonary epithelial membrane permeability in healthy subjects. **Methods:** We evaluated a cohort of 30 healthy subjects (15 males and 15 females) with a mean age of 28.3 ± 5.4 years, a mean FEV_1/FVC ratio of 0.89 ± 0.14, and a mean FEV_1 of 98.5 ± 13.1% of predicted. Subjects underwent technetium-99m-labeled diethylenetriaminepentaacetic acid (^{99m}Tc-DTPA) radioaerosol inhalation lung scintigraphy in two stages: during spontaneous breathing; and while breathing through a PEP mask at one of three PEP levels—10 cmH_2O (n = 10), 15 cmH_2O (n = 10), and 20 cmH_2O (n = 10). The ^{99m}Tc-DTPA was nebulized for 3 min, and its clearance was recorded by scintigraphy over a 30-min period during spontaneous breathing and over a 30-min period during breathing through a PEP mask. **Results:** The pulmonary clearance of ^{99m}Tc-DTPA was significantly shorter when PEP was applied—at 10 cmH_2O (p = 0.044), 15 cmH_2O (p = 0.044), and 20 cmH_2O (p = 0.004)—in comparison with that observed during spontaneous breathing. **Conclusions:** Our findings indicate that PEP, at the levels tested, is able to induce an increase in pulmonary epithelial membrane permeability and lung volume in healthy subjects.

Keywords: Lung/metabolism; Technetium Tc 99m pentetate/pharmacokinetics; Radiopharmaceuticals; Positive-pressure respiration.

INTRODUCTION

The alveolar-capillary barrier, also known as the blood-gas barrier, is excellent at maintaining the separation between alveolar air and pulmonary capillary blood, allowing rapid, efficient exchange of respiratory gases while preventing the diffusion of water-soluble particles suspended in alveolar air.[1,2] The integrity of the blood-gas barrier is extremely important to the maintenance of pulmonary homeostasis. In 1953, Frank Low published the first high-resolution electron micrographs of the human pulmonary blood-gas barrier, showing that a structure only 0.3 µm thick separates capillary blood from alveolar gas, which suggested that the barrier might be vulnerable to mechanical failure if the capillary pressure increased[3] or in states of high lung inflation, in which the capillary wall is under tension because of longitudinal stress in the alveolar walls.[4]

Technetium-99m-labeled diethylenetriaminepentaacetic acid (^{99m}Tc-DTPA) radioaerosol inhalation lung scintigraphy is a rapid, easily performed, extremely sensitive, noninvasive technique for assessing lung epithelial permeability.[5,6] When inhaled, ^{99m}Tc-DTPA particles arrive at the alveolar epithelial surface and then diffuse from the air space into the vascular space. The clearance rate of ^{99m}Tc-DTPA is a reliable index of alveolar epithelial permeability. Therefore, ^{99m}Tc-DTPA aerosol-inhaled scintigraphy has been used in numerous

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experiments and clinical investigations designed to assess the integrity of the respiratory epithelium.[7,8]

Positive expiratory pressure (PEP) therapy involves breathing with slightly active expiration against mild expiratory resistance (typically 10-20 cmH_2O).[9] Its application via a PEP mask represents a reliable, safe, low-cost intervention that can increase lung volumes and intrathoracic pressure.[10,11] It has been shown to improve lung volume, promote dilation of the airways, and decrease pulmonary resistance. The purpose of PEP therapy is to increase the transpulmonary pressure gradient and improve pulmonary expansion, which consequently improves oxygenation and the response to inhaled bronchodilators.[12,13]

The effects of different intensities of PEP on the pulmonary clearance of ^{99m}Tc-DTPA in healthy subjects have been largely unexplored in the literature and require further elucidation. Therefore, the aim of the present study was to evaluate the effects of PEP on pulmonary epithelial membrane permeability in healthy subjects.

METHODS

We studied 30 healthy subjects (15 men and 15 women). The mean age was 28.3 ± 5.4 years. Subjects with cardiovascular or neuromuscular disease were excluded, as were those with a history of smoking or respiratory disease, as well as those who were pregnant. All participants were recruited from a tertiary care hospital in the city of Porto Alegre, Brazil, and were evaluated between January and July of 2012. The study was approved by the Research Ethics Committee of the Porto Alegre *Hospital de Clínicas* (Protocol no. 04-418), which is accredited by the Brazilian National Commission on Research Ethics, and all subjects gave written informed consent.

Pulmonary scintigraphy with ^{99m}Tc-DTPA radioaerosol was conducted over two 30-min periods: during spontaneous breathing; and while subjects were breathing via a PEP mask (Vital Signs/GE Healthcare, Totowa, NJ, USA), which we adapted to fit each subject by using headgear, coupled to a PEP therapy device (Resistex®; Mercury Medical, Clearwater, FL, USA). Using computer-generated randomization codes, we divided the subjects into three groups: those receiving PEP at 10 cmH_2O (PEP_{10}); those receiving PEP at 15 cmH_2O (PEP_{15}); and those receiving PEP at 20 cmH_2O (PEP_{20}). During data acquisition, the subjects were in a sitting position with their hands on their thighs and their arms held away from their body. For each subject, the spontaneous breathing period served as the control.

A spirometer (MasterScreen v4.31; Jaeger, Würzburg, Germany) was used in order to measure FEV_1 and FVC. The technical procedures, acceptability criteria, and reproducibility criteria, as well as standardization of measures, were in accordance with the guidelines established by the Brazilian Thoracic Association.[14] Subjects received instruction regarding the procedures to be performed during the spirometry assessment. The spirometer was routinely calibrated (on a daily basis) with a 3-L syringe in order to compensate for ambient temperature conditions. A minimum of three and a maximum of eight tests were conducted with a 1-min interval between them. Three reproducible maneuvers were performed, and the best curve was considered for the study. Results are expressed as absolute and percent-of-predicted values.[15]

The ^{99m}Tc-DTPA was chelated by adding ^{99m}Tc-pertechnetate ($^{99m}Tc\text{-}O_4^-$, IPEN-TEC; Institute for Energy Research and Nuclear Science, São Paulo, Brazil) to 740 MBq (20 mCi) of DTPA (Institute for Energy Research and Nuclear Science) in 5 mL of normal saline. Using instant thin layer chromatography, we determined the labeling efficiency to be above 98%. The solution was placed in the reservoir of the nebulizer (Aerogama Medical, Porto Alegre, Brazil) and was inhaled by the volunteer during 3 min of normal tidal breathing, with an oxygen flow rate of 9 L/min. During nebulization, the subjects remained under supervision, which allowed us to verify the appropriate performance of the inhalation maneuvers, as well as to correct any errors in inhalation techniques. The subjects were placed in a sitting position in front of a gamma camera (Starcam 4000i; GE Medical Systems, Milwaukee, WI, USA), and images were obtained every 20 s over a 30-min period. Two regions of interest were defined—the left lung and the right lung—and were drawn manually, a time-activity curve being constructed by the same investigator. For each lung, we employed the negative slope of the curve to define clearance, using the minimum and maximum clearance values. The ^{99m}Tc-DTPA clearance rate was expressed as its half-time ($T_{1/2}$)—i.e., the time for its activity to decrease to 50% of the peak value.

All statistical analyses were performed with the SPSS Statistics software package, version 20.0 (IBM Corp., Armonk, NY, USA). The normality of the variables was assessed with the Shapiro-Wilk test. Categorical data are presented as absolute and relative frequencies. Continuous data with normal distribution are expressed as means and standard deviations. Anthropometric variables and lung function parameters were compared among groups by one-way ANOVA (with the exception of gender, which was compared by the chi-square test). The difference in $T_{1/2}$ among groups was determined with one-way analysis of covariance, with body weight, height, and body mass index (BMI) as the dependent variables. The influence of the pressure levels on $T_{1/2}$ was compared among the groups by two-way ANOVA. The level of statistical significance was set at 5% ($p<0.05$).

RESULTS

We evaluated 30 healthy subjects (15 males and 15 females), with a mean age of 28.26 ± 5.40 years, a mean FEV_1/FVC ratio of 0.89 ± 0.14, and a mean FEV_1 of 98.5 ± 13.1% of the predicted value. The anthropometric and lung function parameters are presented in Table 1. The spirometric parameters were

similar among the three study groups. Body weight, height, and BMI were higher in the PEP_{20} group than in the PEP_{15} group (p = 0.038, p = 0.027, and p = 0.015, respectively). The ^{99m}Tc-DTPA pulmonary clearance rate was not found to correlate significantly with age (r = −0.120; p = 0.951), body weight (r = 0.115; p = 0.545), height (r = 0.085; p = 0.655), or BMI (r = 0.120; p = 0.528). In the analysis of the results related to the ^{99m}Tc-DTPA pulmonary clearance rate, we considered the mean values for the left and right lungs together, given that the difference between the two lungs was not found to be statistically significant in the PEP_{10} group (p = 0.258), the PEP_{15} group (p = 0.908), or the PEP_{20} group (p = 0.570).

In comparison with the value obtained during spontaneous breathing, the mean $T_{1/2}$ was significantly lower in the PEP_{10} group—90.3 ± 25.4 min versus 73.3 ± 30.6 min (p = 0.044), as can be seen in Figure 1. That difference was also significant in the PEP_{15} group—89.8 ± 28.9 min versus 63.1 ± 22.1 min (p = 0.044)—and in the PEP_{20} group—99.3 ± 49.6 min versus 64.5 ± 29.6 min (p = 0.004). Regarding the delta variation in $T_{1/2}$ values, no statistically significant difference was found among the groups (p = 0.322).

DISCUSSION

To our knowledge, this was the first study to investigate the effects that different levels of PEP (10, 15, and 20 cmH_2O) have on the rate of pulmonary clearance of ^{99m}Tc-DTPA. We demonstrated that PEP was able to induce increases in epithelial permeability, at all of the levels tested. Another important finding is that no significant variation in pulmonary clearance rate was observed among the three groups under the effects of any of the three PEP levels.

The effect of positive end-expiratory pressure (PEEP) on solute clearance has been described as a sigmoidal dose-response relationship dependent on the pressure level applied (5-15 cmH_2O); in other words, the rate of pulmonary clearance of ^{99m}Tc-DTPA accelerates exponentially due to the increase in lung volume caused by the administration of different PEEP levels.[16] Contrary to our hypothesis, we did not find any differences among the three levels of PEP. In accordance with our results, the study conducted by Bishai et al.[17] showed an increase in the pulmonary epithelial permeability in mice at a PEEP level of 10 cmH_2O. This difference in pulmonary clearance might be because mice have smaller alveoli and are probably more sensitive to the distension of inter-epithelial junctions of the alveolar epithelium induced by the application of lower pressure levels.

Our findings differ from those reported by Paiva et al.,[18] who assessed the permeability of the alveolar

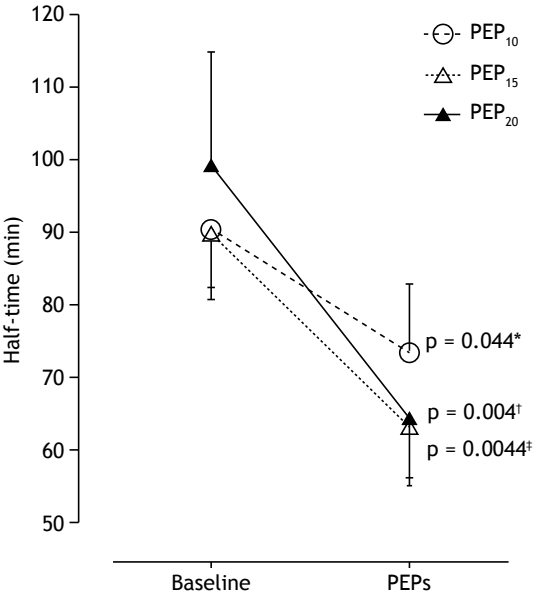

Figure 1. Effects of positive expiratory pressure (PEP) on the pulmonary clearance of technetium-99m-labeled diethylenetriaminepentaacetic acid (^{99m}Tc-DTPA). At all PEP levels, there was a significant decrease in the ^{99m}Tc-DTPA half-time (the time for its activity to decrease to 50% of the peak value) in comparison with the baseline (spontaneous breathing) values (analysis of covariance, p < 0.05 for all). PEP_{10}: PEP at 10 cmH_2O for 30 min; PEP_{15}: PEP at 15 cmH_2O for 30 min; and PEP_{20}: and PEP at 20 cmH_2O for 30 min. *PEP_{10}. †PEP_{20}. ‡PEP_{15}.

Table 1. Baseline characteristics of the study groups.[a]

Variable	PEP group			p*
	PEP10 (n = 10)	PEP15 (n = 10)	PEP20 (n = 10)	
Male gender, n (%)	6 (60)	2 (20)	7 (70)	0.061
Age, years	27.7 ± 5.1	30.4 ± 5.9	26.6 ± 5.1	0.286
Weight, kg	70.7 ± 13.6	60.4 ± 5.2	76.5 ± 11.5	0.009†
Height, cm	173 ± 7.7	165.5 ± 5.5	176.1 ± 8.5	0.017‡
BMI, kg/m2	23.4 ± 2.8	22.1 ± 1.5	24.5 ± 2.1	0.004§
FVC, % of predicted	99.5 ± 15.9	97.1 ± 17.8	99.4 ± 18.5	0.347
FEV1, % of predicted	97.8 ± 12.3	99.3 ± 12.6	98.6 ± 14.4	0.356

[a]Values are expressed in mean ± SD, except where otherwise indicated. PEP: positive expiratory pressure; PEP_{10}: PEP at 10 cmH_2O for 30 min; PEP_{15}: PEP at 15 cmH_2O for 30 min; PEP_{20}: PEP at 20 cmH_2O for 30 min; and BMI: body mass index. *Between-group comparisons. †Significant difference between the PEP_{15} group and the PEP_{20} group (p = 0.038). ‡Significant difference between the PEP_{15} group and the PEP_{20} group (p = 0.027). §Significant difference between the PEP_{15} group and the PEP_{20} group (p = 0.015).

epithelial membrane in 36 healthy individuals submitted to 10 cmH_2O and 20 cmH_2O under continuous positive airway pressure (CPAP). The authors showed that 20 cmH_2O of CPAP induced an increase in epithelial permeability, whereas 10 cmH_2O of CPAP did not.

Previous studies in humans,[19] sheep,[20,21] and dogs[22,23] showed that the application of PEEP increases lung volume and accelerates the rate of pulmonary clearance of ^{99m}Tc-DTPA. Therefore, the increased end-expiratory lung volume produced by PEP reduces airway resistance and promotes an increase in functional residual capacity.[24] However, other factors, such as airway/alveolar distension, prevention of alveolar collapse during expiration, and recruitment of collapsed alveoli, can also increase functional residual capacity.[25]

In keeping with the findings of the present study, Suzuki et al.[26] observed that, during the application of 20 cmH_2O of PEEP, pulmonary clearance of ^{99m}Tc-DTPA increased but returned to baseline values when PEEP was discontinued. That suggests that the increase in the ^{99m}Tc-DTPA pulmonary clearance rate achieved through the application of PEEP is reversible after breathing returns to atmospheric pressure levels.

The mechanisms by which pulmonary insufflation accelerates the pulmonary clearance of ^{99m}Tc-DTPA remain unclear. Some authors attribute this effect to an increase in the alveolar surface area available for diffusion,[22] due to either the increase in epithelial permeability,[27] functional alterations in the surfactant layer,[28] or distension of the intercellular junctions of the alveolar epithelium.[29]

The present study has some limitations. First, we evaluated subjects with healthy lungs. Therefore, any conclusions drawn from this study cannot be applied to patients with lung disease. This needs to be investigated in different, clearly specified disease groups, especially because PEP is not usually applied in patients with healthy lungs. Second, the upper airway critical closing pressure was not measured. Nevertheless, our findings offer new perspectives on the role of noninvasive ventilation, particularly in relation to PEP and its influence on the alveolar epithelium.

On the basis of the findings of the present study, we conclude that the application of 10, 15, or 20 cmH_2O of PEP for 30 min can induce an increase in epithelial permeability and lung volume in healthy subjects. Given that the application of PEP represents a reliable, safe, and low-cost intervention in a variety of clinical situations, future investigations should be conducted with a focus on expanding upon these findings.

REFERENCES

1. West JB. Comparative physiology of the pulmonary blood-gas barrier: the unique avian solution. Am J Physiol Regul Integr Comp Physiol. 2009;297(6):R1625-34. http://dx.doi.org/10.1152/ajpregu.00459.2009
2. Maina JN, West JB. Thin and strong! The bioengineering dilemma in the structural and functional design of the blood-gas barrier. Physiol Rev. 2005;85(3):811-44. http://dx.doi.org/10.1152/physrev.00022.2004
3. West JB. Role of the fragility of the pulmonary blood-gas barrier in the evolution of the pulmonary circulation. Am J Physiol Regul Integr Comp Physiol. 2013;304(3):R171-6. http://dx.doi.org/10.1152/ajpregu.00444.2012
4. Budinger GR, Sznajder JI. The alveolar-epithelial barrier: a target for potential therapy. Clin Chest Med. 2006;27(4):655-69; abstract ix. http://dx.doi.org/10.1016/j.ccm.2006.06.007
5. O'Doherty MJ, Peters AM. Pulmonary technetium-99m diethylene triamine penta-acetic acid aerosol clearance as an index of lung injury. Eur J Nucl Med. 1997;24(1):81-7. http://dx.doi.org/10.1007/BF01728316
6. Cayir D, Demirel K, Korkmaz M, Koca G. Evaluation of lung epithelial permeability in volatile substance abuse using Tc-99m DTPA aerosol scintigraphy. Ann Nucl Med. 2011;25(8):554-9. http://dx.doi.org/10.1007/s12149-011-0498-7
7. Ogi S, Gotoh E, Uchiyama M, Fukuda K, Urashima M, Fukumitsu N. Influence of hilar deposition in the evaluation of the alveolar epithelial permeability on 99mTc-DTPA aerosol inhaled scintigraphy. Jpn J Radiol. 2009;27(1):20-4. http://dx.doi.org/10.1007/s11604-008-0288-x
8. Gumuser G, Vural K, Varol T, Parlak Y, Tuglu I, Topal G, et al. Assessment of lung toxicity caused by bleomycin and amiodarone by Tc-99m HMPAO lung scintigraphy in rats. Ann Nucl Med. 2013;27(7):592-9. http://dx.doi.org/10.1007/s12149-013-0722-8
9. Osadnik C, Stuart-Andrews C, Ellis S, Thompson B, McDonald CF, Holland AE. Positive expiratory pressure via mask does not improve ventilation inhomogeneity more than huffing and coughing in individuals with stable chronic obstructive pulmonary disease and chronic sputum expectoration. Respiration. 2014;87(1):38-44. http://dx.doi.org/10.1159/000348546
10. Ricksten SE, Bengtsson A, Soderberg C, Thorden M, Kvist H. Effects of periodic positive airway pressure by mask on postoperative pulmonary function. Chest. 1986;89(6):774-81. http://dx.doi.org/10.1378/chest.89.6.774
11. Myers TR. Positive expiratory pressure and oscillatory positive expiratory pressure therapies. Respir Care. 2007;52(10):1308-26; discussion 1327.
12. Fink JB. Positive pressure techniques for airway clearance. Respir Care. 2002;47(7):786-96.
13. Alcoforado L, Brandão S, Rattes C, Brandão D, Lima V, Ferreira Lima G, et al. Evaluation of lung function and deposition of aerosolized bronchodilators carried by heliox associated with positive expiratory pressure in stable asthmatics: a randomized clinical trial. Respir Med. 2013;107(8):1178-85. http://dx.doi.org/10.1016/j.rmed.2013.03.020
14. Sociedade Brasileira de Pneumologia e Tisiologia. Diretrizes para testes de função pulmonar. J Pneumol. 2002;28(Suppl 3):S1-238.
15. Pereira CA, Sato T, Rodrigues SC. New reference values for forced spirometry in white adults in Brazil. J Bras Pneumol. 2007;33(4):397-406. http://dx.doi.org/10.1590/S1806-37132007000400008
16. Marks JD, Luce JM, Lazar NM, Wu JN, Lipavsky A, Murray JF. Effect of increases in lung volume on clearance of aerosolized solute from human lungs. J Appl Physiol. 1985;59(4):1242-8.
17. Bishai JM, Mitzner W, Tankersley CG, Wagner EM. PEEP-induced changes in permeability in inbred mouse strains. Respir Physiol Neurobiol. 2007;156(3):340-4. http://dx.doi.org/10.1016/j.resp.2006.10.009
18. Paiva DN, Masiero PR, Spiro BL, Jost RT, Albuquerque IM, Cardoso DM, et al. Continuous positive airway pressure and body position alter lung clearance of the radiopharmaceutical 99mtechnetium-diethylenetriaminepentaacetic acid (99mTc-DTPA). Afr J Biotechnol. 2012;11(99):16519-24. http://dx.doi.org/10.5897/AJB12.2563
19. Rinderknecht J, Shapiro L, Krauthammer M, Taplin G, Wasserman K, Uszler JM, et al. Accelerated clearance of small solutes from the lungs in interstitial lung disease. Am Rev Respir Dis. 1980;121(1):105-17.
20. O'Brodovich H, Coates G, Marrin, M. Effect of inspiratory resistance and PEEP on 99mTc-DTPA clearance. J Appl Physiol (1985). 1986;60(5):1461-5.
21. Cooper JA, van der Zee H, Line BR, Malik AB. Relationship of end-expiratory pressure, lung volume, and 99mTc-DTPA clearance. J

Appl Physiol . 1987;63(4):1586-90.

22. Rizk NW, Luce JM, Hoeffel JM, Price DC, Murray JF. Site of deposition and factors affecting clearance of aerosolized solute from canine lungs, J Appl Physiol Respir Environ Exerc Physiol. 1984;56(3):723-9.
23. Oberdörster G, Utell MJ, Weber DA, Ivanovich M, Hyde RW, Morrow PE. Lung clearance of inhaled 99mTc-DTPA in the dog. J Appl Physiol Respir Environ Exerc Physiol. 1984;57(2):589-95.
24. Finucane KE, Panizza JA, Singh B. Efficiency of the normal human diaphragm with hyperinflation. J Appl Physiol (1985). 2005;99(4):1402-11. http://dx.doi.org/10.1152/japplphysiol.01165.2004
25. Villar J. The use of positive end-expiratory pressure in the management of the acute respiratory distress syndrome. Minerva Anestesiol. 2005;71(6):265-72.
26. Suzuki Y, Kanazawa M, Fujishima S, Ishizaka A, Kubo A. Effect of external negative pressure on pulmonary 99mTc-DTPA clearance in humans. Am J Respir Crit Care Med. 1995;152(1):108-12. http://dx.doi.org/10.1164/ajrccm.152.1.7599807
27. Mason GR, Mena I, Maublant, J, Sietsma K, Effros RM. The effect of PEEP and posture on the clearance of inhaled small solutes from the lungs in normal subjects. Am Rev Respir Dis. 1984;129(4 Pt 2):A346.
28. Groth S. Pulmonary clearance of 99mTc-DTPA. An index of alveolar epithelial permeability. Dan Med Bull. 1991;38(3):189-203.
29. Ludwigs U, Philip A. Pulmonary epithelial permeability and gas exchange: a comparison of inverse ratio ventilation and conventional mechanical ventilation in oleic acid-induced lung injury in rabbits. Chest. 1998;113(2):459-66. http://dx.doi.org/10.1378/chest.113.2.459

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Pulmonary function in children and adolescents with sickle cell disease: have we paid proper attention to this problem?

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ABSTRACT

Objective: To evaluate pulmonary function and functional capacity in children and adolescents with sickle cell disease. **Methods:** This was a cross-sectional study involving 70 children and adolescents (8-15 years of age) with sickle cell disease who underwent pulmonary function tests (spirometry) and functional capacity testing (six-minute walk test). The results of the pulmonary function tests were compared with variables related to the severity of sickle cell disease and history of asthma and of acute chest syndrome. **Results:** Of the 64 patients who underwent spirometry, 15 (23.4%) showed abnormal results: restrictive lung disease, in 8 (12.5%); and obstructive lung disease, in 7 (10.9%). Of the 69 patients who underwent the six-minute walk test, 18 (26.1%) showed abnormal results regarding the six-minute walk distance as a percentage of the predicted value for age, and there was a ≥ 3% decrease in SpO_2 in 36 patients (52.2%). Abnormal pulmonary function was not significantly associated with any of the other variables studied, except for hypoxemia and restrictive lung disease. **Conclusions:** In this sample of children and adolescents with sickle cell disease, there was a significant prevalence of abnormal pulmonary function. The high prevalence of respiratory disorders suggests the need for a closer look at the lung function of this population, in childhood and thereafter.

Keywords: Anemia, sickle cell; Respiratory function tests; Exercise test.

INTRODUCTION

Sickle cell disease (SCD) is the most common monogenic disease in Brazil. The number of individuals with SCD in Brazil is estimated to range from 25,000 to 30,000.[1] The incidence of SCD in the state of Minas Gerais, Brazil, is approximately 1:1,400 live births, according to the Minas Gerais State Neonatal Screening Program.[2] The manifestations of this disease result from a predominance of sickle-shaped red blood cells, which leads to chronic hemolytic disease and vaso-occlusive phenomena.[2] SCD leads to multisystem impairment, with lung involvement being a major cause of morbidity and mortality.[3]

Some studies have been published on assessment of pulmonary function in adults with SCD, showing that the major abnormality is restrictive lung disease (RLD).[4,5] Since the 1970s, studies have been published on pulmonary function in the pediatric age group with SCD,[6] with conflicting results being reported; however, most studies show that obstructive lung disease (OLD) is the most common abnormality.[7,8] RLD is also common in some pediatric studies, highlighting the importance of pulmonary function testing in such children.[9,10]

Another important respiratory disease affecting children with SCD is asthma. Asthma is known to be a comorbidity impacting the course of SCD, leading to increased morbidity and mortality.[11,12] Several studies have reported an association between asthma and an increased number of vaso-occlusive crises or acute chest syndrome (ACS) episodes.[11-14] An association between asthma and pulmonary hypertension in children was described by Hagar et al., raising the suspicion of a shared mechanism, possibly associated with chronic hemolysis.[15]

The mortality associated with lung disease is a serious problem in the SCD population.[16,17] It has been demonstrated that abnormalities in pulmonary function tests are early objective signs of the development of chronic lung disease in SCD.[16] It has recently been published that decreased FEV_1 is associated with increased mortality in adults with SCD.[18] Nevertheless, few authors in Brazil have attempted to investigate pulmonary function in patients with SCD.[19-21] We hypothesize that the onset of pulmonary function abnormalities in SCD occurs as early as childhood. To address this challenge, the objective of the present study was to assess abnormalities in pulmonary function and functional capacity in children and adolescents with SCD, by means of spirometry and the six-minute walk test (6MWT), and to compare these abnormalities with clinical and laboratory variables in these patients.

METHODS

This was a descriptive analytical cross-sectional study. We included children and adolescents aged 8 to 15 years who were enrolled in the Minas Gerais State Neonatal

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Screening Program, in the city of Belo Horizonte, Brazil, had a confirmed diagnosis of SCD at age 1 year, and were followed in the program between February of 2013 and February of 2014. We included patients with SS phenotype or $S\beta^0$-thalassemia—because they are known to have a more severe clinical course—who resided in the city of Belo Horizonte. We excluded patients who were unable to perform the respiratory maneuvers or the 6MWT because of cognitive or physical disability. We also excluded patients who had a severe comorbidity, such as chronic inflammatory diseases, hematological disorders, or neurological disorders.

Data were collected by interview, physical examination, and medical chart review. The interview was conducted using a semi-structured data collection protocol. The physical examination consisted of measurement of vital signs and measurement of weight and height. The medical chart review consisted of identifying clinical and laboratory data relevant to the study. Baseline hemoglobin values and leukocyte and reticulocyte counts were obtained from the arithmetic mean of three complete blood counts before hydroxyurea therapy or blood transfusions.

Medical charts were reviewed for ACS, using the following definition: development of a new pulmonary infiltrate involving at least one lung segment, accompanied by at least another symptom, such as fever, chest pain, tachypnea, wheezing, cough, or hypoxemia.[22] The presence of a history of asthma was based on a physician diagnosis recorded in the chart and on clinical and functional criteria established by the Global Initiative for Asthma.[23]

Spirometry and the 6MWT were performed in the outpatient clinic of a SCD referral center by the same qualified pulmonary function technician. The results were interpreted by pediatric pulmonologists and reviewed by a pulmonologist specializing in pulmonary function.

Spirometry was performed with a Koko PFT spirometer (PDS Instrumentation, Inc., Louisville, CO, USA), with the patient seated and wearing a nose clip. All subjects underwent bronchodilator testing (400 µg of albuterol aerosol), and a positive result was defined as a ≥ 12% increase in FEV_1 or a > 200 mL increase in absolute volume.[24] At least three curves were obtained. FVC, FEV_1, and $FEF_{25-75\%}$ values were derived from these curves and corrected for body temperature, pressure saturated. Tests were interpreted in accordance with the Brazilian Thoracic Association (2002) Guidelines for Pulmonary Function Testing.[25] Test results were expressed as absolute values and as a percentage of predicted according to Mallozzi.[26] The spirometry findings were classified as normal, RLD, OLD, or nonspecific lung disease.[24,25] PEF was measured with a Mini-Wright meter (Clement Clarke International, Essex, UK). The best of three consecutive readings was selected for analysis, using reference values provided by Polgar and Promadhat.[27] There was an interval of at least two weeks between hospital admission or blood transfusion and the test.

The 6MWT was performed in accordance with the American Thoracic Society guidelines.[28] A wrist oximeter (Wrist 3100; Nonin Medical, Plymouth, MN, USA) and a stopwatch were used. The patient was instructed to walk as fast as possible for six minutes. The walks were supervised by the physician responsible for the study. SpO_2 was measured before, during, and immediately after the walk, with care being taken to provide a minimum one-minute interval for the oximeter curve to stabilize. The distance walked in six minutes—six-minute walk distance (6MWD)—was measured in meters. Two tests were performed within 30 minutes, and when there were conflicting results between the tests, a third test was performed. A normal result was defined as a 6MWD > 80% of predicted for age, a moderate result was defined as a 6MWD between 60% and 80% of predicted, and a severe result was defined as a 6MWD < 60% of predicted.[29] A significant decrease in SpO_2 (desaturation) was defined as that ≥ 3% relative to baseline.[30]

Percent predicted 6MWD was calculated following the equation proposed by Priesnitz et al.[31] Because of the lack of studies in Brazil investigating 6MWD reference values in adolescents, the equation proposed by Priesnitz et al.[31] was also used for the patients aged 13 to 15 years.

The study population was characterized with descriptive statistics. Variables were compared with the chi-square test and Fisher's exact test. The Student's t-test was used to compare independent groups. Continuous variables were tested for normality with the Shapiro-Wilk test and/or the Kolmogorov-Smirnov test. The three spirometry-based groups were compared with ANOVA and the Kruskal-Wallis test. The level of statistical significance was set at $p < 0.05$. The sample size calculation was based on the prevalence of abnormal spirometry (37%) reported in a study conducted in Brazil.[19] Therefore, for the sample size of our study (70 cases), the margin of estimation error is 6.3% within a 95% CI. A multivariate logistic regression analysis was performed to determine the factors associated with the outcome measure "oxygen desaturation". The baseline variables were used to build the final model. Given that the initial model included non-significant variables, it had to be reduced to test the significance of the remaining variables, that is, we sequentially removed the variable with the highest p value until we reached a final model with statistically significant variables.

The project was carried out under the auspices of the Graduate Program in Child and Adolescent Health of the Federal University of Minas Gerais School of Medicine. The study was approved by the Research Ethics Committees of the Hemominas Foundation and the Federal University of Minas Gerais—the collaborative institutions involved in the study—under protocol no. CAE-08480212.6.0000.5149. The legal guardians of all participants provided written informed consent. All patients over 13 years of age provided written

informed consent using forms written in language appropriate for their age.

RESULTS

We aimed to recruit 100 patients with SCD by contacting their families over the phone or via a primary health care clinic and inviting these families to participate. Of the targeted 100 patients, 2 had died and 1 had a disabling comorbidity. In addition, 9 families were not located and 18 declined to participate. The sample therefore consisted of 70 patients, of whom 31 (44.3%) were male and 39 (55.7%) were female. The mean age was 11 ± 2.3 years (range, 8-15 years). Sixty-six individuals had the SS homozygous phenotype, whereas 4 had $S\beta^0$-thalassemia. Concomitant α-thalassemia trait was found in 29.1% of the participants.

Thirty-nine patients (55.7%) were being treated with hydroxyurea, and 10 (14.3%) were on a chronic transfusion regimen. Comorbid asthma was identified in 23 patients (33.3%). In the univariate analysis, a diagnosis of asthma was not associated with the number of vaso-occlusive crises or ACS episodes. Forty-four patients (63.1%) had at least one ACS episode, and, of those, 10 (23.1%) experienced two or more episodes.

The descriptive statistics for the spirometric and 6MWT variables are presented in Table 1. Spirometry was completed successfully in 64 of the 70 patients included. Two patients were unable to perform the maneuvers, and 4 did not undergo spirometry because of problems with scheduling. However, these 4 were not excluded, because they underwent the 6MWT. Of the patients who underwent spirometry, 15 (23.4%) had abnormal pulmonary function tests. No patient was classified as having mixed obstructive-restrictive lung disease or nonspecific lung disease. The spirometry results are presented in Table 2.

The results of the univariate analysis comparing the spirometry reports with intervening variables are presented in Table 2. The patients reported as having OLD were older than were those reported as having normal spirometry results or RLD. The group of patients classified as having RLD showed lower baseline pulse oxygen saturation (89.8% ± 5.4%) than did the group of patients with OLD and the group of patients with normal spirometric results (92.3% ± 4.6% and 94.5% ± 4.4%, respectively; p = 0.02).

The 6MWT was administered to 69 patients, and 1 patient, who had undergone spirometry, declined to undergo the test. The results are presented in Table 2. The baseline SpO_2 values reveal that hypoxemia was common in this population: 37 (52.9%) had values < 95%, with a mean of 93.6%. Eighteen patients (26.1%) had a 6MWD < 80% of predicted for their age, and only 1 patient had a 6MWD < 60%. There was a ≥ 3% decrease in SpO_2 in 36 patients (52.2%). Univariate analysis showed that a history of ACS was the only variable of interest that had a statistically significant association with oxygen desaturation, there being an inverse association between the number of ACS episodes and the level of oxygen desaturation (< 3% vs. ≥ 3%), as shown in Table 3. The median (interquartile range) for ACS was 1.0 (0.0-3.0) for the group of patients with desaturation < 3% and 1.0 (0.0-2.0) for the group of patients with desaturation ≥ 3%.

In the univariate analysis, none of the variables of interest were found to have a statistically significant association with 6MWD as a percentage of predicted (Table 3). In contrast, age and hypertransfusion were found to have significant associations with absolute values of 6MWD (Table 3).

The multivariate analysis of possible predictors of oxygen desaturation is presented in Table 4. An interesting observation is that, as in the univariate analysis, a history of ACS was found to be a protective factor against oxygen desaturation during the 6MWT (p < 0.05). According to the measures of accuracy of the logistic regression model, the sensitivity and specificity were 48.4% and 59.0%, respectively.

Table 1. Patient descriptive statistics for the spirometric and six-minute walk test variables.

Variable	Minimum	Maximum	Median	Mean ± SD
PEF, % of predicted	50.0	106.3	81.0	79.4 ±13.9
FVC, % of predicted	63.0	115.0	85.0	85.0 ± 10.6
FEV_1, % of predicted	57.0	117.0	78.5	78.7 ± 10.7
FEV_1/FVC ratio	84.0	112.0	0.86	0.86 ± 0.05
$FEF_{25-75\%}$	43.0	125.0	72.0	76.0 ± 17.6
Baseline SaO_2, %	78.0	99.0	94.0	93.6 ± 4.8
Final SaO_2, %	72.0	99.0	91.0	89.3 ± 7.6
Desaturation, %	−3.0	−26.0	−2.0	−4.6 ± 6.3
6MWD, m	380	640	520.0	527.3 ± 51.4
6MWD, % of predicted	56.4	114.8	85.1	84.9 ± 8.3
Baseline HR, bpm	60.0	120	87.0	87.9 ± 13.7
Final HR, bpm	91.0	175.0	131.0	132.4 ± 18.8
Baseline RR, breaths/min	12.0	28.0	16.0	18.0 ± 3.4
Final RR, breaths/min	20.0	36.0	28.0	27.7 ± 3.6

6MWD: six-minute walk distance; HR: heart rate; and RR: respiratory rate.

Table 2. Comparative statistics across three spirometry-based patient groups (N = 64) for the variables of interest.[a]

Variables	Groups			p*
	Normal (n = 49)	RLD (n = 8)	OLD (n = 7)	
Age, years	11.0 ± 2.3	11.9 ± 1.7	13.3 ± 1.5	0.045
Gender, %				
Male	44.9	25.0	71.4	0.241**
Female	55.1	75.0	28.6	
Baseline hemoglobin, g/dL	8.1 ± 1.2	7.4 ± 0.5	8.0 ± 0.5	0.151
Fetal hemoglobin, %	11.2 ± 8.4	11.7 ± 9.8	12.1 ± 6.7	0.875
Baseline leukocytes/μL	14.542 ± 2.988	14.222 ± 2.680	14.269 ± 4.931	0.979
Reticulocytes, %	14.6 ± 5.6	13.6 ± 3.9	14.9 ± 6.6	0.604
SaO_2, %	94.5 ± 4.6	89.8 ± 5.4	92.3 ± 4.4	0.020
ACS episodes	1.7 ± 2.1	1.4 ± 1.5	0.4 ± 0.5	0.245
Asthma, %	28.6	37.5	57.1	0.274**
Hydroxyurea therapy, %	55.1	28.6	57.1	0.457**
Hypertransfusion, %	16.3	0.0	16.7	0.667**
α-thalassemia trait, %	30.8	0.0	28.6	0.638**
Desaturation, %				
< 3	45.8	50.0	28.6	0.693**
≥ 3	54.2	50.0	71.4	
6MWD, % of predicted	84.1 ± 7.4	84.5 ± 11.1	86 ± 9.3	0.879**

RLD: restrictive lung disease; OLD: obstructive lung disease; ACS: acute chest syndrome; and 6MWD: six-minute walk distance. [a]Values expressed as mean ± SD, except where otherwise indicated. *Kruskal-Wallis test, except where otherwise indicated. **Fisher's exact test.

DISCUSSION

The present study showed that pulmonary function, as measured by spirometry, was abnormal in approximately one fourth of the patients with SCD, the most common abnormality being RLD. A high rate of desaturation during the 6MWT was found, which was not associated with 6MWD or with spirometry-assessed pulmonary function.

A history of asthma was present in one third of the patients, which is double the prevalence observed in the population of children and adolescents in the city of Belo Horizonte (17.8%), according to the International Study of Asthma and Allergies in Childhood.[32] A similar prevalence was found in a retrospective cohort study conducted by Williams et al.,[33] who demonstrated that 35.9% of the patients had a diagnosis of asthma and that a decline in FEV_1 as a percentage of predicted is associated with progression to pulmonary dysfunction. These findings underscore the need for the recognition of asthma, as well as the importance of longitudinal follow-up of pulmonary function, in this population.

Lung disease patterns in SCD are heterogeneous and can change over time. In the present study, 11% of the patients were found to have OLD; of those, 57% had a clinical diagnosis of asthma. Similarly, in a cohort of patients studied by Boyd et al.[12] 13% were found to have OLD, and of those 13%, 77% had a diagnosis of asthma; in addition, an association was found between OLD and increased rates of hospitalization for pain or ACS. Another important study showed that 63% of the patients with asthma had normal spirometry results and that only 40% of the patients classified as having OLD had a history of asthma.[34] These findings indicate that there may be several inflammatory mechanisms involved in the genesis of airway obstruction in SCD. The prevalence of OLD (12.5%) found in the present study was also similar to those found in other studies, such as the ones conducted by Boyd et al. and by Tassel et al., both of which reported a prevalence of 13%.[12,35]

One of the limitations of the present study is the lack of whole-body plethysmographic confirmation of RLD. Longitudinal studies have shown that there is a decline in lung volume and pulmonary function over the years in children with SCD; however, the pathophysiology of respiratory disorders in childhood has not been fully elucidated.[9,35] This decline was reported in a cohort study by Lunt et al.,[36] who demonstrated that a history of ACS episodes was the only independent factor associated with reduced lung volumes. Some biological markers, such as leukocytosis, are known to be associated with SCD severity, but their relationship with pulmonary function has only recently been the subject of investigation.[37] A study by Tassel et al.[35] showed that the decline in pulmonary function in childhood was directly associated with two markers of severity of the underlying disease: leukocytosis and hemolysis. In the present study, an association was noted between baseline hypoxemia and RLD, indicating that this group of patients may tend to experience greater disease severity, given that baseline hypoxemia is associated with the degree of anemia and of hemolysis.[30]

The 6MWT has grown in importance in the follow-up of SCD because studies in adults show a relationship between 6MWD and tricuspid regurgitant jet velocity, which is used to estimate pulmonary artery systolic pressure on echocardiography. This finding suggests

Table 3. Comparative statistics (N = 69 patients) between the outcome measures (oxygen desaturation and six-minute walk distance) and the variables of interest.*

Variable	Desaturation, %		p	6MWD	
	< 3 (n = 33)	≥ 3 (n = 36)		% of predicted	Absolute value, m
Age, years	11.6 ± 2.4	11.0 ± 2.3	0.345	r = −0.15† p = 0.224	r = 0.38† p = 0.001
Gender, %	43.8	47.2	0.774*		
Male	56.3	52.8		85.4 ± 8.0	525.2 ± 54.4
Female				83.8 ± 8.6	518.9 ± 48.9
				p = 0.434	p = 0.623
Baseline hemoglobin, g/dL	7.9 ± 1.1	8.1 ± 1.1	0.378	r = −0.17† p = 0.167	r = −0.15† p = 0.249
Fetal hemoglobin, %	10.1 ± 8.7	13.0 ± 8.1	0.194	r = 0.08† p = 0.544	r = −0.02† p = 0.878
Baseline SaO_2, %	93.6 ± 5.0	93.6 ± 4.7	0.983	r = −0.10† p = 0.429	r = −0.23† p = 0.057
ACS episodes	2.1 ± 2.5	0.9 ± 0.9	0.024	r = −0.11† p = 0.389	r = 0.15† p = 0.229
Asthma, %			0.386**		
Yes	40.6	30.6		82.7 ± 9.0	528.3 ± 55.3
No	59.4	69.4		85.5 ± 7.8	518.2 ± 49.1
				p = 0.210	p = 0.456
Hydroxyurea therapy, %	64.5	44.4	0.100**		
Yes	35.5	55.6		84.9 ± 9.3	519.2 ± 51.6
No				84.4 ± 7.0	525.5 ± 52.0
				p = 0.781	p = 0.619
Hypertransfusion, %	9.7	17.1	0.484***		
Yes	90.3	82.9		80.5 ± 11.9	480.0 ± 56.6
No				85.4 ± 7.6	528.3 ± 48.4
				p = 0.266	p = 0.036
α-thalassemia trait, %	39.1	23.3	0.214**		
Yes	60.9	76.7		86.5 ± 5.7	530.0 ± 37.2
No				84.3 ± 8.0	520.0 ± 55.8
				p = 0.253	p = 0.455
6MWD, % of predicted	84.6 ± 9.3	85.0 ± 7.7	0.849		

ACS: acute chest syndrome; and 6MWD: six-minute walk distance. *Student's t-test for independent samples, except where otherwise indicated. **Chi-square test. ***Fisher's exact test. †Pearson's correlation coefficient for continuous variables (r value) and its respective p value.

Table 4. Multivariate logistic regression analysis for identification of factors associated with six-minute walk test desaturation (≥ 3%).

Variable	β	(Wald) chi-square	p
Initial model			
Intercept	−1.116	0.157	0.692
Gender	0.213	0.134	0.715
Baseline hemoglobin	0.183	0.355	0.551
SaO_2	0.170	0.058	0.810
Asthma	−0.158	0.065	0.799
Hydroxyurea therapy	0.085	0.016	0.901
Acute chest syndrome	−0.309	2.024	0.155
6MWD, % of predicted	0.003	< 0.001	0.996
Final model			
Intercept	0.570	2.642	0.104
Acute chest syndrome	−0.393	4.207	0.040

6MWD: six-minute walk distance.

that the 6MWT can be used as a noninvasive measure of severity of pulmonary hypertension and functional capacity in this population.[38] Studies in the pediatric population remain scarce. An important study of children and adolescents carried out by Minniti et al. observed that elevated tricuspid regurgitant jet velocity was associated with a decline in SpO_2 during the 6MWT but not with a shorter 6MWD, as occurs

in adults.[39] In addition, a study conducted by Waltz et al. reported a decline in SpO_2 during the 6MWT in patients with HbSS genotype (in 34%) and in patients with HbSC (in 18%).[40]

The 6MWD as a percentage of predicted for age was below normal in 26.1% of the patients; however, severe impairment was found in only 1 patient. A similar result was reported by Dedeken et al.,[29] who found that 30% of a sample of 46 children and adolescents had abnormal 6MWT. The role of the 6MWT in children and adolescents with SCD has yet to be fully determined; however, it seems that > 3% desaturation during the 6MWT may serve as an early marker of development of pulmonary hypertension in this population.[30]

In the present study, 52% of the patients had a significant decrease in post-6MWT pulse SpO_2, a prevalence that is higher than that reported in other studies, such as the ones by Waltz et al.[40] (34%) and by Campbell et al.[30] (8%), the latter of which involved patients with other phenotypes (SC, SD, and others). This difference needs to be confirmed in other studies in Brazil, because the present study is the first of its kind in the country and shows the importance of functional assessment in this population.

In the logistic regression analysis, a history of ACS was surprisingly found to be a protective factor against oxygen desaturation during the 6MWT. This is likely a reflection of further treatment intensification in the patients who experienced ACS, including hydroxyurea therapy and/or chronic transfusion. This finding was also reported in a study that sought to understand the differences between adults and children with pulmonary hypertension.[15] That study demonstrated that a history of ACS was a protective factor against pulmonary hypertension in the adult population.[15] In the present study, the low sensitivity and specificity of the multivariate analysis model do not allow the elucidation of this complex pathophysiological process, and it is possible that clinical variables other than the ones we measured are associated.

As far as limitations of this study are concerned, we acknowledge that it was conducted in a single blood bank and was cross-sectional and that important tests, such as echocardiography and whole-body plethysmography were not performed, because they were not part of the research protocol. Therefore, further longitudinal studies with a large number of centers are warranted to verify the results obtained here and to determine which clinical and laboratory variables in SCD are of importance in clinical practice, because, in the literature, there is a lack of data on the factors actually influencing the development of lung function impairment.

Finally, the present study showed a relevant prevalence of abnormal pulmonary function and of significantly decreased SpO_2 during the 6MWT in a sample of patients aged 8 to 15 years, indicating the early onset of chronic lung disease in SCD. The common finding of obstructive and of restrictive pulmonary function abnormalities in this population underscores the need for a closer look at lung function, with the aid of objective measures, such as spirometry, in childhood and thereafter, in order to screen for chronic lung disease.

In summary, the data presented here, indicating that the prevalence of pulmonary function abnormalities in patients with SCD may be higher in Brazil, emphasize how important it is that studies of lung function in this population be conducted in the country. This subject must be researched extensively and thoroughly, including incorporating other methods of assessment, such as whole-body plethysmography and echocardiography, and is a large field of research yet to be explored in Brazil.

REFERENCES

1. Cançado RD, Jesus JA. Sickle cell disease in Brazil [Article in Portuguese]. Rev Bras Hematol Hemoter. 2007;29(3):204-6.
2. Fernandes AP, Januário JN, Cangussu CB, Macedo DL, Viana MN. Mortality of children with sickle cell disease: a population study. J Pediatr (Rio J). 2010;86(4):279-84. http://dx.doi.org/10.2223/jped.2005
3. Darbari DS, Kple-Faget P, Kwagyan J, Rana S, Gordeuk VR, Castro O. Circumstances of death in adult sickle cell disease patients. Am J Hematol. 2006;81(11):858-63. http://dx.doi.org/10.1002/ajh.20685
4. Klings ES, Wyszynski DF, Nolan VG, Steinberg MH. Abnormal pulmonary function in adults with sickle cell anemia. Am J Resp Crit Care Med. 2006;173(11):1264-9. http://dx.doi.org/10.1164/rccm.200601-125OC
5. Young RC Jr, Rachal RE, Reindorf CA, Armstrong EM, Polk OD Jr, Hackney RL Jr, et al. Lung function in sickle cell hemoglobinopathy patients compared with healthy subjects. J Nat Med Assoc. 1988;80(5):509-14.
6. Wall MA, Platt OS, Strieder DJ. Lung function in children with sickle cell anemia. Am Rev Respir Dis. 1979;120(1):210-4.
7. Koumbourlis AC, Hurlet-Jensen A, Bye MR. Lung function in infants with sickle cell disease. Pediatr Pulmonol. 1997;24(4):277-81. http://dx.doi.org/10.1002/(SICI)1099-0496(199710)24:4<277::AID-PPUL6>3.0.CO;2-H
8. Santoli F, Zerah F, Vasile N, Bachir D, Galacteros F, Atlan G. Pulmonary function in sickle cell disease with or without acute chest syndrome. Eur Resp J. 1998;12(5):1124-9. http://dx.doi.org/10.1183/09031936.98.12051124
9. Boyd JH, DeBaun MR, Morgan WJ, Mao J, Strunk RC. Lower airway obstruction is associated with increased morbidity in children with sickle cell disease. Pediatr Pulmonol. 2009;44(3):290-6. http://dx.doi.org/10.1002/ppul.20998
10. MacLean JE, Atenafu E, Kirby-Allen M, MacLusky IB, Stephens D, Grasemann H, et al. Longitudinal decline in lung volume in a population of children with sickle cell disease. Am J Resp Crit Care Med. 2008;178(10):1055-9. http://dx.doi.org/10.1164/rccm.200708-1219OC
11. Boyd JH, Macklin EA, Strunk RC, DeBaun MR. Asthma is associated with acute chest syndrome and pain in children with sickle cell anemia. Blood. 2006;108(9):2923-7. http://dx.doi.org/10.1182/blood-2006-01-011072
12. Boyd JH, Macklin EA, Strunk RC, DeBaun MR. Asthma is associated with increased mortality in individuals with sickle cell anemia. Haematologica. 2007;92(8):1115-8. http://dx.doi.org/10.3324/haematol.11213
13. Bernaudin F, Strunk RC, Kamdem A, Arnaud C, An P, Torres M, et al. Asthma is associated with acute chest syndrome, but not with an increased rate of hospitalization for pain among children in France with sickle cell anemia: a retrospective cohort study. Haematologica. 2008;93(12):1917-8. http://dx.doi.org/10.3324/haematol.13090
14. Glassberg J, Spivey JF, Strunk R, Boslaugh S, DeBaun MR.

Painful episodes in children with sickle cell disease and asthma are temporally associated with respiratory symptoms. J Pediatr Hematol Oncol. 2006;28(8):481-5. http://dx.doi.org/10.1097/01.mph.0000212968.98501.2b

15. Hagar RW, Michlitsch JG, Gardner J, Vichinsky, EP, Morris CR. Clinical differences between children and adults with pulmonary hypertension and sickle cell disease. Br J Haematol. 2008;140(1):104-12.
16. Hamideh D, Alvarez O. Sickle cell disease related mortality in the United States (1999-2009). Pediatr Blood Cancer. 2013;60(9):1482-6. http://dx.doi.org/10.1002/pbc.24557
17. Powars D, Weidman JA, Odom-Maryon T, Niland JC, Johnson C. Sickle cell chronic lung disease: prior morbidity and the risk of pulmonary failure. Medicine (Baltimore). 1988;67(1):66-76. http://dx.doi.org/10.1097/00005792-198801000-00005
18. Low forced expiratory volume is associated with earlier death in sickle cell anemia. Blood. 2015;126(13):1544-50. http://dx.doi.org/10.1182/blood-2015-05-644435
19. Souza LC, Viegas CA. Quality of sleep and pulmonary function in clinically stable adolescents with sickle cell anemia. J Bras Pneumol. 2007;33(3):275-81. http://dx.doi.org/10.1590/S1806-37132007000300008
20. Fonseca CS, Araújo-Melo CA, Carvalho RM, Barreto-Neto J, Araújo JG, Cipolotti R. Lung function in patients with sickle cell anemia. Rev Paul Pediatr. 2011;29(1):85-90. http://dx.doi.org/10.1590/S0103-05822011000100014
21. Ohara DG, Ruas G, Walsh IA, Castro SS, Jamami M. Lung function and six-minute walk test performance in individuals with sickle cell disease. Braz J Phys Ther. 2014;18(1):79-87. http://dx.doi.org/10.1590/S1413-35552012005000139
22. Castro O, Brambilla DJ, Thorington B, Reindorf CA, Scott RB, Gillette P, et al. The acute chest syndrome in sickle cell disease: incidence and risk factors. The Cooperative Study of Sickle Cell Disease. Blood. 1994;84(2):643-9.
23. Global Initiative for Asthma [homepage on the Internet]. Bethesda: Global Initiative for Asthma. [cited 2016 Feb 01]. Global Strategy for Asthma Management and Prevention 2012. [Adobe Acrobat document, 128p.]. Available from: http://www.ginasthma.org/local/uploads/files/GINA_Report_March13.pdf
24. Lung function testing: selection of reference values and interpretative strategies. American Thoracic Society. Am Rev Respir Dis. 1991;144(5):1202-18. http://dx.doi.org/10.1164/ajrccm/144.5.1202
25. Sociedade Brasileira de Pneumologia e Tisiologia. Diretrizes para testes de função pulmonar. J Pneumol. 2002;28(Suppl 3):S1-S238.
26. Mallozi MC. Valores de referência para espirometria em crianças e adolescentes, calculados a partir de uma amostra da cidade de São Paulo [thesis]. São Paulo: Escola Paulista de Medicina/Universidade Federal de São Paulo; 1995.
27. Polgar G, Promadhat V. Pulmonary function testing in children: techniques and standards. Philadelphia: WB Saunders; 1971.
28. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. Am J Resp Crit Care Med. 2002;166(1):111-7. http://dx.doi.org/10.1164/ajrccm.166.1.at1102
29. Dedeken L, Chapusette R, Lê PQ, Heijmans C, Devalck C, Huybrechts S, et al. Reduction of the six-minute walk distance in children with sickle cell disease is correlated with silent infarct: results from a cross-sectional evaluation in a single center in Belgium. PloS One. 2014; 9(9):e108922. http://dx.doi.org/10.1371/journal.pone.0108922
30. Campbell A, Minniti CP, Nouraie M, Arteta M, Rana S, Onyekwere O, et al. Prospective evaluation of haemoglobin oxygen saturation at rest and after exercise in paediatric sickle cell disease patients. Br J Haematol. 2009;147(3):352-9. http://dx.doi.org/10.1111/j.1365-2141.2009.07854.x
31. Priesnitz CV, Rodrigues GH, Stumpf Cda S, Viapiana G, Cabral CP, Stein RT, et al. Reference values for the 6-min walk test in healthy children aged 6-12 years. Pediatric Pulmonol. 2009; 44(12):1174-9. http://dx.doi.org/10.1002/ppul.21062
32. Solé D, Wandalsen GF, Camelo-Nunes IC, Naspitz CK. Prevalence of symptoms of asthma, rhinitis, and atopic eczema among Brazilian children and adolescents identified by the International Study of Asthma and Allergies in Childhood (ISAAC) - Phase 3. J Pediatr (Rio J). 2006;82(5): 341-6. http://dx.doi.org/10.1590/S0021-75572006000600006
33. Williams SN, Nussbaum E, Yoonessi L, Morphew T, Randhawa I. Progression and prognostic indicators of bronchial disease in children with sickle cell disease. Lung. 2014;192(3):385-93. http://dx.doi.org/10.1007/s00408-014-9572-y
34. Koumbourlis AC, Lee DJ, Lee A. Longitudinal changes in lung function and somatic growth in children with sickle cell disease. Pediatric Pulmonol. 2007;42(6):483-8. http://dx.doi.org/10.1002/ppul.20601
35. Tassel C, Arnaud C, Kulpa M, Fleurence E, Kandem A, Madhi F, et al. Leukocytosis is a risk factor for lung function deterioration in children with sickle cell disease. Respir Med. 2011;105(5):788-95. http://dx.doi.org/10.1016/j.rmed.2010.12.024
36. Lunt A, McGhee E, Sylvester K, Rafferty G, Dick M, Rees D, et al. Longitudinal assessment of lung function in children with sickle cell disease. Pediatr Pulmonol. 2016;51(7):717-23. http://dx.doi.org/10.1002/ppul.23367
37. Okpala I. Leukocyte adhesion and the pathophysiology of sickle cell disease. Curr Opin Hematol. 2006;13(1):40-4. http://dx.doi.org/10.1097/01.moh.0000190108.62414.06
38. Anthi A, Machado RF, Jison ML, Taveira-Dasilva AM, Rubin LJ, Hunter L, et al. Hemodynamic and functional assessment of patients with sickle cell disease and pulmonary hypertension. Am J Resp Crit Care Med. 2007;175(12):1272-9. http://dx.doi.org/10.1164/rccm.200610-1498OC
39. Minniti CP, Sable C, Campbell A, Rana S, Ensing G, Dham N, et al. Elevated tricuspid regurgitant jet velocity in children and adolescents with sickle cell disease: association with hemolysis and hemoglobin oxygen desaturation. Haematologica. 2009;94(3):340-7. http://dx.doi.org/10.3324/haematol.13812
40. Waltz X, Romana M, Lalanne-Mistrih ML, Machado RF, Lamarre Y, Tarer V, et al. Hematologic and hemorheological determinants of resting and exercise-induced hemoglobin oxygen desaturation in children with sickle cell disease. Haematologica. 2013;98(7):1039-44. http://dx.doi.org/10.3324/haematol.2013.083576

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Temporal analysis of reported cases of tuberculosis and of tuberculosis-HIV co-infection in Brazil between 2002 and 2012

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ABSTRACT

Objective: To investigate the reported cases of tuberculosis and of tuberculosis-HIV co-infection in Brazil between 2002 and 2012. **Methods:** This was an observational study based on secondary time series data collected from the Brazilian Case Registry Database for the 2002-2012 period. The incidence of tuberculosis was stratified by gender, age group, geographical region, and outcome, as was that of tuberculosis-HIV co-infection. **Results:** Nationally, the incidence of tuberculosis declined by 18%, whereas that of tuberculosis-HIV co-infection increased by 3.8%. There was an overall decrease in the incidence of tuberculosis, despite a significant increase in that of tuberculosis-HIV co-infection in women. The incidence of tuberculosis decreased only in the 0- to 9-year age bracket, remaining stable or increasing in the other age groups. The incidence of tuberculosis-HIV co-infection increased by 209% in the ≥ 60-year age bracket. The incidence of tuberculosis decreased in all geographical regions except the south, whereas that of tuberculosis-HIV co-infection increased by over 150% in the north and northeast. Regarding the outcomes, patients with tuberculosis-HIV co-infection, in comparison with patients infected with tuberculosis only, had a 48% lower chance of cure, a 50% greater risk of treatment nonadherence, and a 94% greater risk of death from tuberculosis. **Conclusions:** Our study shows that tuberculosis continues to be a relevant public health issue in Brazil, because the goals for the control and cure of the disease have yet to be achieved. In addition, the sharp increase in the incidence of tuberculosis-HIV co-infection in women, in the elderly, and in the northern/northeastern region reveals that the population of HIV-infected individuals is rapidly becoming more female, older, and more impoverished.

Keywords: Tuberculosis/epidemiology; HIV infections/epidemiology; Comorbidity.

INTRODUCTION

Tuberculosis is an infectious disease caused by *Mycobacterium tuberculosis* and continues to be a prevalent communicable disease in underdeveloped countries. Although there is treatment and means of prevention, approximately 9 million new cases are reported annually worldwide. Brazil is one of the 22 countries that collectively account for 80% of the global tuberculosis burden, with approximately 4,500 deaths from tuberculosis each year. In 2009 alone, 72,000 new cases were reported, which corresponds to an incidence rate of 38/100,000 population.[1] These data demonstrate the severity of the tuberculosis problem in Brazil.

M. tuberculosis is transmitted by exhalation of infectious droplets, and its infectivity is directly related to the immune status of contacts.[2] Chief among the factors contributing to the transmission and manifestation of tuberculosis are conurbations, poor sanitary conditions, limited access to health care, inadequate nutrition, and presence of other diseases, such as alcoholism, diabetes, and, in particular, HIV infection.[1] Therefore, socioeconomically disadvantaged populations are at increased risk of contracting tuberculosis.

In the 1980s, with the advent of AIDS in the world, the tuberculosis problem worsened again. The presence of HIV resulted in tuberculosis changing from an endemic to an epidemic disease. The rate of tuberculosis-HIV co-infection has increased, and tuberculosis-HIV co-infection has been changing the epidemiological and prognostic aspects of tuberculosis.[1,3,4] The mortality rate from tuberculosis increases by 2.4- to 19-fold in patients with tuberculosis-HIV co-infection, in comparison with HIV-negative patients.[5] In addition, an analysis on the relationship between tuberculosis and HIV in Brazil, performed by Jamal et al.,[6] pointed out that the risk of developing tuberculosis is 10% per year for HIV-positive individuals, whereas, for HIV-negative patients, that risk is 10% over the course of their lifetime.

On the basis of clinical and epidemiological data, the World Health Organization (WHO), in 1993, designated tuberculosis as a priority in health policies. In Brazil, three years earlier, the *Ministério da Saúde* (MS, National Ministry of Health) had launched the *Plano Emergencial*

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para o Controle da Tuberculose (Emergency Plan for Tuberculosis Control), in which the implementation of a supervised treatment—a groundbreaking treatment worldwide—was recommended.[7] In 2003, the Brazilian MS declared tuberculosis to be one of the five diseases that are a priority for control in Brazil, including it in various action plans, such as *Pacto pela Vida* (Pact for Life), *Mais Saúde* (More Health), and *Programação das Ações de Vigilância em Saúde* (Programming of Health Surveillance Actions), and bringing information and efforts together in the *Programa Nacional de Controle da Tuberculose* (PNCT, Brazilian National Tuberculosis Control Program). Among the main objectives of the PNCT are the established goal of achieving a cure rate of 85% and an incidence rate below 25.6 cases/100,000 population by 2015, as well as the decrease in the rate of treatment nonadherence and the prevention of the emergence of resistant bacilli, so as to thus enable effective control of tuberculosis in Brazil.[8,9]

In view of the epidemiological importance of tuberculosis and the lack of recent analyses of data collected from the *Sistema de Informação de Agravos de Notificação* (SINAN, Brazilian Case Registry Database), it is essential that the tuberculosis problem in Brazil and its relationship with HIV be studied. Such studies will provide a basis for the development of new guidelines. Therefore, the present study investigated, through data obtained from SINAN for the 2002-2012 period, the evolution of tuberculosis and of tuberculosis-HIV co-infection in Brazil for different clinical and epidemiological variables.

METHODS

This was an observational study based on secondary time series data collected directly from SINAN, through the national database of the Brazilian Unified Health Care System, for the 2002-2012 period. The dependent variable was the incidence rate of tuberculosis and that of tuberculosis-HIV co-infection over the analysis period, calculated as the number of new cases reported or recorded as "does not know" per year of diagnosis, as recommended by SINAN, divided by the number of inhabitants in the same period per region of residence, using the 100,000 constant. The number of inhabitants per region was obtained from census data (2000 and 2010) and inter-census population estimates, all of which were provided by the *Instituto Brasileiro de Geografia e Estatística* (Brazilian Institute of Geography and Statistics). Only patients who were reported as HIV-positive were considered to have HIV infection. The independent variables collected included gender (male and female); age group (0-9, 10-19, 20-39, 40-59, and ≥ 60 years); outcome (cure, nonadherence, death from tuberculosis, and multidrug-resistant tuberculosis); and geographical region of residence (north, northeast, southeast, south, and central-west).

The data were summarized as incidence rates, measures of central tendency, measures of growth, and proportions. The data were tabulated into a Microsoft Excel 2010 spreadsheet and subsequently analyzed using the Graphpad Prism statistical software program, version 5.0 (GraphPad Inc., San Diego, CA, USA). Prais-Winsten generalized linear regression was used to analyze growth trends in the time series. This procedure made it possible to determine whether the variations were upward, downward, or stable, by analyzing the measures of growth and the significance level ($p < 0.05$). Total variation was calculated as the difference in proportion between the incidence in 2002 and the incidence in 2012. In addition, categorical variables were tested for associations by using odds ratios and the chi-square test. For all tests, the significance level was set at 95%.

RESULTS

Table 1 shows the data obtained from SINAN regarding the crude and relative incidence of tuberculosis and of tuberculosis-HIV co-infection, as well as the ratio between the two incidences. Over the study period, there was a decrease in the incidence of tuberculosis, both in absolute numbers and per 100,000 population. In terms of total variation, the crude incidence of tuberculosis decreased by 9.66%, whereas the relative incidence decreased by 18.66%. As for tuberculosis-HIV co-infection, the crude incidence increased by 15.19%, whereas the incidence per 100,000 population increased by almost 4%. Nevertheless, the tuberculosis-HIV co-infection/tuberculosis ratio increased by 27.51% over the analysis period, indicating the growing importance of HIV in the epidemiology of tuberculosis.

Table 2 presents the incidence per 100,000 population of tuberculosis and of tuberculosis-HIV co-infection in each year studied, by gender. There was a reduction in the incidence of tuberculosis in men (−14.52%) and in women (−25.41%). However, the incidence of tuberculosis-HIV co-infection increased by almost 8% in women, a variation that is 5.4% higher than that found in males. This reveals that the population of HIV-infected individuals is rapidly becoming more female.

Table 3 shows the incidence per 100,000 population of tuberculosis and of tuberculosis-HIV co-infection in each year studied, by age group. There was statistical significance for the incidence of tuberculosis only in the 0- to 9-year and the 40- to 59-year age groups. A substantial reduction of 31% can be seen in the 0- to 9-year age group, being in contrast with the almost 11% increase observed in the 40- to 59-year age group. The picture is reversed when looking at the behavior of tuberculosis-HIV co-infection. There was a reduction only in the 0- to 9-year age group (−36.36%), whereas there were substantial increases in the other age groups: more than 50% in the 10- to 19-year age group; 11.32% in the 20- to 39-year age group; and over 76% in the 40- to 49-year age group. The most remarkable finding was the 209% increase in the incidence of tuberculosis-HIV co-infection in the ≥ 60-year age group.

Table 1. Incidence of reported cases of tuberculosis and of tuberculosis-HIV co-infection, Brazil, 2002-2012.

Year	TB		TB-HIV co-infection		TB-HIV co-infection/ TB ratio, %
	Crude incidence	Incidence/ 100,000 population	Crude incidence	Incidence/ 100,000 population	
2002	77,507	44.38	5,943	3.40	7.67
2003	78,599	44.44	6,068	3.43	7.72
2004	77,691	43.38	5,835	3.26	7.51
2005	76,751	41.67	5,841	3.17	7.61
2006	71,831	38.46	6,162	3.30	8.58
2007	71,629	37.83	6,398	3.38	8.93
2008	73,427	38.72	6,630	3.50	9.03
2009	72,895	38.07	6,771	3.54	9.29
2010	71,390	37.42	7,037	3.69	9.86
2011	73,168	38.03	7,150	3.72	9.77
2012	70,023	36.10	6,846	3.53	9.78
Total variation, %	−9.66	−18.66	15.19	3.82	27.51
p	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05

TB: tuberculosis.

Table 2. Incidence of reported cases of tuberculosis and of tuberculosis-HIV co-infection, by gender, Brazil, 2002-2012.

Year	Incidence of TB/ 100,000 population		Incidence of TB-HIV co-infection/ 100,000 population	
	Males	Females	Males	Females
2002	57.64	31.44	4.93	1.92
2003	57.69	31.58	4.92	1.99
2004	56.64	30.50	4.64	1.92
2005	54.66	29.04	4.49	1.89
2006	50.48	26.80	4.67	1.97
2007	50.33	25.75	4.84	1.97
2008	51.69	26.19	4.96	2.08
2009	50.91	25.67	5.00	2.12
2010	50.52	24.86	5.27	2.17
2011	51.58	25.04	5.34	2.16
2012	49.27	23.45	5.05	2.07
Total variation, %	−14.52	−25.41	2.43	7.81
p	< 0.05	< 0.05	< 0.05	< 0.05

TB: tuberculosis.

Table 3. Incidence of reported cases of tuberculosis and of tuberculosis-HIV co-infection, by age group in years, Brazil, 2002-2012.

Year	Incidence of TB/ 100,000 population					Incidence of TB-HIV co-infection/ 100,000 population				
	Age group, years					Age group, years				
	0-9	10-19	20-39	40-59	≥ 60	0-9	10-19	20-39	40-59	≥ 60
2002	6.28	18.78	102.31	70.79	29.12	0.33	0.32	11.51	5.00	0.32
2003	5.96	18.31	102.22	71.76	29.28	0.27	0.33	11.17	5.50	0.37
2004	5.40	17.43	99.96	70.77	28.43	0.33	0.37	10.32	5.36	0.38
2005	5.07	16.62	95.25	68.63	27.63	0.25	0.29	9.83	5.52	0.41
2006	4.52	13.85	87.34	65.05	25.73	0.31	0.37	9.52	6.18	0.59
2007	4.78	15.69	95.74	69.54	27.66	0.22	0.38	10.79	7.12	0.61
2008	4.45	16.16	96.73	70.37	28.14	0.22	0.47	10.74	7.10	0.68
2009	4.62	16.12	100.81	73.23	28.25	0.24	0.50	11.24	7.82	0.89
2010	4.59	17.32	100.52	74.20	32.42	0.23	0.50	11.57	8.19	0.93
2011	4.68	18.41	112.27	82.32	33.78	0.24	0.60	13.49	9.54	0.90
2012	4.32	17.40	106.12	78.34	31.37	0.21	0.49	12.80	8.83	0.99
Total variation, %	−31.21	−7.35	3.72	10.67	7.73	−36.36	53.13	11.21	76.60	209.38
p	< 0.05	0.73	0.24	< 0.05	0.06	< 0.05	< 0.05	0.05	< 0.05	< 0.05

TB: tuberculosis.

Table 4 presents the data regarding the incidence per 100,000 population of tuberculosis and of tuberculosis-HIV co-infection in the years under study, by geographical region. In terms of total variation, the incidence of tuberculosis decreased by 20.19% in the southeast, by 20.14% in the northeast, by 12.37% in the north, and by 7.80% in the central-west. In the south, that incidence remained stable.

Also according to Table 4, the incidence of tuberculosis-HIV co-infection increased substantially in the north and northeast, with total variation exceeding 150% over the 11-year period studied. In the south, there were no significant differences in incidence, whereas, in the central-west, there was an increase of almost 47%. In the southeast, unlike in the other regions, there was a 25% reduction in the rates of tuberculosis-HIV co-infection.

Regarding the outcomes, Table 5 shows that the cure rate in patients with tuberculosis-HIV co-infection was 50.74%, whereas, in patients infected with tuberculosis only, that rate was higher: 71.10%. Calculation of odds ratios indicated that tuberculosis-HIV co-infection decreased the chance of being cured of tuberculosis by 58%. In addition, the rate of treatment nonadherence was 13.60% in patients with tuberculosis-HIV co-infection, compared with 9.52% in patients infected with tuberculosis only. Therefore, HIV infection increased the risk of treatment nonadherence by 50% in patients infected with tuberculosis. Taken together, the previous data indicate that patients with tuberculosis-HIV co-infection, in comparison with patients infected with tuberculosis only, had a 94% greater risk of dying from tuberculosis. Nevertheless, tuberculosis-HIV co-infection was not associated with multidrug-resistant tuberculosis.

DISCUSSION

The data from the present study show that there was a significant decrease in the incidence of tuberculosis in Brazil between 2002 and 2012. This decrease was

Table 4. Incidence of reported cases of tuberculosis and of tuberculosis-HIV co-infection, by geographical region, Brazil, 2002-2012.

Year	Incidence of TB/ 100,000 population					Incidence of TB-HIV co-infection/ 100,000 population				
	N	NE	SE	S	CW	N	NE	SE	S	CW
2002	51.03	44.15	48.73	34.64	26.29	1.39	0.94	4.8	5.42	1.49
2003	49.97	46.14	47.27	35.41	27.08	1.96	1.28	4.55	5.41	1.58
2004	50.6	45.9	45.52	34.08	24.7	1.64	1.48	4.21	5.04	1.49
2005	47.32	45.54	42.9	32.32	25.34	1.95	1.46	3.95	5.03	1.68
2006	46.05	41.03	40.53	30.48	24.27	1.96	1.56	4.47	4.69	1.67
2007	45.01	39.49	40.68	31.83	23.13	2.27	1.88	4.14	5.23	2.08
2008	44.69	38.13	40.37	31.84	22.8	3.18	2.05	4.01	5.71	1.97
2009	47.78	38.85	41.01	33.21	21.91	3.41	2.19	4.00	5.58	2.06
2010	40.88	33.95	36.45	30.35	20.98	3.83	2.48	3.93	6.08	2.03
2011	46.42	37.7	41.48	33.26	23.08	3.67	2.64	3.97	5.92	2.04
2012	44.72	35.26	38.89	32.06	24.24	3.81	2.7	3.59	5.48	2.19
Total variation, %	−12.37	−20.14	−20.19	−7.45	−7.80	174.10	187.23	−25.21	1.11	46.98
p	< 0.05	< 0.05	< 0.05	0.08	< 0.05	< 0.05	< 0.05	< 0.05	0.07	< 0.05

TB: tuberculosis; N: north; NE: northeast; SE: southeast; S: south; and CO: central-west.

Table 5 . Association between tuberculosis-HIV co-infection and observed outcomes, Brazil, 2002-2012.

Outcome	Cases reported to SINAN, %		OR (CI 95%)	p
	TB-HIV co-infection	TB[a]		
Cure				
Yes	50.74	71.10	0.42 (0.41-0.42)	< 0.05
No	49.26	28.90	Ref.	
Nonadherence				
Yes	13.60	9.52	1.50 (1.46-1.53)	< 0.05
No	86.40	90.48	Ref.	
Death from TB				
Yes	3.63	1.90	1.94 (1.86-2.02)	< 0.05
No	96.37	98.10	Ref.	
Multidrug-resistant TB				
Yes	0.17	0.17	0.95 (0.75-1.21)	0.70
No	99.83	99.83	Ref.	

SINAN: *Sistema de Informação de Agravos de Notificação* (Brazilian Case Registry Database); TB: tuberculosis; and Ref.: reference. [a]Difference between the total number of reported cases of tuberculosis and the number of cases diagnosed as HIV-positive.

found to be more prominent in women and children in all geographical regions except the south. In contrast, we found that the incidence rates of tuberculosis remain high in men aged between 20 and 59 years. In addition, the cure rates fall short of the goal established by the PNCT, which is 85%.[1] The picture changes when looking at tuberculosis-HIV co-infection. Not only did the total incidence of tuberculosis-HIV co-infection increased, but it was greater in women, in the elderly, and in residents of the northern and northeastern regions, which reveals that the population of HIV-infected individuals is rapidly becoming more female, older, and more impoverished. Finally, the data showed that, in patients with tuberculosis-HIV co-infection, the cure rates were lower, whereas the rates of treatment nonadherence and the rates of death were higher. The present study adds to the debate about the public policies to control tuberculosis and tuberculosis-HIV co-infection in Brazil, demonstrating the impact of those policies on our country and on at-risk populations, their possible shortcomings, and possible areas for improvement. Regarding the incidence of tuberculosis, we found a reduction both in absolute numbers and per 100,000 population. According to Guimarães et al.,[10] the incidence of tuberculosis decreased by 48.8% between 1990 and 2010 in Brazil, being as low as 43/100,000 population in the last year studied. That result supports our analysis that the incidence of tuberculosis has decreased. However, our data differ in that they show an increased incidence in some age groups and a less precipitous drop. This disparity between results may have been due to the use of different databases.

The same was not found for the incidence of tuberculosis-HIV co-infection, which in fact increased by 3.82% over the study period. It is clear that HIV has contributed to the growing number of cases of tuberculosis,[6,11] especially because of the increased risk of contracting this disease, given the immunosuppression caused by the virus.[2,6] Therefore, we found an increase of 27.51% in the tuberculosis-HIV co-infection/tuberculosis ratio over the study period, which underscores the significance of this co-infection for the adequate control of tuberculosis. In 2011, the Brazilian MS recognized that, given the high prevalence of tuberculosis-HIV co-infection and the increased rates of death from tuberculosis among HIV-positive patients, tuberculosis-HIV co-infection needed to be controlled.[1] However, up until 2012, the number of reported cases of tuberculosis-HIV co-infection increased significantly, which emphasizes the need for more actions aimed at preventing the spread of HIV, as well as for treating and following co-infected patients more thoroughly.

When analyzed by gender, the incidence of tuberculosis was twice as high in males as in females. This finding substantiates the indication that, in Brazil, tuberculosis primarily affects males,[12] in whom the risk of developing the disease is twice as high.[7] It is necessary to comment that there was a greater reduction in the incidence of tuberculosis in females, probably because women take better care of their health.[13] However, the incidence of tuberculosis-HIV co-infection was high in females, indicating a greater number of new HIV-positive women. These data support those of other studies conducted in Brazil that showed a higher incidence and prevalence of tuberculosis and HIV infection in males, as well as increased rates of tuberculosis-HIV co-infection,[3,14] which is influenced by genetic, environmental, and immunological factors and of which better understanding would lead to advances in diagnosis that would favor the development of new technologies and treatments for both diseases.[15]

When analyzed by age group, the incidence of tuberculosis was found to have decreased by one third in children aged 0-9 years. This implies greater effectiveness of treatment and greater effectiveness of prophylaxis of contacts, as well as improvements in housing, sanitary conditions, quality of diet, and access to health care, including adherence to vaccination schedules, since these characteristics are intrinsically associated with the decrease in the incidence of tuberculosis, especially in children,[16] although the diagnosis is difficult in such cases.[17] However, in all other age groups, except the 10- to 19-year age group, there were increases in the incidence of tuberculosis, as was also found in the Brazilian literature until 2004.[18] In addition, we detected a substantial increase in the co-infection rate in the 10- to 19-year age group, as well as in others. In a study conducted in Brazil, dos Santos Dias et al.[19] reported worse outcomes and greater likelihood of unfavorable results in patients co-infected with HIV. This leads us to a social problem: the economically active population is increasingly developing tuberculosis, which is more prevalent in marginalized and impoverished segments of society.[20]

The increase of 209% in the incidence of tuberculosis-HIV co-infection in the ≥ 60-year age group requires the development of elderly-targeted public policies that encourage educational interventions and gradually act on the sexual issue and on the prevention of sexually transmitted diseases. In addition to the increase in the number of elderly in the population, the improvement in quality of life and the use of medications for erectile dysfunction have increased the prevalence of HIV infection, worsening the already existing public health problem. The elderly are known to be more susceptible to illness, because they have decreased immunity, as well as to have comorbidities and to be on polypharmacy, both of which are pointed out as risk factors for recurrence of tuberculosis.[21] Therefore, the increased tuberculosis-HIV co-infection rate in this population implies higher mortality from tuberculosis. The study by Chaimowicz[22] suggested that there will be a reduction in the tuberculosis-HIV co-infection rate in the ≥ 60-year age group over the next 50 years. However, this will only be possible if public policies aimed at this population are implemented.

When analyzed by geopolitical regions in Brazil, the incidence of tuberculosis was found to have decreased in all regions except the south. This decrease may be

directly related to the implementation of the PNCT[1] in those regions, as well as to the fact that the WHO has declared tuberculosis a health emergency, expanding the disease control interventions. In contrast, the increase in the incidence of tuberculosis-HIV co-infection in all regions strengthens the notion that HIV infection is the major risk factor for the development of tuberculosis.[7] The 150% increase found in the northern and northeastern regions reveals that the population of HIV-infected individuals is becoming more rural, which is an aggravating factor to the tuberculosis problem, because marginalized regions with poor social and health indicators are more vulnerable.[18,23] Nevertheless, Prado et al.[24] reported that patients co-infected with HIV were less likely to live in rural areas. Considering all the evidence, it is necessary to structure primary health care clinics so that they can meet the needs of those regions and to implement social development policies in those regions so that they are no longer vulnerable. It is of note that direct income transfer programs seem to contribute to increasing the cure rates for tuberculosis in Brazil.[25] Therefore, in order to achieve far-reaching and robust results, public health policies should address the various facets of the disease, such as social, economic, environmental, and clinical problems.[21,26-28]

After analyzing the temporal evolution of tuberculosis and of tuberculosis-HIV co-infection for different epidemiological profiles, we extracted the outcome data for the same period in order to assess the goals of the PNCT[1] and the influence of tuberculosis-HIV co-infection on outcome. The difference in the cure rate between HIV-negative and HIV-positive patients is clear. Whereas the former had a cure rate of 71%, the latter had a cure rate of only 50%, which means that patients with tuberculosis-HIV co-infection had a 48% lower chance of cure than did HIV-negative patients. This relationship has been reported in other studies[29,30] and is related to the immunodeficiency caused by HIV in such patients, the time from diagnosis to treatment initiation, and the limited access to health care.[31] Even after the launch of the PNCT and after the establishment of the WHO and the Brazilian MS goal of curing 85% of reported cases by 2015, Brazil has not yet achieved this purpose, as shown by our analysis of the 2002-2012 period.[1]

The rates of treatment nonadherence for the reported cases of tuberculosis and of tuberculosis-HIV co-infection were 9% and 13%, respectively, being similar to those found in previous studies.[18,20,29,32] Although treatments are available free of charge in the public health care system, the dispensing of medications and treatment follow-up are performed at different places. In addition, the long duration and the side effects of the treatment favor nonadherence.[6]

The rate of death from tuberculosis was found to be almost 3-fold higher in patients with tuberculosis-HIV co-infection than in HIV-negative patients. These data are similar to those found in other studies[18,29] and, once again, are related to the immune profile of HIV-positive patients[33] and to the rates of treatment nonadherence, which are higher in this population, as demonstrated in the present study. Nevertheless, Dowdy et al.[34] reported similar decreases in quality of life across groups of patients with tuberculosis, with HIV, and with tuberculosis-HIV co-infection, by using a validated self-assessment instrument. It is of note that we found no differences in the rate of multidrug-resistant tuberculosis between the groups. Although some studies support this finding,[7,18] others suggest the opposite, and this information is relevant to disease outcome.[1,33,35,36]

The major limitation of the present study is the use of secondary data, given that such data can affect the analysis, especially because of poor record completion.[37,38] Therefore, it is essential to ensure the sensitivity and reliability of the SINAN data so that they can be safely used by researchers, health care managers, and health care professionals in an equal fashion nationwide.

In summary, our findings suggest, within the limits of this study, that the epidemiological behavior of the reported new cases of tuberculosis and that of the cases of tuberculosis-HIV co-infection showed opposite trends between 2002 and 2012. Infection with HIV is an important factor in the course of tuberculosis. This information is essential to the implementation of a policy aimed at informing the care of HIV-positive patients so that more effective monitoring measures can be made available. Conversely, despite advances in the treatment and prevention of HIV infection, it is necessary not to neglect the continued spread of this infection in Brazil, especially in women, in the elderly, and in less developed regions. In addition, it is necessary to expand the PNCT[1] uniformly in the whole country so that it is possible to achieve the established goals, as well as to offer structured and effective care nationwide. Finally, encouraging and facilitating the functioning of primary health care clinics, through continuing education, that are apt to diagnose and treat tuberculosis is indispensable to improving data on this disease.

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REFERENCES

1. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de Vigilância Epidemiológica. Manual de recomendações para o controle da tuberculose no Brasil. Brasília: Ministério da Saúde; 2011.
2. Orme IM, Robinson RT, Cooper AM. The balance between protective and pathogenic immune responses in the TB-infected lung. Nat

Immunol. 2015;16(1):57-63. http://dx.doi.org/10.1038/ni.3048

3. Cheade Mde F, Ivo ML, Siqueira PH, Sá RG, Honer MR. Characterization of tuberculosis among HIV/AIDS patients at a referral center in Mato Grosso do Sul [Article in Portuguese]. Rev Soc Bras Med Trop. 2009;42(2):119-25.
4. Corbett EL, Watt CJ, Walker N, Maher D, Williams BG, Raviglione MC, et al. The growing burden of tuberculosis: global trends and interactions with the HIV epidemic. Arch Intern Med. 2003;163(9):1009-21. http://dx.doi.org/10.1001/archinte.163.9.1009
5. de Carvalho LG, Buani AZ, Zöllner MS, Scherma AP. Co-infection with Mycobacterium tuberculosis and human immunodeficiency virus: an epidemiological analysis in the city of Taubaté, Brazil. J Bras Pneumol. 2006;32(5):424-9. http://dx.doi.org/10.1590/S1806-37132006000500009
6. Jamal LF, Moherdaui F. Tuberculosis and HIV infection in Brazil: magnitude of the problem and strategies for control [Article in Portuguese]. Rev Saude Publica. 2007;41 Suppl 1:104-10. http://dx.doi.org/10.1590/S0034-89102007000800014
7. Barbosa IR, Costa IC. The emergency of tuberculosis-HIV co-infection in Brazil [Article in Portuguese]. Hygea. 2012;8(15):232-44.
8. Brasil. Ministério da Saúde. Programa Nacional de Controle da Tuberculose. Brasília: Ministério da Saúde; 2003.
9. Augusto CJ, Carvalho Wda S, Gonçalves AD, Ceccato Md, Miranda SS. Characteristics of tuberculosis in the state of Minas Gerais, Brazil: 2002-2009. J Bras Pneumol. 2013;39(3):357-64. http://dx.doi.org/10.1590/S1806-37132013000300013
10. Guimarães RM, Lobo Ade P, Siqueira EA, Borges TF, Melo SC. Tuberculosis, HIV, and poverty: temporal trends in Brazil, the Americas, and worldwide. J Bras Pneumol. 2012;38(4):511-7. http://dx.doi.org/10.1590/S1806-37132012000400014
11. Ruffino-Netto A. Tuberculosis: the negleted calamity [Article in Portuguese]. Rev Soc Bras Med Trop. 2002;35(1):51-8. http://dx.doi.org/10.1590/S0037-86822002000100010
12. Maruza M, Albuquerque MF, Coimbra I, Moura LV, Montarroyos UR, Miranda Filho DB, et al. Risk factors for default from tuberculosis treatment in HIV-infected individuals in the state of Pernambuco, Brazil: a prospective cohort study. BMC Infect Dis. 2011;11:351. http://dx.doi.org/10.1186/1471-2334-11-351
13. Machin R, Couto MT, Silva GS, Schraiber LB, Gomes R, Figueiredo WS, et al. Concepts of gender, masculinity and healthcare: a study of primary healthcare professionals [Article in Portuguese]. Cien Saude Col. 2011;16(11):4503-12. http://dx.doi.org/10.1590/S1413-81232011001200023
14. Garrido Mda S, Bührer-Sékula S, Souza AB, Ramasawmy R, Quincó Pde L, Monte RL, et al. Temporal distribution of tuberculosis in the State of Amazonas, Brazil. Rev Soc Bras Med Trop. 2015;48 Suppl 1:63-9. http://dx.doi.org/10.1590/0037-8682-0055-2014
15. Raghavan S, Alagarasu K, Selvaraj P. Immunogenetics of HIV and HIV associated tuberculosis. Tuberculosis (Edinb). 2012;92(1):18-30. http://dx.doi.org/10.1016/j.tube.2011.08.004
16. Getahun H, Sculier D, Sismanidis C, Grzemska M, Raviglione M. Prevention, diagnosis, and treatment of tuberculosis in children and mothers: evidence for action for maternal, neonatal, and child health services. J Inf Dis. 2012;205 Suppl 2:S216-27. http://dx.doi.org/10.1093/infdis/jis009
17. Pedrozo C, Sant'Anna CC, March Mde F, Lucena SC. Efficacy of the scoring system, recommended by the Brazilian National Ministry of Health, for the diagnosis of pulmonary tuberculosis in children and adolescents, regardless of their HIV status. J Bras Pneumol. 2010;36(1):92-8.
18. Bierrenbach AL, Gomes AB, Noronha EF, de Souza Mde F. Tuberculosis incidence and cure rates, Brazil, 2000-2004 [Article in Portuguese]. Rev Saude Publica. 2007;41 Suppl 1:24-33.
19. dos Santos Dias E, do Prado TN, da Silva Guimarães AL, Ramos MC, Sales CM, de Fátima Almeida Lima E, et al. Childhood tuberculosis and human immunodeficiency virus status in Brazil: a hierarchical analysis. Int J Tuberc Lung Dis. 2015;19(11):1305-11. http://dx.doi.org/10.5588/ijtld.14.0619
20. Santos Neto M, Silva FL, Sousa KR, Yamamura M, Popolin MP, Arcêncio RA. Clinical and epidemiological profile and prevalence of tuberculosis/HIV co-infection in a regional health district in the state of Maranhão, Brazil. J Bras Pneumol. 2012;38(6):724-32. http://dx.doi.org/10.1590/S1806-37132012000600007
21. Oliveira HB, Moreira-Filho DC. Recidivas em tuberculose e seus fatores de risco. Rev Panam Salud Publica. 2000;7(4):232-41. http://dx.doi.org/10.1590/S1020-49892000000400004
22. Chaimowicz F. Age transition of tuberculosis incidence and mortality in Brazil. Rev Saude Publica. 2001;35(1):81-7. http://dx.doi.org/10.1590/S0034-89102001000100012
23. de Oliveira NF, Gonçalves MJ. Social and environmental factors associated with the hospitalization of tuberculosis patients. Rev Lat Am Enfermagem. 2013;21(2):507-14. http://dx.doi.org/10.1590/S0104-11692013000200006
24. do Prado TN, Miranda AE, de Souza FM, Dias Edos S, Sousa LK, Arakaki-Sanchez D, et al. Factors associated with tuberculosis by HIV status in the Brazilian national surveillance system: a cross sectional study. BMC Infect Dis. 2014;14:415. http://dx.doi.org/10.1186/1471-2334-14-415
25. Torrens AW, Rasella D, Boccia D, Maciel EL, Nery JS, Olson ZD, et al. Effectiveness of a conditional cash transfer programme on TB cure rate: a retrospective cohort study in Brazil. Trans R Soc Trop Med Hyg. 2016;110(3):199-206. http://dx.doi.org/10.1093/trstmh/trw011
26. Ranzani OT, Carvalho CR, Waldman EA, Rodrigues LC. The impact of being homeless on the unsuccessful outcome of treatment of pulmonary TB in São Paulo State, Brazil. BMC Med. 2016;14:41. http://dx.doi.org/10.1186/s12916-016-0584-8
27. Reis-Santos B, Gomes T, Macedo LR, Horta BL, Riley LW, Maciel EL. Prevalence and patterns of multimorbidity among tuberculosis patients in Brazil: a cross-sectional study. Int J Equity Health. 2013;12:61. http://dx.doi.org/10.1186/1475-9276-12-61
28. Gupta S, Granich R, Date A, Lepere P, Hersh B, Gouws E, et al. Review of policy and status of implementation of collaborative HIV-TB activities in 23 high-burden countries. Int J Tuberc Lung Dis. 2014;18(10):1149-58. http://dx.doi.org/10.5588/ijtld.13.0889
29. Muniz JN, Ruffino-Netto A, Villa TC, Yamamura M, Arcencio R, Cardozo-Gonzales RI. Epidemiological aspects of human immunodeficiency virus/tuberculosis co-infection in Ribeirão Preto, Brazil from 1998 to 2003. J Bras Pneumol. 2006;32(6):529-34. http://dx.doi.org/10.1590/S1806-37132006000600010
30. Ambadekar NN, Zodpey SP, Soni RN, Lanjewar SP. Treatment outcome and its attributes in TB-HIV co-infected patients registered under Revised National TB Control Program: a retrospective cohort analysis. Public Health. 2015;129(6):783-9. http://dx.doi.org/10.1016/j.puhe.2015.03.006
31. Hino P, da Costa-Júnior ML, Sassaki CM, Oliveira MF, Villa TC, dos Santos CB. Time series of tuberculosis mortality in Brazil (1980-2001). Rev Lat Am Enfermagem. 2007;15(5):936-41. http://dx.doi.org/10.1590/S0104-11692007000500009
32. Silva Pda F, Moura GS, Caldas Ade J. Factors associated with pulmonary TB treatment dropout in Maranhão State, Brazil, from 2001 to 2010 [Article in Portuguese]. Cad Saude Publica. 2014;30(8):1745-54.
33. Middelkoop K, Bekker LG, Mathema B, Myer L, Shashkina E, Whitelaw A, et al. Factors affecting tuberculosis strain success over 10 years in a high TB-and HIV-burdened community. Int J Epidemiol. 2014;43(4):1114-22. http://dx.doi.org/10.1093/ije/dyu044
34. Dowdy DW, Israel G, Vellozo V, Saraceni V, Cohn S, Cavalcante S, et al. Quality of life among people treated for tuberculosis and human immunodeficiency virus in Rio de Janeiro, Brazil. Int J Tuberc Lung Dis. 2013;17(3):345-7. http://dx.doi.org/10.5588/ijtld.12.0123
35. Dean AS, Zignol M, Falzon D, Getahun H, Floyd K. HIV and multidrug-resistant tuberculosis: overlapping epidemics. Eur Resp J. 2014;44(1):251-4. http://dx.doi.org/10.1183/09031936.00205413
36. Post FA, Grint D, Werlinrud AM, Panteleev A, Riekstina V, Malashenkov EA, et al. Multi-drug-resistant tuberculosis in HIV positive patients in Eastern Europe. J Infect. 2014;68(3):259-63. http://dx.doi.org/10.1016/j.jinf.2013.09.034
37. Coeli CM. Sistemas de Informação em Saúde e uso de dados secundários na pesquisa e avaliação em saúde. Cad Saude Colet. 2010;18(3):335-6.
38. Santos NP, Lírio M, Passos LA, Dias JP, Kritski AL, Galvão-Castro B, et al. Completeness of tuberculosis reporting forms in five Brazilian capitals with a high incidence of the disease. J Bras Pneumol. 2013;39(2):221-5. http://dx.doi.org/10.1590/S1806-37132013000200014

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http://dx.doi.org/10.1590/S1806-37562015000600006

ORIGINAL ARTICLE

Association between severe asthma and changes in the stomatognathic system

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ABSTRACT

Objective: To describe orofacial muscle function in patients with severe asthma. **Methods:** This was a descriptive study comparing patients with severe controlled asthma (SCA) and severe uncontrolled asthma (SUA). We selected 160 patients, who completed a sociodemographic questionnaire and the 6-item Asthma Control Questionnaire (ACQ-6), as well as undergoing evaluation of orofacial muscle function. **Results:** Of the 160 patients evaluated, 126 (78.8%) and 34 (21.2%) presented with SCA and SUA, respectively, as defined by the Global Initiative for Asthma criteria. Regardless of the level of asthma control, the most frequent changes found after evaluation of muscle function were difficulty in chewing, oronasal breathing pattern, below-average or poor dental arch condition, and difficulty in swallowing. When the sample was stratified by FEV_1 (% of predicted), was significantly higher proportions of SUA group patients, compared with SCA group patients, showed habitual open-mouth chewing (24.8% vs. 7.7%; $p < 0.02$), difficulty in swallowing water (33.7% vs. 17.3%; $p < 0.04$), and voice problems (81.2% vs. 51.9%; $p < 0.01$). When the sample was stratified by ACQ-6 score, the proportion of patients showing difficulty in swallowing bread was significantly higher in the SUA group than in the SCA group (66.6% vs. 26.6%; $p < 0.01$). **Conclusions:** The prevalence of changes in the stomatognathic system appears to be high among adults with severe asthma, regardless of the level of asthma control. We found that some such changes were significantly more common in patients with SUA than in those with SCA.

Keywords: Speech/physiology; Stomatognathic system/physiopathology; Asthma/complications; Deglutition disorders; Mastication/physiology.

INTRODUCTION

The 2015 update of the Global Initiative for Asthma (GINA) guidelines[1] indicates that, in 10-40% of patients with (allergic or non-allergic) asthma, the disease may be associated with rhinitis. However, a study conducted at a referral center in the city of Salvador, Brazil, found a 100 percent association between asthma and allergic rhinitis.[2] Allergic rhinitis, in turn, can cause nasal obstruction, with consequent oral breathing at rest, even when individuals with severe asthma are experiencing stable periods.[3] Oral breathing can change the functions of the stomatognathic system (breathing, sucking, chewing, swallowing, and speech), functions that affect vital and social aspects.[4]

The literature has demonstrated that oral breathing in children and adults with severe asthma can cause changes in the structures and functions of the stomatognathic system, which are represented, for example, by maxillary atresia and a high-arched palate; protrusion of the tongue between or against the dental arches; open bite and crossbite; hypotonic lips and lip occlusion with muscle tension; and inappropriate patterns of breathing, chewing, and swallowing.[5-8]

The static and mobile structures of the stomatognathic system act jointly and synchronously to perform the functions of breathing, sucking, chewing, swallowing, and speech. One can hypothesize that a change in an upper airway structure may change its corresponding function, such an example being that missing dental units will affect chewing. When a structure or function is changed, the other structures and functions may play their roles in a way befitting that new condition, one such example being that of hypotonia of the tongue leading to changes in executing swallowing movements.

Severe asthma can be identified by difficulty in controlling the disease or achieving treatment response, as well as by the presence of at least one of the following indicators: poor symptom control, as indicated by an Asthma Control Questionnaire (ACQ) score > 1.5 or an Asthma Control Test score < 20; frequent exacerbations requiring two or more doses of systemic corticosteroids (> 3 times a day) in the previous year; severe exacerbations in the previous year, with at least one requiring hospitalization or mechanical ventilation; airflow limitation after bronchodilator use, with an FEV_1 < 80% of predicted; and frequent symptoms of nocturnal asthma and limitation

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in physical activities.[9-11] Patients with severe asthma tend to show a high rate of allergic rhinitis, one of the clinical symptoms of which is nasal obstruction, and consequently have predominantly oral breathing. In such cases, the phonoarticulatory organs are positioned improperly and can lead to impairment of the functions of sucking, chewing, swallowing, and speech. Therefore, the objective of the present study was to describe orofacial muscle function in patients with severe asthma.

METHODS

This was a cross-sectional study of a consecutive sample selected in an asthma referral center—*Programa de Controle da Asma e da Rinite Alérgica da Bahia* (ProAR, Bahia State Program for the Control of Asthma and Allergic Rhinitis)—in the city of Salvador, Brazil. The inclusion criteria were as follows: having been diagnosed with severe asthma in accordance with the Global Initiative for Asthma criteria[12]; and being 18 to 85 years of age. The exclusion criteria were as follows: having a neurological disorder, a genetic syndrome, a heart disease, a debilitating disease, facial trauma, cognitive deficit, or difficulty in understanding and performing the requested movements; having a history of head and neck surgery; and being pregnant.

Of the 160 subjects invited to participate in the study, all completed a sociodemographic questionnaire and the 6-item ACQ (ACQ-6), with the cut-off point for control being 1.5.[13] The evaluation of muscle function consisted of observation of the face and oral function, following a validated protocol.[8] The data for FEV_1 were obtained from medical records, which had to have been completed within twelve months previously.

To calculate the sample size required to estimate the frequency of myofunctional dysfunction in patients with severe asthma, we used the PEPI-Sample software (Sagebush Press, Salt Lake City, UT, USA) and the following parameters: a confidence level of 95%; an estimated prevalence of myofunctional changes in the general population of 30-40%; population from which the sample was drawn: approximately 2,000 severe asthma patients enrolled in the ProAR; and a difference in prevalence of 10% as being acceptable. To achieve the study objective, the required sample size was estimated at 145 patients. Allowing for a loss to follow-up rate of 10%, a sample of 160 patients was determined.

Data were tabulated and analyzed with the IBM SPSS Statistics software package, version 20.0 (IBM Corporation, Armonk, NY, USA). Quantitative variables were expressed as mean ± standard deviation or as median (interquartile range). Qualitative variables were expressed as absolute and relative frequencies. Proportions were compared with the chi-square test. Two means were compared with the Student's t-test for independent samples. Values of $p < 0.05$ were considered statistically significant.

The present study was approved by the Research Ethics Committee of the Federal University of Bahia (Protocol No. 088/2010; Additional Resolution No. 41/2013). Written informed consent was given by the patients at the time they agreed to participate in the study.

RESULTS

A total of 160 adult patients (age ≥ 18 years) were invited to participate in the evaluation of orofacial muscle function in patients with severe asthma. On the basis of the GINA criteria for classification of asthma,[12] 126 patients (79%) had controlled asthma and 34 (21%) had uncontrolled asthma. Table 1 shows the sociodemographic aspects of the severe asthma patients enrolled in the ProAR, providing data on gender, skin color, level of education, family income, age, BMI, spirometry, and ACQ-6 scores.

At the time of the evaluation of muscle function, 4 of the 160 invited patients (3 with severe controlled asthma and 1 with severe uncontrolled asthma) were excluded because they were unable to perform the requested movements. Figure 1 shows, by level of asthma control, the results for dental arch condition and presence/absence of fixed or removable dental prostheses in the severe asthma patients enrolled in the ProAR.

Figure 2 shows, by level of asthma control, the results of the evaluation of masticatory function (solid food: milk bread) in the severe asthma patients enrolled in the ProAR.

Figure 3 shows, by level of asthma control, the results for swallowing function (solid food and liquids) in the severe asthma patients enrolled in the ProAR.

The evaluation of orofacial muscle function, the responses on the ACQ-6, and the spirometric data revealed changes in breathing, voice, tongue mobility,

Table 1. Sociodemographic aspects, as well as clinical and spirometric characteristics, of the patients with severe asthma included in the study (N = 160).[a]

Variable	Patients
Gender (female)	123 (76.9)
Skin color (brown)	100 (62.7)
Level of education (< 9 years of schooling)	80 (50.0)
Family income (one time the national minimum wage)	80 (50.0)
Age, years	51.5 ± 12.6
BMI, kg/m^2	29.0 ± 5.2
Pre-bronchodilator FEV_1, % of predicted	63.7 (49.6-76.0)
Post-bronchodilator FEV_1, % of predicted	69.5 (57.5-82.0)
ACQ-6 score	0.66 (0.50-1.33)

ACQ-6: 6-item Asthma Control Questionnaire. [a]Values expressed as mean ± SD or as median (interquartile range).

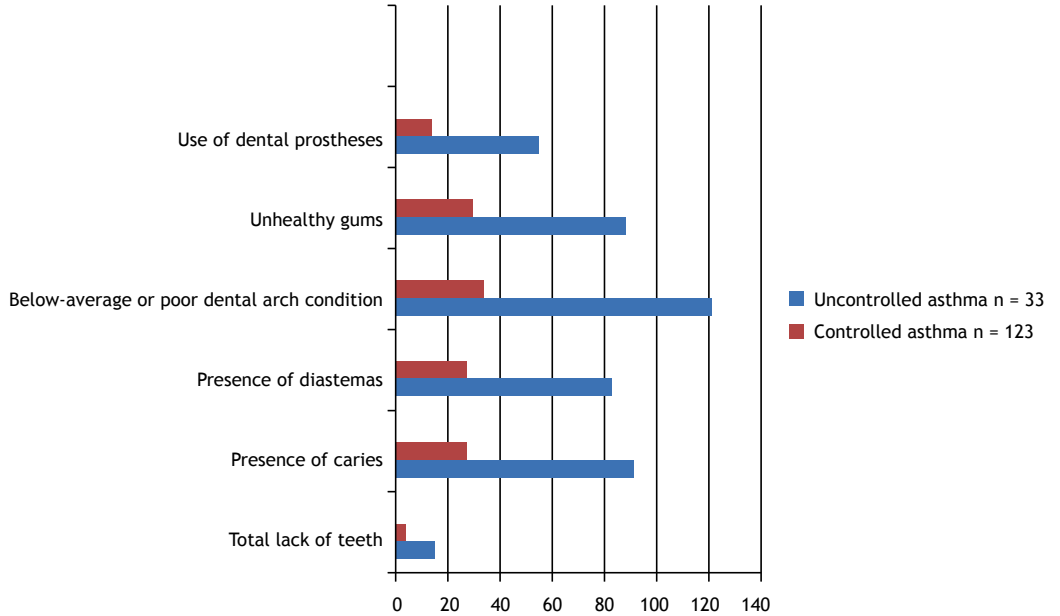

Figure 1. Comparison of dental arch characteristics in patients with severe asthma, by level of asthma control. Chi-square test; $p < 0.05$.

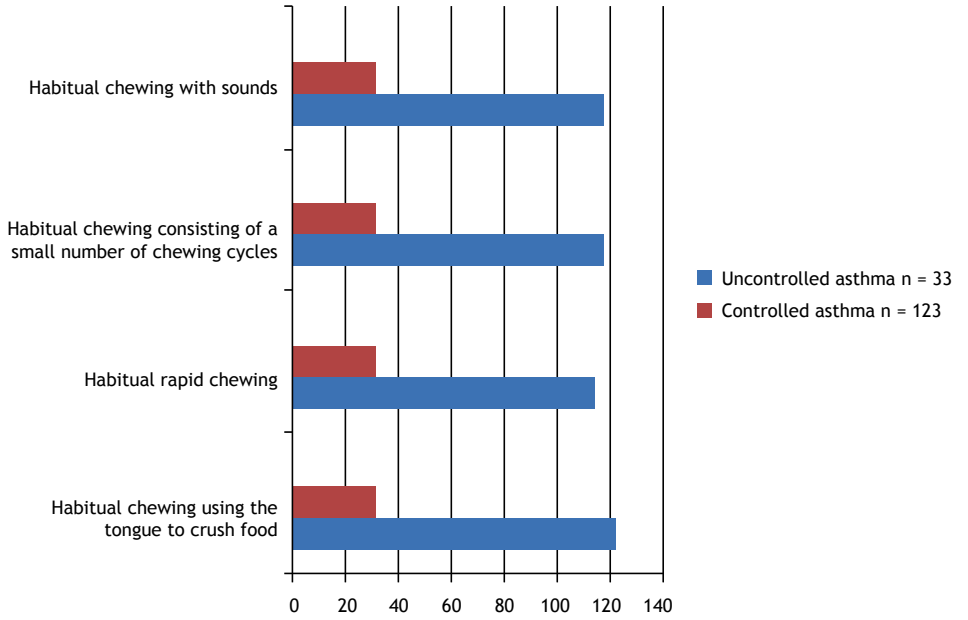

Figure 2. Comparison of masticatory function (solid food) in patients with severe asthma, by level of asthma control. Chi-square test; $p < 0.05$.

masticatory function, and swallowing function. To gain a better understanding of these changes in asthma patients, the variables were analyzed by comparing these results on the basis of the two asthma control measures used. Table 2 shows, by FEV_1 in % of predicted after bronchodilator use, the results of the statistical analysis (chi-square test) for tongue mobility, masticatory function, swallowing function, and voice complaints.

Table 3 shows, by level of asthma control as determined by the ACQ-6, the results of the statistical analysis (chi-square test) for tongue mobility, masticatory function, swallowing function, and voice complaints.

DISCUSSION

Our study results revealed that the frequency of changes in the stomatognathic system was high in patients with severe controlled asthma as well as in those with severe uncontrolled asthma. Two references were used as parameters for assessing asthma control: an objective one and a subjective one. Spirometry is an

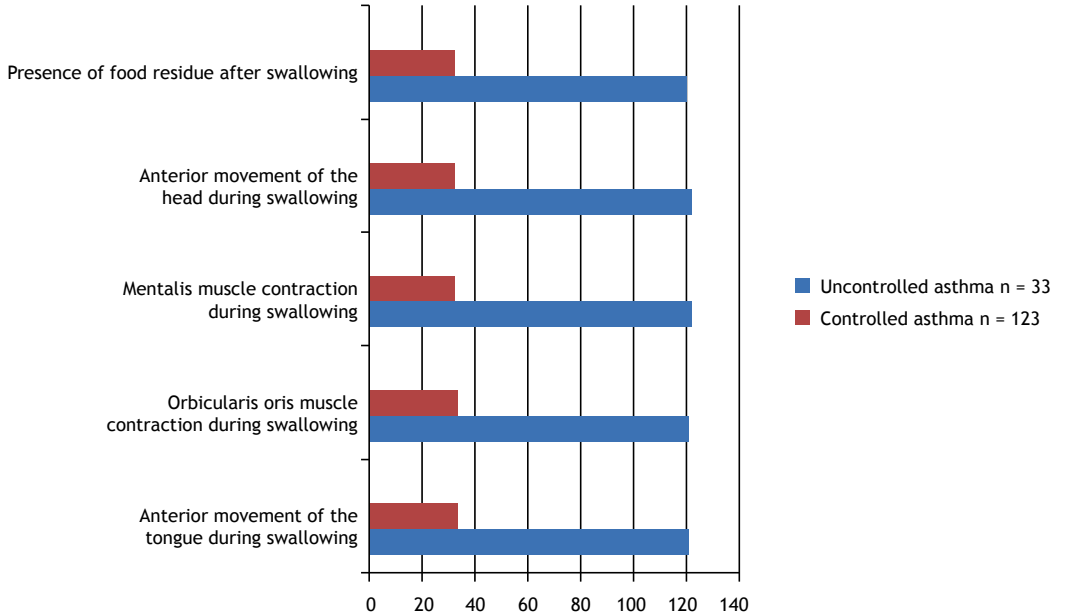

Figure 3. Comparison of swallowing function in patients with severe asthma, by level of asthma control. Chi-square test; $p < 0.05$.

objective test and provides pre- and post-bronchodilator FEV_1 values. The ACQ is a subjective questionnaire for assessing asthma control that uses patients' memories and perceptions of their health status in the last seven days. The two parameters were associated with the variables studied.

In the present study, the results for the muscles and functions of the stomatognathic system were associated with asthma severity both with the use of FEV_1 and ACQ-6 score. Campanha et al. also observed associations between changes in the stomatognathic system and FEV_1 in patients with uncontrolled asthma.[14] In contrast, when asthma patients undergo speech therapy to restore a nasal breathing pattern, it can be seen that the clinical and functional improvement relative to an oronasal breathing pattern is evidenced by the increase in PEF and FEV_1 percentage values, indicating the superiority of nasal breathing.[15]

In the present study, voice changes (Tables 2 and 3) were common in the asthma patients and can be described as hoarseness, throat clearing, scratchy voice, dry throat, burning sensation when talking, and faulty or difficult voice. The literature shows that asthma treatment can affect patients' voices. The findings of the present study corroborate those of Stanton et al., who concluded that impaired voice quality is common in patients with asthma and that the **G**rade-**R**oughness-**B**reathiness-**A**sthenicity-**S**train system (GRBAS), which is a voice assessment scale, should be included in ear, nose, and throat assessment and in speech pathology assessment in asthma patients.[11]

Regarding the posture of the articulators, the findings of the present study were as follows: a habitual anterior tongue posture; a low tongue tip posture (on the floor of the mouth); a lowered posture of the tongue dorsum; a broad and tall maxilla; use of dental prostheses; and an elongated, edematous uvula. Corroborating these results, Berlese et al. found several orofacial changes in oral breathers, such as dry, open lips; a short, hypofunctioning upper lip; a full, everted lower lip; a lowered, hypotonic tongue; maxillary atresia and a high-arched palate; open bite and crossbite; hypotonic orofacial muscles; a flat nose with small nostrils; and protruding upper teeth.[7]

We found that 18.3% of our study participants were totally edentulous. As for dental arch condition, it was possible to observe caries and diastemas in the teeth, regardless of their position; poor overall condition; unhealthy gums; and use of fixed or removable dental prostheses. In a study of children with asthma conducted in 2007, Shashikiran et al. found an association between bronchodilator use, causing local effects such as a decrease in salivary pH, and changes in salivary secretion levels and composition, which explains the increased incidence of caries and periodontal disease and draws attention to need for more effective hygiene as a means of preventing caries.[16] Another study, which found asthma to be associated with orthodontic changes, facial symmetry, and Angle's classification of dental occlusion, observed the presence of crossbite, overbite, and diastemas,[17] corroborating the findings of the present study.

Changes in masticatory function include crushing food with the tongue and chewing rapidly and insufficiently. Da Cunha et al. suggested that chewing duration tends to be decreased in asthma patients. Breathing difficulties and incoordination of breathing may be associated with decreased chewing duration, since asthma patients have difficulty in maintaining the balance required for breathing during feeding.[18]

Table 2. Data from the evaluation of orofacial muscle function in adults with asthma, by FEV_1 in % of predicted after bronchodilator use.[a]

Variable	$FEV_1 \geq 80\%$ (n = 52)	$FEV_1 < 80\%$ (n = 101)	p*
Tongue, flaccid tone	19 (35.8)	54 (51.9)	0.06
Tongue, asymmetric sucking	14 (26.4)	34 (32.7)	0.47
Tongue, changes in the 4 cardinal points	3 (5.8)	14 (13.9)	0.18
Habitual open-mouth chewing	4 (7.7)	25 (24.8)	0.02
Habitual chewing more on one side	46 (88.5)	92 (91.1)	0.58
Difficulty in swallowing bread	15 (28.8)	38 (37.6)	0.37
Mentalis muscle contraction during water swallowing	51 (98.1)	100 (99.0)	1.00
Difficulty in swallowing water	9 (17.3)	34 (33.7)	0.04
Chocking during water swallowing	13 (25.0)	37 (36.6)	0.20
Voice problems	27 (51.9)	82 (81.2)	0.01

[a]Values expressed as n (%). *Chi-square test or Fisher's exact test.

Table 3. Data from the evaluation of orofacial muscle function in adults with severe controlled asthma or severe uncontrolled asthma, as determined by the 6-item Asthma Control Questionnaire (ACQ-6).[a]

Variable	Patients[b]		p*
	Controlled asthma (n = 123)	Uncontrolled asthma (n = 33)	
Tongue, flaccid tone	55 (43.7)	19 (56.0)	0.25
Tongue, asymmetric sucking	36 (28.6)	13 (38.2)	0.30
Tongue, changes in the 4 cardinal points	11 (9.0)	6 (18.1)	0.12
Habitual open-mouth chewing	21 (17.0)	9 (27.3)	0.14
Habitual chewing more on one side	111 (90.2)	30 (91.0)	0.65
Difficulty in swallowing bread	32 (26.0)	22 (66.6)	0.01
Mentalis muscle contraction during water swallowing	121 (98.4)	33 (100.0)	0.62
Difficulty in swallowing water	31 (25.2)	14 (42.4)	0.05
Chocking during water swallowing	39 (31.7)	13 (38.2)	0.26
Voice problems	87 (71.0)	25 (76.0)	0.66

[a]Values expressed as n (%). [b]Controlled asthma: ACQ-6 scores ≥ 1.5; and uncontrolled asthma: ACQ-6 scores < 1.5. *Chi-square test or Fisher's exact test.

Using the tongue to help chewing, promoting food crushing, is consistent with the result of Lemos et al., who show that chewing is a learned function and may undergo changes.[6] The patients in the present study made a lot of random chewing sounds. This result may be associated with the high frequency of oral breathers in the study population. Oliveira et al. define masticatory performance as a measure of the ability to grind food.[19] They believe that nasal obstruction produces sounds and changes in the posture of the tongue, lips, and jaw. Therefore, oral breathers, as well as asthma patients, do not eat well, undermining their craniomaxillary and orofacial development.

Studies of the functions of the stomatognathic system draw attention to the fact that the age at which an individual develops a mature swallowing pattern is controversial, ranging from 18 months to 6 years of age. Lemos et al., in 2009, pointed out that there is a relationship between oral breathing and the presence of changes in the swallowing pattern.[6] Drozdz et al. reported that the act of swallowing depends on a complex and dynamic process using structures in common with the act of breathing, and, therefore, respiratory problems can cause swallowing difficulties.[20] Berlese et al. agreed on the fact that oral breathing causes functional changes, such as adaptive swallowing, which can be characterized by the association of lip action, mentalis muscle action, and tongue protrusion, which occurs because of decreased tongue tone and a lowered tongue posture.[7] In an attempt to correct these changes, the perioral muscles, including the orbicularis oris and the mentalis muscle, act more actively to reestablish the lip seal required for proper breathing.[7]

We emphasize the importance of the originality of the present study, which involved adults with severe asthma. The limitations of the present study are considered to be the lack of a control group, the fact that the study's convenience sample was drawn consecutively, the probability that the subjective responses on the ACQ-6 negatively affected the correct perception of asthma control, and the lack of an otolaryngologist to diagnose and quantify the presence of allergic rhinitis. However, this loss of information is in line with the literature.

Our study results revealed that the frequency of changes in the stomatognathic system affecting muscles and structures was higher in patients with severe uncontrolled asthma than in those with severe controlled asthma; that the frequency of oronasal

breathing, dental arch changes, and voice changes was high in patients with severe asthma, regardless of the level of asthma control; and that the frequency of changes in the stomatognathic system affecting the functions of breathing, chewing, and swallowing was higher in patients with severe uncontrolled asthma than in those with severe controlled asthma.

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REFERENCES

1. Global Initiative for Asthma - GINA. [homepage on the Internet]. Bethesda: Global Initiative for Asthma. [cited 2015 Apr 1]. Pocket Guide for Health Professionals Updated 2015. [Adobe Acrobat document, 28p.]. Available from: http://ginasthma.org/wp-content/uploads/2016/01/GINA_Pocket_2015.pdf
2. Salles C, Cruz AA. Vias Aéreas Unidas. Rinite Alérgica: Conhecendo Melhor. 1st ed. São Paulo: Conexão Editorial; 2010, vol 1, p. 177-91.
3. Kairaitis K, Garlick SR, Wheatley JR, Amis TC. Route of breathing in patients with asthma. Chest. 1999;116(6):1646-52. http://dx.doi.org/10.1378/chest.116.6.1646
4. de Felicio CM, de Oliveira MM, da Silva MA. Effects of orofacial myofunctional therapy on temporomandibular disorders. Cranio. 2010;28(4):249-59. http://dx.doi.org/10.1179/crn.2010.033
5. Abreu RR, Rocha RL, Lamounier JA, Guerra AF. Prevalence of mouth breathing among children. J Pediatr (Rio J). 2008;84(5):467-70. http://dx.doi.org/10.1590/S0021-75572008000600015
6. Lemos CM, Wilhelmsen NS, Mion Ode G, Mello Júnior JF. Functional alterations of the stomatognathic system in patients with allergic rhinitis: case-control study. Braz J Otorhinolaryngol. 2009;75(2):268-74. http://dx.doi.org/10.1016/S1808-8694(15)30789-8
7. Berlese DB, Fontana PF, Botton L, Weimnann AR, Haeffner LS. Myofunctional characteristics of obese mouth and nose breathers. Rev Soc Bras Fonoaudiol. 2012;17(2):171-6. http://dx.doi.org/10.1590/S1516-80342012000200012
8. Castro MS, Toro AA, Sakano E, Ribeiro JD. Evaluation of oral functions of the stomatognathic system according to the levels of asthma severity. J Soc Bras Fonoaudiol. 2012;24(2):119-24. http://dx.doi.org/10.1590/S2179-64912012000200005
9. Fonseca JA, Botelho C. Severe asthma: definition [Article in Portuguese]. Rev Bras Alerg Imunopatol. 2006;29(2):70-6.
10. Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J. 2014;43(2):343-73. Erratum in: Eur Respir J. 2014;43(4):1216. http://dx.doi.org/10.1183/09031936.00202013
11. Stanton AE, Sellars C, Mackenzie K, McConnachie A, Bucknall CE. Perceived vocal morbidity in a problem asthma clinic. J Laryngol Otol. 2009;123(1):96-102. http://dx.doi.org/10.1017/S002221510800323X
12. Global Initiative for Asthma. Global strategy for asthma management and prevention. Bethesda: National Institutes of Health; 2011.
13. Leite M, Ponte EV, Petroni J, D'Oliveira Júnior A, Pizzichini E, Cruz AA. Evaluation of the asthma control questionnaire validated for use in Brazil. J Bras Pneumol. 2008;34(10):756-63. http://dx.doi.org/10.1590/S1806-37132008001000002
14. Campanha SM, Freire LM, Fontes MJ. Impact of asthma, allergic rhinitis and mouth breathing in life quality of children and adolescents. Rev CEFAC. 2008;10(4):513-9. http://dx.doi.org/10.1590/S1516-18462008000400011
15. Campanha SM, Fontes MJ, Santos JL. Dyspnea in patients with asthma, allergic rhinitis and mouth breathing. Rev CEFAC. 2012;14(2):268-73.
16. Shashikiran ND, Reddy VV, Raju PK. Effect of antiasthmatic medication on dental disease: dental caries and periodontal disease. J Indian Soc Pedod Prev Dent. 2007;25(2):65-8. http://dx.doi.org/10.4103/0970-4388.33450
17. Faria VC, de Oliveira MA, Santos LA, Santoro IL, Fernandes AL. The effects of asthma on dental and facial deformities. J Asthma. 2006;43(4):307-9. http://dx.doi.org/10.1080/02770900600623305
18. da Cunha DA, da Silva HJ, Nascimento GK, da Silva EG, da Cunha RA, Régis RM, et al, Analysis of the masticatory process of asthmatic children: Clinical and electromyographic research. Int Arch Otorhinolaryngol. 2012;16(3):358-64.
19. Oliveira RL, Noronha WP, Bonjardim LR. Masticatory performance evaluation in patients with nasal and mouth breathing [Article in Portuguese]. Rev CEFAC. 2012;14(1):114-21. http://dx.doi.org/10.1590/S1516-18462011005000112
20. Drozdz DR, Costa CC, Jesus PR, Trindade MS, Weiss G, Neto AB, et al. Pharyngeal swallowing phase and chronic cough. Int Arch Otorhinolaryngol. 2012;16(4):502-8.

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Perme Intensive Care Unit Mobility Score and ICU Mobility Scale: translation into Portuguese and cross-cultural adaptation for use in Brazil

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ABSTRACT

Objective: To translate the Perme Intensive Care Unit Mobility Score and the ICU Mobility Scale (IMS) into Portuguese, creating versions that are cross-culturally adapted for use in Brazil, and to determine the interobserver agreement and reliability for both versions. **Methods:** The processes of translation and cross-cultural validation consisted in the following: preparation, translation, reconciliation, synthesis, back-translation, review, approval, and pre-test. The Portuguese-language versions of both instruments were then used by two researchers to evaluate critically ill ICU patients. Weighted kappa statistics and Bland-Altman plots were used in order to verify interobserver agreement for the two instruments. In each of the domains of the instruments, interobserver reliability was evaluated with Cronbach's alpha coefficient. The correlation between the instruments was assessed by Spearman's correlation test. **Results:** The study sample comprised 103 patients—56 (54%) of whom were male—with a mean age of 52 ± 18 years. The main reason for ICU admission (in 44%) was respiratory failure. Both instruments showed excellent interobserver agreement ($\kappa > 0.90$) and reliability ($\alpha > 0.90$) in all domains. Interobserver bias was low for the IMS and the Perme Score (−0.048 ± 0.350 and −0.06 ± 0.73, respectively). The 95% CIs for the same instruments ranged from −0.73 to 0.64 and −1.50 to 1.36, respectively. There was also a strong positive correlation between the two instruments ($r = 0.941$; $p < 0.001$). **Conclusions:** In their versions adapted for use in Brazil, both instruments showed high interobserver agreement and reliability.

Keywords: Physical therapy modalities; Intensive care units; Translations; Validation studies.

INTRODUCTION

Early mobilization is part of the rehabilitation process for ICU patients and is currently considered a way to prevent ICU-acquired muscle weakness and worsening of physical function.[1,2] Some studies have associated the practice of early mobilization with decreased duration of mechanical ventilation and reduced length of ICU and hospital stays, as well as with the promotion of functional improvement in ICU survivors.[1,3,4]

There are currently 26 published instruments that purport to assess function in ICU patients. Of those, the Functional Independence Measure and the Barthel index have been used both in clinical practice and in research.[1,5] However, few of these instruments were developed and validated to assess function and/or mobility in ICU patients. In fact, only 6 were developed specifically for the ICU setting and have published clinimetric data. These instruments are the Physical Function in Intensive care Test scored, the Chelsea Critical Care Physical Assessment tool, the Perme Intensive Care Unit Mobility Score, the Surgical intensive care unit Optimal Mobilization Score, the ICU mobility scale, and the Functional Status Score for the ICU.[6] However, none of them are considered "gold standard" to assist multidisciplinary teams in quantifying the patient's degree of mobility in a rapid, easy, and objective way.[7,8] In addition, there are conditions extrinsic to the patient that affect the patient's mobility in bed, such as the presence of access ports, lines, and chest tubes, which can be interpreted as a barrier to mobility, and this presence is not scored or considered in most instruments.[5,9-11]

Taking into account such limitations, Perme et al.[12] developed a specific instrument for measuring improvement in mobility status, with a view to standardizing the evaluation of ICU patients—the Perme Intensive Care Unit Mobility Score—hereafter referred to as the Perme Score, which is an instrument that objectively measures the mobility status of ICU patients, starting with the ability to follow commands and culminating in the distance walked in two minutes. This mobility instrument is scored from 0 to 32 and comprises 15 items grouped into 7 categories: mental status; potential mobility barriers; functional strength; bed mobility; transfers; gait (with

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or without assistive devices); and endurance. In this instrument, a high score indicates high mobility and a decreased need for assistance. In contrast, a low score indicates low mobility and an increased need for assistance.[12]

With similar objectives to those of the Perme Score, Hodgson et al.[8] also developed an instrument for measuring mobility status in ICU patients objectively. Designated the ICU Mobility Scale (IMS), this single-domain instrument is scored from 0 to 10, with a score of 0 meaning low mobility (interpreted as a patient being capable of performing only passive exercises in bed) and a score of 10 meaning high mobility (interpreted as a patient being capable of independent ambulation, without aid).[8]

The clinical utility of a tool has to be determined on the basis of a logical assessment of its validation, reliability, and applicability.[13] In order to choose the best tool that can effectively assess the functional changes that will occur in the patient during the ICU stay, health care professionals and researchers should consider which tools have clinimetric data that are more robust and appropriate for the functional outcomes that they want to analyze.[6,14] To date, neither the Perme Score nor the IMS has been appropriately translated and validated for use in Brazil, taking into account the language and cultural differences. Therefore, the objective of the present study was to translate these two ICU mobility instruments into Portuguese, creating versions that are cross-culturally adapted for use in Brazil, and to determine inter-rater agreement and reliability for both versions.

METHODS

The present study was approved by the Research Ethics Committee and the *Comissão de Análises de Projetos de Pesquisa* (CAPPesq, Committee for the Analysis of Research Projects) of the University of São Paulo School of Medicine *Hospital das Clínicas* (Ruling no. 657.496). The translated instruments were evaluated at two clinical ICUs (10 beds) and one surgical ICU (20 beds) of the University of São Paulo School of Medicine *Hospital das Clínicas* Central Institute, in the city of São Paulo, Brazil, between April and June of 2015. In the phase of instrument testing, since physical therapy evaluation was part of the routine care at those ICUs, being performed several times a day, the health care professionals who participated in the study, scoring and comparing the instruments, gave written informed consent, rather than the patients.

The methodology for translating and cross-cultural adapting and validating the instruments followed a rigorous process, in accordance with current guidelines for the translation and cross-cultural adaptation of instruments.[15,16] The following steps were performed: 1) Preparation: the author of the project contacted the authors of the original instruments and obtained the rights to use, translate, and cross-culturally validate the instruments; 2) Translation from English into Portuguese: the instruments were independently translated into the target language by two translators who were native speakers of Portuguese and fluent in English, one of whom was familiar with the instruments and was aware of the objective of the present study and the other of whom was not familiar with the instruments; 3) Reconciliation and synthesis: the two initial Portuguese-language versions were compared, item by item, with the original English-language versions by two physical therapists who were familiar with the instruments. Any existing discrepancies were analyzed and discussed by three researchers, leading to the production of a second Portuguese-language version for each of the two instruments; 4) Back-translation: the second Portuguese-language version of each of the two instruments was sent to two translators who were native speakers of English and fluent in Portuguese, neither of whom had contact with the original English-language versions, for back-translation[15-17]; 5) Review and harmonization of the back-translation: the back-translated versions of the instruments were compared with their original English-language versions by a review committee comprising three researchers, in order to identify potential discrepancies and make the necessary adjustments, item by item, thereby producing the final back-translated version of each of the two instruments; 6) Approval from the authors of the original instruments: the final back-translated versions were sent to the authors of the original instruments for evaluation and comments on their consistency. An expert committee comprising three physical therapists analyzed the evaluations and comments of the authors of the original instruments, incorporating their suggestions, and thereby produced the final Portuguese-language version of each of the two instruments; and 7) Pre-test: raters were trained on the administration and scoring of the final Portuguese-language version of each of the two instruments. After training, a pilot study involving 40 patients was conducted in which two raters administered the two instruments following the methodology described in the original articles; during these evaluations, the raters could discuss the scores and the difficulties in administering each instrument.[13]

Data were collected by two raters, one of whom was a senior (> 5 years of experience) physical therapist (rater 1) and one of whom was a junior (< 5 years of experience) physical therapist (rater 2). The two raters performed the scoring according to the rules of the two mobility instruments, which were administered after an initial evaluation made by the ICU physical therapist. While one of the raters evaluated the patient, the other one only observed the procedure, without having any physical contact with the patient. Each rater was responsible for 50% of the evaluations, and the functions of rater and observer were swapped every two patients. Both raters completed the scoring sheet of the Perme Score and of the IMS according to the highest activity level. In an attempt to avoid biases, the scoring sheets were completely separate and there was no communication between the raters.[7,8]

Data on age, gender, reason for ICU admission, mechanical ventilation use, vasoactive drug use, and score on the Simplified Acute Physiology Score 3 were collected to determine the clinical characteristics of the population.

The sample size was calculated with a level of significance of 5% and a power of 80%, taking into account that the instruments could be equal (50%) or not (50%). This is possible through the use of the Bernoulli probability distribution; in addition, we considered a delta of 10%, that is, the probability of equality could range from 40% to 60%, and found that a sample size of 100 individuals was required. Statistical analysis was performed with the Statistical Package for the Social Sciences, version 17 (SPSS Inc., Chicago, IL, USA).

The clinical characteristics of the patients were descriptively expressed as mean and standard deviation, median and interquartile range, or proportion, depending on data type and normality of distribution. The level of inter-rater agreement in the scoring of each instrument was determined using weighted kappa statistics and 95% CI. Inter-rater reliability (internal consistency) in scoring was determined using Cronbach's alpha coefficient. For the Perme Score, inter-rater agreement and reliability were assessed individually for each domain (items 1 to 15). In addition, Bland-Altman plots were used to determine inter-rater agreement in total score (sum of all domains) both for the Perme Score and the IMS. The proportions of evaluations with minimum scores (floor effect) and maximum scores (ceiling effect) were also calculated. Finally, the Kolmogorov-Smirnov test and Levene's test were used to determine normality and homoscedasticity, respectively. Since these principles were not met, Spearman's correlation coefficient was used to test the correlation between the two instruments.[7,8,13] For this correlation analysis, we used the values from the two raters.

RESULTS

Table 1 shows the clinical characteristics of the patients evaluated in the present study. Slightly more than half (54%; n = 56) of our sample was male and 67% (n = 69) of the patients were admitted for clinical reasons, the most prevalent being respiratory disorders (n = 45). Mechanical ventilation was present in 36% (n = 37) of the cases, and vasoactive drug use occurred in 51% (n = 53). Appendices show the Portuguese-language versions of the IMS and the Perme Score, both of which were translated from the original instruments. They are available online at http://www.jornaldepneumologia.com.br/detalhe_anexo.asp?id=47

Table 2 shows the inter-rater agreement (kappa statistics and 95% CI) and reliability (internal consistency, Cronbach's alpha coefficient) for the IMS and for each domain of the Perme Score. The IMS showed excellent inter-rater agreement and reliability. In addition, the inter-rater agreement for each item of the Perme Score ranged from 78% to 100%, and the inter-rater reliability (Cronbach's alpha coefficient) ranged from 88% to 100%, meaning that there was excellent inter-rater agreement and reliability for all items. Figure 1 presents the Bland-Altman plots for the IMS and for the total score on the Perme Score. Inter-rater bias was low both for the IMS (−0.048 ± 0.35) and the Perme Score (−0.06 ± 0.73). The 95% CIs ranged from −0.73 to 0.64 for the IMS and from −1.50 to 1.36 for the Perme Score.

Table 1. Characteristics of the patients (N = 103).[a]

Characteristic	Result
Age, years[b]	52 ± 18
Male gender	56 (54)
SAPS3[c]	66 [24]
Reason for ICU admission	
Clinical	69 (67)
Respiratory	45 (44)
Renal	9 (9)
Neurological	8 (8)
Rheumatological	5 (5)
Hepatic	2 (2)
Surgical	26 (25)
Gastroenterological	11 (11)
Hepatic	9 (9)
Cardiac	3 (3)
Neurological	2 (2)
Respiratory	1 (1)
Trauma	8 (8)
Vasoactive drug use	53 (51)
Mechanical ventilation	37 (36)
Duration of mechanical ventilation, days[c]	4 [6]
Tracheostomy	9 (9)
Length of ICU stay at the time of evaluation, days[c]	5.5 [7]

SAPS3: Simplified Acute Physiology Score 3. [a]Values expressed as n (%), except where otherwise indicated. [b]Value expressed as mean ± SD. [c]Values expressed as median [interquartile range].

The floor effect for the IMS and the Perme Score was found to be 36% and 20%, respectively. The ceiling effect for the IMS and the Perme Score was found to be 6% and 3%, respectively.

The mean completion time for the scoring sheets was two minutes for the Perme Score and less than one minute for the IMS. There was also a strong positive correlation between the use of the two instruments in the evaluation of the patients ($r = 0.941$; $p < 0.001$).

DISCUSSION

For the present study, two instruments for evaluating mobility in ICU patients were carefully translated into Portuguese and validated for use in Brazil, with technical and semantic equivalence having been achieved between the original versions and the Portuguese-language versions. Our results show that, in their versions adapted for use in Brazil, both instruments showed

Table 2. Inter-rater reliability and agreement for the ICU Mobility Scale (IMS) and the Perme ICU Mobility Score.

Instrument	Rater 1 Median [min-max]	Rater 2 Median [min-max]	Reliability (Cronbach's alpha coefficient)	Agreement κ (95% CI)
IMS	1 [0-10]	1 [0-10]	0.99	0.99 (0.98-0.99)
Perme ICU Mobility Score				
a) Mental status: item 1	2 [0-2]	2 [0-2]	0.97	0.94 (0.92 - 0.96)
b) Mental status: item 2	1 [0-1]	1 [0-1]	1.00	1.00
c) Potential barriers: item 3	1 [0-1]	1 [0-1]	1.00	1.00
d) Potential barriers: item 4	0 [0-1]	0 [0-1]	0.96	0.92 (0.88 - 0.94)
e) Potential barriers: item 5	0 [0-1]	0 [0-1]	0.97	0.95 (0.93 - 0.96)
f) Potential barriers: item 6	0 [0-1]	0 [0-1]	0.88	0.78 (0.70-0.85)
g) Functional strength: item 7 (left leg)	1 [0-1]	1 [0-1]	0.99	0.98 (0.97-0.98)
h) Functional strength: item 7 (right leg)	1 [0-1]	1 [0-1]	1.00	1.00
i) Functional strength: item 8 (right arm)	0 [0-1]	0 [0-1]	0.99	0.98 (0.97-0.98)
j) Functional strength: item 8 (left arm)	1 [0-1]	1 [0-1]	0.99	0.98 (0.97-0.98)
k) Bed mobility: item 9	0 [0-3]	0 [0-3]	0.98	0.97 (0.96-0.98)
l) Bed mobility: item 10	0 [0-3]	0 [0-3]	0.99	0.99 (0.99-0.99)
m) Transfers: item 11	0 [0-3]	0 [0-3]	0.98	0.97 (0.95-0.98)
n) Transfers: item 12	0 [0-3]	0 [0-3]	0.99	0.99 (0.99-0.99)
o) Transfers: item 13	0 [0-3]	0 [0-3]	0.99	0.99 (0.99-0.99)
p) Gait item 14	0 [0-3]	0 [0-3]	1.00	1.00
q) Endurance: item 15	0 [0-3]	0 [0-3]	0.99	0.99 (0.98-0.99)
r) Perme ICU Mobility Score (Total)	8 [0-32]	8 [0-32]		

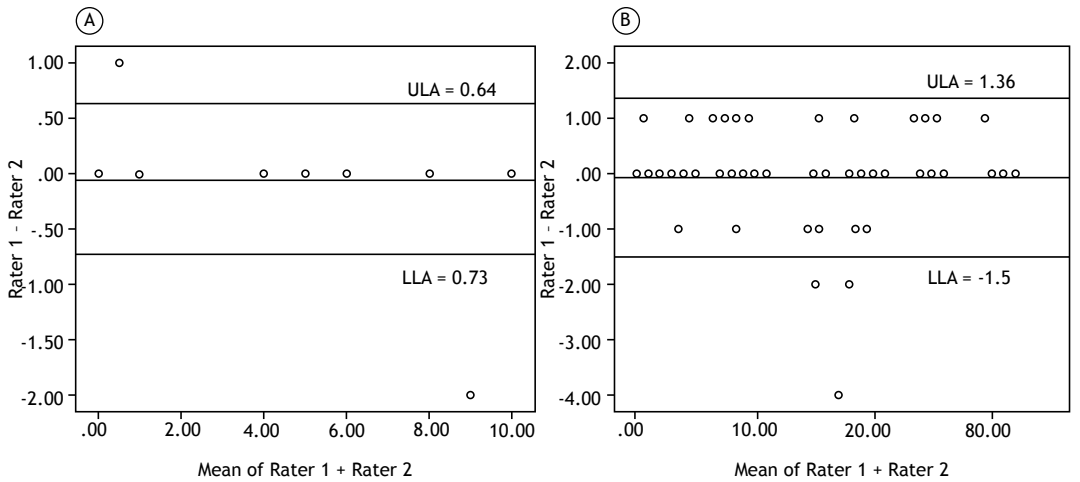

Figure 1. Bland-Altman plots of inter-rater score differences and mean scores for the ICU Mobility Scale (in A) and the Perme ICU Mobility Score (in B).[a] ULA: upper 95% limit of agreement; and LLA: lower 95% limit of agreement. [a]There are superimposed points in the figure.

high inter-rater agreement and reliability after a brief period of familiarization and training with them. In addition, there was a strong positive correlation between the two instruments.

Performing physical therapy in critically ill patients is currently in the spotlight, with numerous publications commenting on its prevalence and benefits.[18-20] In this context, some instruments for evaluating function and mobility have been developed specifically for this population in order to improve physical therapy care in terms of performing and progressing the exercises in ICU patients according to the mobility milestones that each individual can reach.[8] To date, as mentioned above, no instrument for evaluating mobility in ICU patients has been cross-culturally adapted for use in Brazil. The careful translation and cross-cultural validation of such an instrument makes it possible for health care professionals nationwide to have access to a tool that can improve the quality of care to critically ill patients in the ICU, as well as allowing the comparison of results across studies conducted in different countries.[15]

In their versions adapted for use in Brazil, both the IMS and the Perme Score showed excellent inter-rater

agreement and reliability (κ > 0.9 and α > 0.9 for most domains). Although the group who developed the Perme Score reported moderate to high reliability, our study reported an even higher level of inter-rater reliability.[7,12] One possible explanation for this finding it that, in our study, the sample size was larger than those of the two previous studies.[7,12] In view of the ease of learning and ease of use of the Perme Score, any disagreements in score had a lesser impact in our study than in the validation studies for the original English-language version of the instrument.[7,12] Our study also reported higher inter-rater reliability for the Portuguese-language version of the IMS than that reported in the validation study for the original English-language version of the instrument.[8] In this case, the collection method may have affected the result. In our study, the raters performed the scoring simultaneously but in an independent fashion, each being blinded to the scoring by the other rater, whereas in the study by Hodgson et al.,[8] each assessor separately evaluated the patient at 30-min intervals.[8]

Interestingly, the IMS showed excellent Inter-rater reliability and agreement, although its single domain is scored from 0 to 10, an 11-point range. Although it is a greater range than that in each domain of the Perme Score, the IMS comprises mobility milestones that are clear and can easily be evaluated by the rater.

Item 6 in the Perme Score, "potential mobility barriers–continuous intravenous infusion", was the one showing the lowest inter-rater reliability and agreement in our study. Although some patients had venous access for administration of saline or drugs, in some cases, the infusion was not being administered at the time of evaluation, which may have confused the raters in scoring this item. However, we emphasize that, even with this likely difference, the reported inter-rater reliability and agreement were higher than 75-80%.

The Bland-Altman plots showed high inter-rater score agreement and low inter-rater score variability for the IMS and for the sum of all domains of the Perme Score. Since the evaluation of each domain had shown excellent inter-rater agreement and reliability, the sum of all domains did not change this behavior. On the basis of the 95% CIs, the maximum inter-rater difference was 2 points for the Perme Score and less than 1 point for the IMS.

It was expected that the scores on the two instruments would be highly correlated, given that both instruments measure the same property and therefore should show a similar behavior.

Finally, instrument floor and ceiling effects of 15% or less are considered acceptable. In our study, floor effects were found to be higher for the two instruments (20% and 36% for the Perme Escore and the IMS, respectively). Knowing that these instruments purport to assess functioning, floor effects were expected to be higher than normal, given the high incidence of sedated or unconscious patients in ICUs. Although data collection was performed at three different ICUs in order to try to minimize this drawback, in 35% of the evaluations, the patients were unconscious or had lethargic responses, which made it impossible to perform more functional tasks or mobilizations at the time of evaluation. The lower floor effect of the Perme Score as compared with that of the IMS can be explained by the scoring of the different domains of the former, such as patient cooperation, presence of pain, and presence of barriers to mobilization. Although they are not mobilization aspects per se, they end up affecting the ease or difficulty of mobilization.

Some limitations of our study should be taken into account. First, no clinimetric analyses were performed other than inter-rater reliability and agreement testing and inter-instrument correlation analysis. However, the primary objective of the present study was the cross-cultural validation of the instruments for use in Brazil. We recognize that the applicability of the instruments and their predictive and concurrent validity have yet to be tested. Although the clinimetric properties of the IMS were tested against those of the Physical Function in Intensive care Test scored,[6] the same was not true for the Perme Score. Second, in our study, the two participating raters who were tested for inter-rater reliability and agreement were physical therapists. Knowing that such health care professionals are directly related to the process of functional evaluation and early mobilization of critically ill patients, analysis of inter-rater reliability and agreement involving such professionals was fundamental. However, we cannot state that the characteristics reported in the present study can be obtained by the other health care professionals who comprise multidisciplinary ICU teams, such as nurses and physicians, and will eventually use the instruments. Finally, the evaluations took place concurrently. Therefore, aspects such as tone of voice, personal approach, and instruction of patients, all of which may differ from one health care professional to another, were not fully evaluated in our study. However, each rater was responsible for half of the evaluations, which to some extent minimized this effect.

Therefore, we conclude that the Brazilian Portuguese-language versions of the IMS and the Perme Score were appropriately translated and cross-culturally validated, following strict guidelines, and can be used in Brazil. Both versions showed excellent inter-rater agreement and reliability.

REFERENCES

1. Schweickert WD, Pohlman MC, Pohlman AS, Nigos C, Pawlik AJ, Esbrook CL, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients : a randomised controlled trial. Lancet. 2009;373(9678):1874-82. http://dx.doi.org/10.1016/S0140-6736(09)60658-9
2. Burtin C, Clerckx B, Robbeets C, Ferdinande P, Langer D, Troosters T, et al. Early exercise in critically ill patients enhances short-term functional recovery. Crit Care Med. 2009;37(9):2499-505. http://dx.doi.org/10.1097/CCM.0b013e3181a38937
3. Morris PE, Goad A, Thompson C, Taylor K, Harry B, Passmore L, et

al. Early intensive care unit mobility therapy in the treatment of acute respiratory failure. Crit Care Med. 2008;36(8):2238-43. http://dx.doi.org/10.1097/CCM.0b013e318180b90e

4. Needham DM, Korupolu R, Zanni JM, Pradhan P, Colantuoni E, Palmer JB, et al. Early physical medicine and rehabilitation for patients with acute respiratory failure : a quality improvement project. Arch Phys Med Rehabil. 2010;91(4):536-42. http://dx.doi.org/10.1016/j.apmr.2010.01.002
5. Montagnani G, Vagheggini G, Panait Vlad E, Berrighi D, Pantani L, Ambrosino N. Use of the Functional Independence Measure in people for whom weaning from mechanical ventilation is difficult. Phys Ther. 2011;91(7):1109-15. http://dx.doi.org/10.2522/ptj.20100369
6. Parry SM, Denehy L, Beach LJ, Berney S, Williamson HC, Granger CL. Functional outcomes in ICU – what should we be using ? – an observational study. Crit Care. 2015;19:127. http://dx.doi.org/10.1186/s13054-015-0829-5
7. Nawa RK, Lettvin C, Winkelman C, Evora PR, Perme C. Initial interrater reliability for a novel measure of patient mobility in a cardiovascular intensive care unit. J Crit Care. 2014;29(3):475.e1-5. http://dx.doi.org/10.1016/j.jcrc.2014.01.019
8. Hodgson C, Needham D, Haines K, Bailey M, Ward A, Harrold M, et al. Feasibility and inter-rater reliability of the ICU Mobility Scale. Hear Lung. 2014;43(1):19-24. http://dx.doi.org/10.1016/j.hrtlng.2013.11.003
9. MAHONEY FI, BARTHEL DW. FUNCTIONAL EVALUATION: THE BARTHEL INDEX. Md State Med J. 1965;14:61-5.
10. Skinner EH, Berney S, Warrillow S, Denehy L. Development of a physical function outcome measure (PFIT) and a pilot exercise training protocol for use in intensive care. Crit Care Resusc. 2009;11(2):110-5.
11. Thrush A, Rozek M, Dekerlegand JL. The clinical utility of the functional status score for the intensive care unit (FSS-ICU) at a long-term acute care hospital: a prospective cohort study. Phys Ther. 2012;92(12):1536-45. http://dx.doi.org/10.2522/ptj.20110412
12. Perme C, Nawa RK, Winkelman C, Masud F. A tool to assess mobility status in critically ill patients: The Perme Intensive Care Unit Mobility Score. Methodist Debakey Cardiovasc J. 2014;10(1):41-9. http://dx.doi.org/10.14797/mdcj-10-1-41
13. Nassar Junior AP, Pires Neto RC, de Figueiredo WB, Park M. Validity, reliability and applicability of Portuguese versions of sedation-agitation scales among critically ill patients. Sao Paulo Med J. 2008;126(4):215-9. http://dx.doi.org/10.1590/S1516-31802008000400003
14. Parry SM, Granger CL, Berney S, Jones J, Beach L, El-Ansary D, et al. Assessment of impairment and activity limitations in the critically ill : a systematic review of measurement instruments and their clinimetric properties. Intensive Care Med. 2015;41(5)744-62. http://dx.doi.org/10.1007/s00134-015-3672-x
15. Beaton DE, Bombardier C, Guillemin F, Ferraz MB. Guidelines for the process of cross-cultural adaptation of self-report measures. Spine (Phila Pa 1976). 2000;25(24):3186-91. http://dx.doi.org/10.1097/00007632-200012150-00014
16. Wild D, Grove A, Martin M, Eremenco S, McElroy S, Verjee-Lorenz A, et al. Principles of Good Practice for the Translation and Cultural Adaptation Process for Patient-Reported Outcomes (PRO) Measures : report of the ISPOR Task Force for Translation and Cultural Adaptation. Value Health. 2005;8(2):94-104. http://dx.doi.org/10.1111/j.1524-4733.2005.04054.x
17. Tavares MG, Pizzichini MM, Steidle LJ, Nazário NO, Rocha CC, Perraro MC, et al. The Asthma Control Scoring System: translation and cross-cultural adaptation for use in Brazil. J Bras Pneumol. 2010;36(6):683-92.
18. Morris PE. Moving our critically ill patients: mobility barriers and benefits. Crit Care Clin. 2007;23(1):1-20. http://dx.doi.org/10.1016/j.ccc.2006.11.003
19. Lima NP, Silva GM, Park M, Pires-Neto RC. Mobility therapy and central or peripheral catheter-related adverse events in an ICU in Brazil. J Bras Pneumol. 2015;41(3):225-30. http://dx.doi.org/10.1590/S1806-37132015000004338
20. Denehy L, Skinner EH, Edbrooke L, Haines K, Warrillow S, Hawthorne G, et al. Exercise rehabilitation for patients with critical illness: a randomized controlled trial with 12 months of follow-up. Crit Care. 2013;17(4):R156. http://dx.doi.org/10.1186/cc12835
21. Terwee CB, Bot SD, de Boer MR, Van der Windt DA, Knol DL, Dekker J, et al. Quality criteria were proposed for measurement properties of health status questionnaires. J Clin Epidemiol. 2007;60(1):34-42. http://dx.doi.org/10.1016/j.jclinepi.2006.03.012

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ORIGINAL ARTICLE

The halo sign: HRCT findings in 85 patients

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Study carried out at the Irmandade da Santa Casa de Misericórdia de Porto Alegre, Porto Alegre (RS) Brasil.

ABSTRACT

Objective: The halo sign consists of an area of ground-glass opacity surrounding pulmonary lesions on chest CT scans. We compared immunocompetent and immunosuppressed patients in terms of halo sign features and sought to identify those of greatest diagnostic value. **Methods:** This was a retrospective study of CT scans performed at any of seven centers between January of 2011 and May of 2015. Patients were classified according to their immune status. Two thoracic radiologists reviewed the scans in order to determine the number of lesions, as well as their distribution, size, and contour, together with halo thickness and any other associated findings. **Results:** Of the 85 patients evaluated, 53 were immunocompetent and 32 were immunosuppressed. Of the 53 immunocompetent patients, 34 (64%) were diagnosed with primary neoplasm. Of the 32 immunosuppressed patients, 25 (78%) were diagnosed with aspergillosis. Multiple and randomly distributed lesions were more common in the immunosuppressed patients than in the immunocompetent patients ($p < 0.001$ for both). Halo thickness was found to be greater in the immunosuppressed patients ($p < 0.05$). **Conclusions:** Etiologies of the halo sign differ markedly between immunocompetent and immunosuppressed patients. Although thicker halos are more likely to occur in patients with infectious diseases, the number and distribution of lesions should also be taken into account when evaluating patients presenting with the halo sign.

Keywords: Tomography, X-ray computed; Aspergillosis; Lung neoplasms.

INTRODUCTION

The CT halo sign consists of an area of ground-glass opacity surrounding a pulmonary nodule or mass.[1] The halo sign was first described in 1985 by Kuhlman et al., who reviewed chest CT scans of nine patients with acute leukemia who developed invasive pulmonary aspergillosis.[2] Since then—and despite its infrequency—the halo sign has been reported in association with a variety of conditions.[3,4] Its pathophysiology usually involves one of three mechanisms: hemorrhage, inflammation, or neoplastic growth.[5]

Most of the available information about the halo sign has been derived from patients with pre-existing conditions. However, there are limited data on its potential usefulness in predicting the final diagnosis (or diagnostic group, e.g., infection or malignancy). Therefore, the objective of the present study was to determine the diagnostic value of the halo sign by exploring associations between CT measurements and immunological status in a cohort of patients presenting with the CT halo sign.

METHODS

This was a multicenter retrospective study of CT images obtained between January of 2010 and May of 2014 from patients presenting at any of seven tertiary care centers in southern Brazil, which is an endemic area for granulomatous diseases. Scans were selected by searching the picture archiving and communication systems (PACSs) of all participating institutions using the terms "halo" and "halo sign", as well as the following combinations of terms: "ground-glass" + "nodule"; "nodule" + "surround"; "nodule" + "periphery"; and "ground-glass" + "periphery". The research protocol was approved by the local research ethics committee (Protocol no. 243.155). Given the retrospective nature of the study, informed consent was waived.

A general radiologist reviewed the files retrieved from the PACSs in order to confirm the presence of the halo sign. Medical records were reviewed in order to determine patient immune status. For the purpose of the present study, patients were considered immunosuppressed in the presence of AIDS; any form of congenital immunodeficiency; or a recent (≤ two-month) history of chemotherapy, radiation therapy, or decreased white blood cell count (lymphopenia [absolute lymphocyte count $\leq 1.0 \times 10^9$ L] or neutropenia [absolute neutrophil count $\leq 1.5 \times 10^9$ L]).[6,7] All other patients were considered to be immunocompetent. If a final diagnosis had not been reached by the time of medical record review, patients were followed until a definitive diagnosis was made, with serological, histological, or microbiological confirmation. Histological sampling varied across the participating institutions, including transthoracic needle biopsy,

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video-assisted thoracotomy, and open thoracotomy. Although serological and microbiological tests were performed in accordance with the corresponding (updated) guidelines, their performance was dependent on patient clinical background.

All CT scans were performed with multidetector scanners with at least 16 rows of detectors, the acquisition parameters being as follows: slice thickness, ≤ 1.25 mm; rotation time, 0.5 s; voltage, 120 kV; and electric current, 150-400 mA. Automatic exposure control was enabled. No contrast medium was used.

For each examination, the number of lesions, as well as their outline (regular vs. irregular), size, and distribution, together with any other associated findings, were recorded. The criteria for CT findings were those defined in the Fleischner Society Glossary of Terms.[1] A nodule was defined as a rounded or irregular opacity that was well or poorly defined and ≤ 3 cm in diameter. Mediastinal and hilar lymph nodes range in size from sub-CT resolution to 10 mm. A cavity was defined as a gas-filled space, seen as a lucency or low-attenuation area within a pulmonary consolidation, mass, or nodule. The tree-in-bud pattern refers to centrilobular branching structures that resemble a budding tree. Ground-glass opacities were defined as hazy areas of increased opacity or attenuation with no obscuration of the underlying vessels. Consolidation was defined as homogeneous opacification of the parenchyma with obscuration of the underlying vessels. Abnormalities were classified as being located in the upper lobes, located in the lower lobes, or randomly distributed.

The CT scans were independently reviewed in random order by two chest radiologists who had more than 10 years of experience and who were blinded to patient clinical information. Subsequently, the two aforementioned radiologists and a third chest radiologist (with more than 40 years of experience) together reviewed the scans in order to make a final consensus decision. The diameters of the nodules and halos were measured at their widest points on axial CT scans with lung window settings.

Microsoft Excel was used for data storage and descriptive analysis, and the Statistical Package for the Social Sciences, version 14.0 (SPSS Inc., Chicago, IL, USA), was used for correlations. The chi-square test was used for qualitative variables. The Kolmogorov-Smirnov test was used in order to determine whether quantitative data were normally distributed. For parametric variables, the Student's t-test was used. For nonparametric variables, the Mann-Whitney U test was used. All tests were two-tailed, and a significance level of 0.05 was used throughout.

RESULTS

Of the 20,210 CT examinations retrieved from the PACSs of the participating centers, 85 cases (0.42%) were selected for inclusion in the present study. Of those 85 patients, 46 were male. In addition, 32 were classified as being immunosuppressed at the time of CT examination, and 53 were immunocompetent. Of those, 34 (64%) were diagnosed with a primary malignancy; of those, 24 had histopathologically confirmed adenocarcinoma. Of the 32 patients who were classified as being immunosuppressed, 25 (78%) had findings suggestive of invasive aspergillosis (positive results on direct mycological examination or histological findings). All but one of the immunosuppressed patients presenting with invasive aspergillosis were found to have neutropenia. In addition, 7 of those 25 were diagnosed with proven invasive fungal disease (on the basis of specimen culture results and radiological findings), and 18 were diagnosed with probable invasive aspergillosis (on the basis of positive microbiological studies and radiological findings).[8] Other causes of the CT halo sign included metastases, lymphoproliferative diseases, tuberculosis, plasmacytoma, staphylococcal pneumonia, actinomycosis, cryptococcosis, and histiocytosis. Table 1 and Figure 1 show the frequencies of these diagnoses in the two study groups.

The number and distribution of lesions on CT scans were found to vary significantly according to patient immune status, with immunosuppressed patients tending to exhibit multiple and randomly distributed lesions (Table 2). In cases of multiple lesions, halo thickness tended to be greater (≥ 9 mm) in immunosuppressed patients ($p < 0.05$; Figure 2); the same was not true for single lesions ($p = 0.299$).

DISCUSSION

The present retrospective study revealed ten different etiologies of the CT halo sign in 85 individuals. Pathological findings of tumor cells, inflammatory infiltrates, and, most commonly, alveolar hemorrhage have been reported to account for the ground-glass opacities surrounding pulmonary lesions on CT

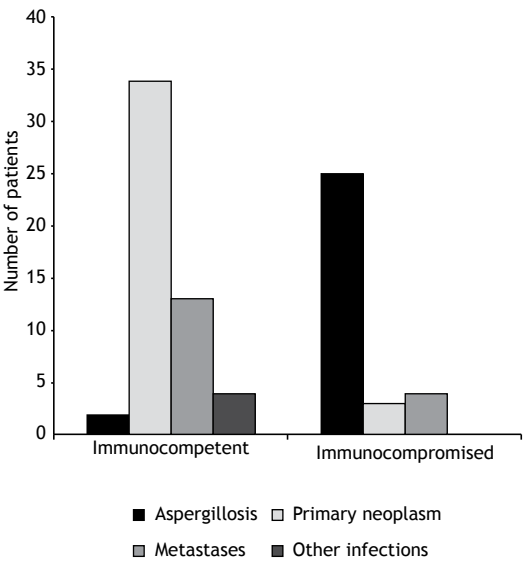

Figure 1. Bar chart showing final diagnosis in immunocompetent and immunocompromised patients presenting with the CT halo sign.

Table 1. Etiology of the CT halo sign, by patient immune status.[a]

Variable	Immunocompetent patients (n = 53)	Immunocompromised patients (n = 32)
Primary neoplasm	34 (64)	-
Invasive aspergillosis	-	25 (78)
Metastases	13 (25.0)	2 (6.3)
Lymphoproliferative diseases	-	3 (9.4)
Tuberculosis	2 (3.8)	-
Plasmacytoma	-	2 (6.3)
Staphylococcal pneumonia	1 (1.8)	-
Actinomycosis	1 (1.8)	-
Cryptococcosis	1 (1.8)	-
Histiocytosis	1 (1.8)	-

[a]Data presented as n (%).

Table 2. Demographic data and CT findings, by patient immune status.[a]

	Total	Immunocompetent patients (n = 53)	Immunocompromised patients (n = 32)	p
Demographic data				
Male gender[b]	46 (54)	29 (55)	17 (53)	0.887
Age, years	53 ± 17	55 ± 14	48 ± 21	0.135
CT findings				
Number of nodules[c]	3 (1-16)	2 (1-15)	5 (1-16)	< 0.001
1[b]	41 (48)	38 (72)	3 (9)	< 0.001
> 1[b]	44 (52)	15 (28)	29 (91)	
Nodule outline[b,*]				
Regular	46 (54)	31 (58)	15 (47)	0.298
Irregular	39 (46)	22 (42)	17 (53)	
Nodule size, mm[†]				
Solitary nodule	25 ± 13	26 ± 14	16 ± 9	0.231
Largest nodule	16 ± 8	12 ± 8	19 ± 7	0.805
Smallest nodule	6 ± 3	6 ± 4	5 ± 2	0.007
Halo thickness, mm[†]				
Solitary nodule	7 ± 3	7 ± 3	5 ± 1	0.299
Largest nodule	8 ± 4	5 ± 2	9 ± 4	0.001
Smallest nodule	5 ± 1	3 ± 1	5 ± 1	0.002
Lesion distribution[b]				
Random	47 (55)	15 (28)	28 (91)	< 0.001
Upper lobe	23 (27)	23 (44)	1 (3)	< 0.001
Lower lobe	15 (18)	15 (28)	2 (6)	0.003
Associated findings[b]				
Consolidation	5 (63)	-	5 (100)	0.016
Tree-in-bud pattern	2 (25)	2 (67)	-	
Cavitated nodules	1 (12)	1 (33)	-	
Diagnostic confirmation (n = 105)[b,‡]				
Serological	30 (30)	4 (7)	26 (53)	< 0.001
Microbiological	22 (20)	2 (4)	20 (41)	< 0.001
Histological	53 (50)	50 (89)	3 (6)	< 0.001

[a]Data presented as mean ± SD, except where otherwise indicated. [b]Data presented as n (%). [c]Data presented as median (range). *For nodules presenting with a peripheral halo sign. [†]For patients with multiple lesions, data for the largest and smallest lesions are displayed separately. [‡]The number of diagnostic confirmations exceeds the number of cases because some diagnoses were confirmed by more than one method.

scans. [4,9] Although the halo sign has been causally associated with numerous other conditions, its presence is generally more helpful than challenging.[9] Studies involving immunocompromised patients have confirmed the diagnostic value of the halo sign, demonstrating that its specificity increases as patient immune status deteriorates.[10,11] However, most available evidence consists of descriptive data. To our knowledge, the

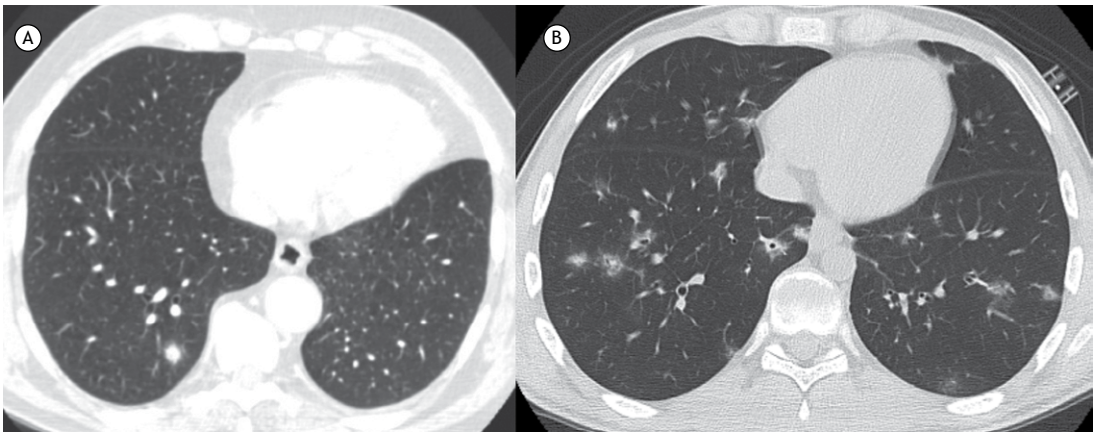

Figure 2. In A, axial CT scan of the chest of an asymptomatic, immunocompetent 54-year-old male patient, showing a right lower lobe pulmonary nodule surrounded by areas of ground-glass opacity (the CT halo sign); the final diagnosis was primary adenocarcinoma. In B, axial CT scan of the chest of an immunosuppressed 19-year-old male patient, showing multiple, randomly distributed pulmonary nodules surrounded by ground-glass opacities (the CT halo sign); the final diagnosis was aspergillosis.

present study was the first to address the correlations between the halo sign and patient immune status. In addition, our study demonstrated that thicker halos are associated with infectious diseases, whereas thinner halos are associated with neoplastic diseases. In agreement with the results of previous studies, the results of the present study showed that adenocarcinoma and pulmonary aspergillosis were the conditions that were most commonly associated with the halo sign in immunocompetent and immunosuppressed patients, respectively.[4,12] In cases of multiple pulmonary nodules, halo thickness tended to be greater in immunocompromised patients than in immunocompetent patients. This finding is consistent with those of a study investigating characteristics of the reversed halo sign, in which greater rim thickness was associated with invasive fungal infection.[13] The same cannot be concluded for solitary nodules, and this is possibly due to a statistically insufficient number of single lesions among the immunosuppressed patients (i.e., only three).

According to Gao et al., the relationships between ground-glass lung nodules and adjacent blood vessels can aid in establishing a final diagnosis based on the presence and degree of vascular distortion.[14] This is particularly relevant for immunocompetent patients presenting with the CT halo sign. In the present study, a neoplastic etiology was found to be more common in the immunocompetent patients than in the immunosuppressed patients. However, given the reduced halo thickness in the former and the variety of possible pathophysiological mechanisms underlying the halo sign, further studies are needed in order to determine whether this correlation can be extrapolated to smaller areas of ground-glass opacities.

Our study has some limitations. First, the retrospective nature of the study increases the likelihood that medical record inaccuracies affected our results. Second, the relatively small sample size did not allow us to perform an analysis of covariance in order to determine the combined contribution of halo sign features in predicting the final diagnosis. Third, dynamic changes observed in the long-term evaluation of the appearance of the halo sign, particularly in cases of infectious disease, might have affected some of our results. Finally, the definition of immunosuppression used in our study might be in disagreement with the constant improvements in the toxicity of chemotherapy and radiation therapy; however, that definition was adopted for research purposes only, and many other clinical parameters should be taken into account in a more practical scenario.

In summary, our findings are consistent with available data on the etiologies of the CT halo sign in immunocompetent and immunosuppressed patients. Given the differences in radiological presentation between these two groups of patients, appropriate assessment of halo sign features can be useful in clinical investigation. A diagnosis of primary neoplasm appears to be common among immunocompetent patients, as does a diagnosis of invasive aspergillosis among immunosuppressed patients. Thicker halos are associated with infectious diseases, whereas thinner halos are associated with neoplastic diseases; the number and distribution of lesions should also be taken into account, given that they can predict the final diagnosis.

REFERENCES

1. Hansell DM, Bankier AA, MacMahon H, McLoud TC, Müller NL, Remy J. Fleischner Society: glossary of terms for thoracic imaging. Radiology. 2008;246(3):697-722. http://dx.doi.org/10.1148/radiol.2462070712
2. Kuhlman JE, Fishman EK, Siegelman SS. Invasive pulmonary aspergillosis in acute leukemia: characteristic findings on CT, the CT halo sign, and the role of CT in early diagnosis. Radiology. 1985;157(3):611-4. http://dx.doi.org/10.1148/

radiology.157.3.3864189

3. Lee YR, Choi YW, Lee KJ, Jeon SC, Park CK, Heo JN. CT halo sign: the spectrum of pulmonary diseases. Br J Radiol. 2005;78(933):862-5. http://dx.doi.org/10.1259/bjr/77712845
4. Kim Y, Lee KS, Jung KJ, Han J, Kim JS, Suh JS. Halo sign on high resolution CT: findings in spectrum of pulmonary diseases with pathologic correlation. J Comput Assist Tomogr. 1999;23(4):622-6.
5. Parrón M, Torres I, Pardo M, Morales C, Navarro M, Martínez-Schmizcraft M. The halo sign in computed tomography images: differential diagnosis and correlation with pathology findings [Article in Spanish]. Arch Bronconeumol. 2008;44(7):386-92. http://dx.doi.org/10.1016/S0300-2896(08)70453-8
6. Ng WL, Chu CM, Wu AK, Cheng VC, Yuen KY. Lymphopenia at presentation is associated with increased risk of infections in patients with systemic lupus erythematosus. QJM. 2006;99(1):37-47. http://dx.doi.org/10.1093/qjmed/hci155
7. Valent P. Low blood counts: immune mediated, idiopathic, or myelodysplasia. Hematology Am Soc Hematol Educ Program. 2012;2012:485-91. http://dx.doi.org/10.1182/asheducation-2012.1.485
8. De Pauw B, Walsh TJ, Donnelly JP, Stevens DA, Edwards JE, Calandra T, et al. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. Clin Infect Dis. 2008;46(12):1813-21. http://dx.doi.org/10.1086/588660
9. Pinto PS. The CT Halo Sign. Radiology. 2004;230(1):109-10. http://dx.doi.org/10.1148/radiol.2301020649
10. Escuissato DL, Gasparetto EL, Marchiori E, Rocha Gde M, Inoue C, Pasquini R, et al. Pulmonary infections after bone marrow transplantation: high-resolution CT findings in 111 patients. AJR Am J Roentgenol. 2005;185(3):608-15. http://dx.doi.org/10.2214/ajr.185.3.01850608
11. Blum U, Windfuhr M, Buitrago-Tellez C, Sigmund G, Herbst EW, Langer M. Invasive pulmonary aspergillosis. MRI, CT, and plain radiographic findings and their contribution for early diagnosis. Chest. 1994;106(4):1156-61. http://dx.doi.org/10.1378/chest.106.4.1156
12. Gaeta M, Blandino A, Scribano E, Minutoli F, Volta S, Pandolfo I. Computed tomography halo sign in pulmonary nodules: frequency and diagnostic value. J Thorac Imaging. 1999;14(2):109-13.
13. Marchiori E, Marom EM, Zanetti G, Hochhegger B, Irion KL, Godoy MC. Reversed halo sign in invasive fungal infections: criteria for differentiation from organizing pneumonia. Chest. 2012;142(6):1469-73. http://dx.doi.org/10.1378/chest.12-0114
14. Gao F, Li M, Ge X, Zheng X, Ren Q, Chen Y, et al. Multi-detector spiral CT study of the relationships between pulmonary ground-glass nodules and blood vessels. Eur Radiol. 2013;23(12):3271-7. http://dx.doi.org/10.1007/s00330-013-2954-3

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Educational interventions to improve inhaler techniques and their impact on asthma and COPD control: a pilot effectiveness-implementation trial

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Study carried out in the Departamento de Pneumologia, Centro Hospitalar do Baixo Vouga, Aveiro, Portugal.

ABSTRACT

To assess the impact that educational interventions to improve inhaler techniques have on the clinical and functional control of asthma and COPD, we evaluated 44 participants before and after such an intervention. There was a significant decrease in the number of errors, and 20 patients (46%) significantly improved their technique regarding prior exhalation and breath hold. In the asthma group, there were significant improvements in the mean FEV_1, FVC, and PEF (of 6.4%, 8.6%, and 8.3% respectively). Those improvements were accompanied by improvements in Control of Allergic Rhinitis and Asthma Test scores but not in Asthma Control Test scores. In the COPD group, there were no significant variations. In asthma patients, educational interventions appear to improve inhaler technique, clinical control, and functional control.

Keywords: Asthma, Pulmonary disease, chronic obstructive; Nebulizers and vaporizers.

Inhalation therapy is the most effective modality for the treatment of asthma and COPD. The various types of inhalers available on the market have different specifications and require different techniques, leading to a number of errors in performance, thus reducing treatment efficacy and adherence. Up to 76% of patients make some type of error in their inhaler technique.[1] Growing evidence suggests that educational interventions and reviews of the technique have a positive impact on disease control.[2,3] This study was performed in the context of an interventional trial, with the aim of assessing the impact that an educational intervention to improve inhaler technique has on the clinical and functional control of asthma and COPD. Preliminary results containing the cross-sectional baseline analysis of the patients enrolled in the trial have previously been published.[4] The results suggest a significant relationship between the number of errors committed and the level of clinical and functional control achieved in asthma patients.

We included patients with asthma or COPD, all of whom were receiving treatment with at least one inhaler device. The patients were evaluated in two different visits, with a six- to eight-month interval between visits. After the first visit, the patients were taught how to use their devices correctly. The inhaler technique was evaluated only for the main treatment device, and the use of a device for symptom relief was therefore not evaluated. The variables under study were demographic data; clinical control—by means of the Asthma Control Test (ACT), Control of Allergic Rhinitis and Asthma Test (CARAT), modified Medical Research Council (mMRC) scale, and COPD Assessment Test (CAT); functional control—absolute FEV1 (in percentage of the predicted value and in mL), PEF (in percentage of the predicted value and in mL), FVC (in mL and in percentage of the predicted value), FEV_1/FVC ratio, $FEF_{25-75\%}$, and SpO_2; and number of steps of the inhaler technique correctly performed (per definition, step 1: device actuation; step 2: exhalation; step 3: inhalation; and step 4: a 5-10 s breath hold). The data were compiled in Microsoft Office Excel 2010, and statistical analyses were performed with IBM SPSS Statistics software package, version 20.0 (IBM Corporation; Armonk, NY, USA). The level of significance was set at $p < 0.05$.

Of the initial 62 patients invited to participate in the study, 18 dropped out. Therefore, 44 patients were included in the follow-up re-evaluation (mean age, 59 ±16 years). Of the 44 patients in the sample, 21 (47.8%) were men, and 23 (52.2%) were women. Among the 44 patients, 23 (52.2%) and 21 (47.8%) were diagnosed with asthma and COPD, respectively. In the first visit, a small number of technical errors was significantly associated with previous teaching of inhaler technique ($p < 0.05$; Fisher's exact test) and with age ($p < 0.05$; $R = 0.13$; Pearson's correlation coefficient), although not with the number of years since diagnosis (Pearson's correlation coefficient). There was an association between a smaller number of errors and better clinical control in the asthma group, indicated by the ACT scores (maximum mean difference, 11.6 points) and CARAT scores (maximum mean difference, 12.3 points; $p < 0.05$; ANOVA). However, although a similar graphic

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pattern was found in the COPD group, the differences within that group were not statistically significant.

Figure 1 includes the main results obtained. At the second visit, there was a significant decrease in the number of errors after the educational session, with a mean decrease of 0.7 errors (range, 0.29-1.02; $p < 0.05$; t-test for paired samples). Among the 44 patients, 20 (46%) improved their inhaler technique, with significant results found in step 2 (relative improvement of 45.5%) and step 4 (relative improvement of 52%; t-test for paired samples for both). In the asthma group, there were post-intervention improvements in the functional parameters (in percentages of the predicted values): the mean FEV_1 increased from −10.26% to −2.52% (a relative improvement of 6.4%); the mean FVC increased from −12.99% to −4.14% (a relative improvement of 8.6%); and the mean PEF increased from −14.35% to −2.35% (a relative improvement of 8.3%). Comparing the pre- and post-intervention functional parameter values, we found the differences to be significant ($p < 0.05$ for all; t-test for paired samples). In addition, improved inhaler technique was significantly correlated with an improvement in the CARAT score (OR = 14.4; $p < 0.05$; Fisher's exact test), although not in the ACT score. However, regarding the asthma group, if we defined a > 4 point increase in the CARAT score as a clinically significant improvement in control, we would find that only 5 participants (23.8%) met the criterion for such improvement. Using the same approach, if we established a > 3 point increase in the ACT score as a clinically significant improvement in control, we would find that only 8 participants (38.0%) met the criterion. In the COPD group, there were no significant variations in clinical or functional control variables. However, if we defined a > 1 point increase in the mMRC score as a clinically significant improvement in control, we would find that 6 patients (28.6%) met the criterion. If we defined a > 2 point increase in the CAT score as a clinically significant improvement in control, we would find that 5 participants (23.8%) met the criterion.

In a post-hoc analysis of the functional parameters, in absolute values (mL), we found a statistically significant improvement in FEV_1 in the COPD group (mean increase, 145.7 mL; 95% CI: 11.7-279.8; $p = 0.035$; t-test for paired samples). In the asthma group, there was improvement, although the difference was not statistically significant (mean increase, 105.9 mL; 95% CI: −47.6 to 259.4; $p = 0.17$; t-test for paired samples). For PEF (in mL), there were improvements that were found to be statistically significant in the asthma group (mean increase, 460 mL; 95% CI: 30.9-890.0; $p = 0.037$; t-test for paired samples) but not in the COPD group (mean increase, 212.9 mL; 95% CI: −184.0 to 609.7; $p = 0.276$; t-test for paired samples).

These results show that most patients make errors in the inhaler technique, and that seems to be associated with age and previous training regarding the technique. Younger patients made fewer errors, which might be due to differences in literacy levels. The small sample size might have reduced the statistical power of some findings, such as the association with the number of years since diagnosis. Our results also show that proper inhaler technique was associated with better clinical control in asthma patients, and improving the technique could also affect functional parameters, mainly those directly related to airway obstruction, such as FEV_1, FVC, and PEF. When comparing CARAT with ACT scores, we found that the former was more sensitive in detecting such changes, possibly because CARAT is a more comprehensive clinical test.[5] In patients with COPD, no significant improvements were observed, either in clinical control or in functional parameters (in percentage of the predicted value), which, as previously mentioned, might be due to the small sample size, or even to the pathophysiological differences between the diseases. However, some of those patients showed clinically significant improvement after the educational intervention, which supports the hypothesis that larger samples and continuous training might be more accurate in detecting statistically significant differences. However, we found some improvement in functional performance (FEV_1 in mL). Although that finding was statistically significant, FEV_1 in percentage of the predicted value was not. That discrepancy can be explained by the fact that over 50% of our COPD patients were classified as having stage 1 or 2 disease according to the Global Initiative for Chronic Obstructive Lung Disease criteria. Therefore, those patients had higher FEV_1 values, which meant that a relative increase of 145.7 mL represented a small proportion of the total value, leading to the underestimation of this finding. In addition, patients with severe COPD are older than are those with milder forms of the disease and are therefore less sensitive to educational interventions to improve inhaler technique and, consequently, to their potential beneficial impact. In our study, although adjusting for age had no effect on the results of the statistical analysis of functional and clinical impacts, age was found to be a determinant of the performance on inhaler technique tests. Further studies should be performed in elderly populations, because they have particular characteristics that might influence the inhaler technique and its impact. The fact that airway obstruction is more reversible in asthma patients might also justify a greater difference in their functional measurements, as well as in their perception of respiratory symptoms. These findings are consistent with those obtained in another study.[6] A large trial is currently ongoing in order to address the impact of different educational approaches on patients with COPD, and its results are expected to be enlightening.[7]

The establishment of a query surveillance program in the primary health care setting could represent one solution to the problem of limited patient knowledge of proper inhaler technique, allowing the treatment of a greater number of patients in the general population. In such a network, other health care professionals, such as physicians from other specialties, respiratory

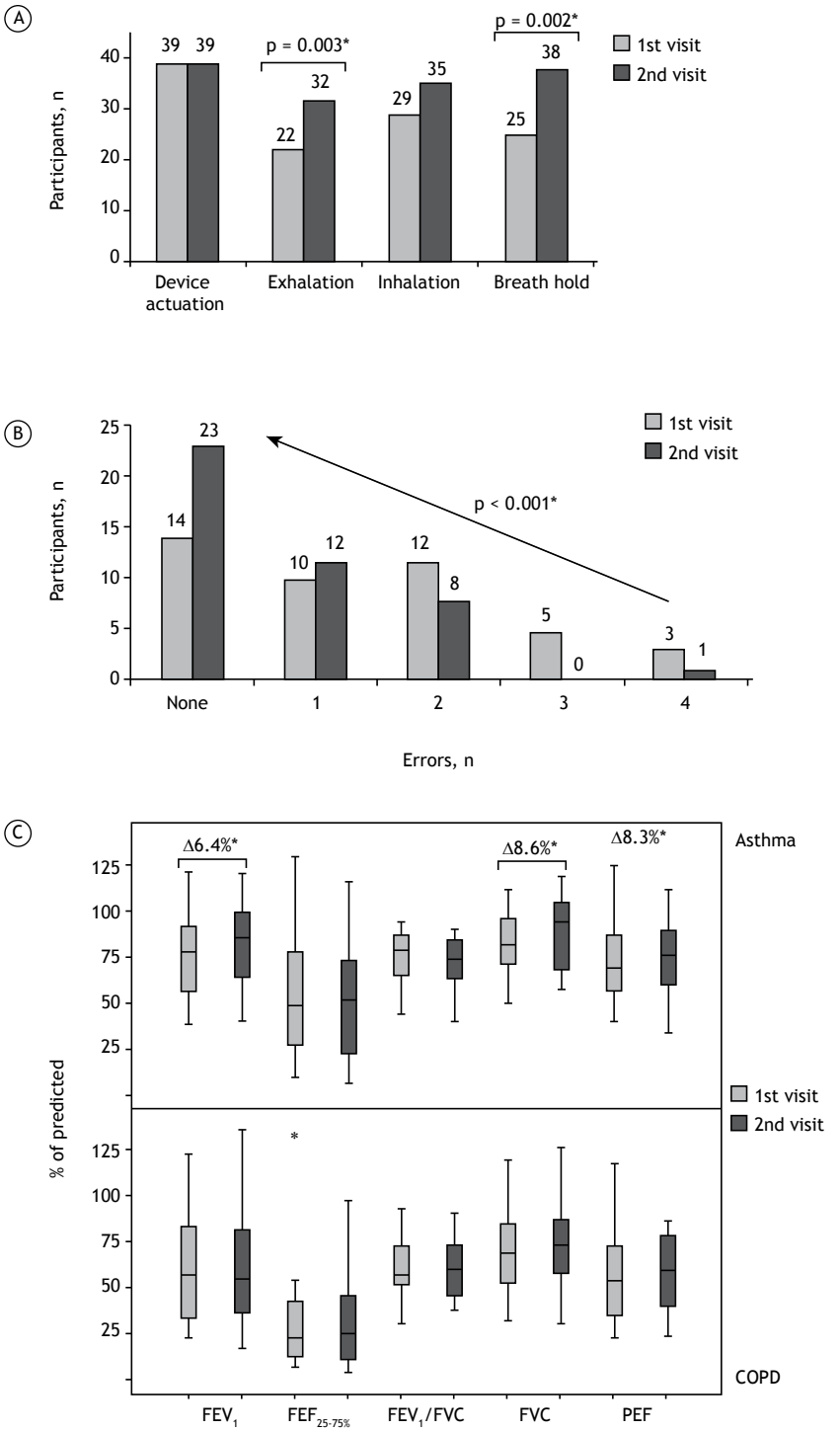

Figure 1. Number of participants using the inhaler device correctly, according to the pre-established steps (in A); the number of errors committed in the inhaler technique at the first and second visits (in B); and the functional control parameters at the first and second visits in the asthma and COPD groups (in C). *p < 0.05; t-test for paired samples.

therapists, nurses, and pharmacists, could be involved in the education of those patients. Some studies have tested the teaching of inhaler techniques and suggested that rechecking and regular refresher courses are needed, because proper inhalation technique deteriorates after the initial intervention.[8,9] The loss of skills is accompanied by the deterioration of asthma control as soon as three months after the intervention. Although various strategies can be used in order to provide this type of educational intervention, it is best delivered through verbal instructions and physical demonstration of the technique by a skilled educator,

either on video or face to face, as we did in our study.[8,9] Some other educational techniques should be studied and tested in studies with appropriate designs, such as those involving large cohorts that provide large follow-up data sets. In addition, alternative ways of integrating multidisciplinary teams and different health care professionals should be addressed, as should the effect of training those professionals to properly educate their patients in the use of their inhalers.

We conclude that educational interventions to teach inhaler techniques improve the performance of patients, leading to improvements in the clinical and functional control of asthma. In COPD, the pathophysiological hallmark of irreversible obstruction might limit this benefit. Further studies on asthma should focus on patient outcomes that matter, in terms of the impact that educational interventions to teach inhaler techniques have on patient performance of those techniques, such as decreasing the risk of exacerbations. The same approach should be adopted for COPD patients, adjusting sample sizes to optimize the statistical power of randomized control trials and obtain good evidence.

REFERENCES

1. Molimard M, Raherison C, Lignot S, Depont F, Abouelfath A, Moore N. Assessment of handling of inhaler devices in real life: an observational study in 3811 patients in primary care. J Aerosol Med. 2003;16(3):249-54. https://doi.org/10.1089/089426803769017613
2. Lavorini F, Magnan A, Dubus JC, Voshaar T, Corbetta L, Broeders M, et al. Effect of incorrect use of dry powder inhalers on management of patients with asthma and COPD. Respir Med. 2008;102(4):593-604. https://doi.org/10.1016/j.rmed.2007.11.003
3. Giraud V, Allaert FA, Roche N. Inhaler technique and asthma: feasability and acceptability of training by pharmacists. Respir Med. 2011;105(12):1815-22. https://doi.org/10.1016/j.rmed.2011.07.004
4. Maricoto T, Rodrigues LV, Teixeira G, Valente C, Andrade L, Saraiva A. Assessment of Inhalation Technique in Clinical and Functional Control of Asthma and Chronic Obstructive Pulmonary Disease. Acta Med Port. 2015;28(6):702-7. https://doi.org/10.20344/amp.5905
5. Domingues M, Amaral R, Fonseca JA, Azevedo P, Correia-de-Sousa J. Assessment of asthma control using CARAT in patients with and without Allergic Rhinitis: A pilot study in primary care. Rev Port Pneumol (2006). 2016;22(3):163-6. https://doi.org/10.1016/j.rppnen.2015.10.014
6. Press VG, Arora VM, Shah LM, Lewis SL, Charbeneau J, Naureckas ET, et al. Teaching the use of respiratory inhalers to hospitalized patients with asthma or COPD: a randomized trial. J Gen Intern Med. 2012;27(10):1317-25. https://doi.org/10.1007/s11606-012-2090-9
7. Leiva-Fernández F, Leiva-Fernández J, Zubeldia-Santoyo F, García-Ruiz A, Prados-Torres D, Barnestein-Fonseca P. Efficacy of two educational interventions about inhalation techniques in patients with chronic obstructive pulmonary disease (COPD). TECEPOC: study protocol for a partially randomized controlled trial (preference trial). Trials. 2012;13:64. https://doi.org/10.1186/1745-6215-13-64
8. Basheti IA, Armour CL, Bosnic-Anticevich SZ, Reddel HK. Evaluation of a novel educational strategy, including inhaler-based reminder labels, to improve asthma inhaler technique. Patient Educ Couns. 2008;72(1):26-33. https://doi.org/10.1016/j.pec.2008.01.014
9. Crompton GK, Barnes PJ, Broeders M, Corrigan C, Corbetta L, Dekhuijzen R, et al. The need to improve inhalation technique in Europe: a report from the Aerosol Drug Management Improvement Team. Respir Med. 2006;100(9):1479-94. https://doi.org/10.1016/j.rmed.2006.01.008

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An initial experience with a digital drainage system during the postoperative period of pediatric thoracic surgery

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ABSTRACT

Objective: To report an initial experience with a digital drainage system during the postoperative period of pediatric thoracic surgery. **Methods:** This was a prospective observational study involving consecutive patients, ≤ 14 years of age, treated at a pediatric thoracic surgery outpatient clinic, for whom pulmonary resection (lobectomy or segmentectomy via muscle-sparing thoracotomy) was indicated. The parameters evaluated were air leak (as quantified with the digital system), biosafety, duration of drainage, length of hospital stay, and complications. The digital system was used in 11 children (mean age, 5.9 ± 3.3 years). The mean length of hospital stay was 4.9 ± 2.6 days, the mean duration of drainage was 2.5 ± 0.7 days, and the mean drainage volume was 270.4 ± 166.7 mL. The mean maximum air leak flow was 92.78 ± 95.83 mL/min (range, 18-338 mL/min). Two patients developed postoperative complications (atelectasis and pneumonia, respectively). The use of this digital system facilitated the decision-making process during the postoperative period, reducing the risk of errors in the interpretation and management of air leaks.

Keywords: Drainage; Thoracic surgery; Pediatrics.

INTRODUCTION

Most patients undergoing lung surgery require adequate drainage of the pleural cavity to remove air or fluid and to allow expansion of the remaining lung. It is necessary that the health care team be qualified to manage the drainage system correctly.[1] The measurement or grading of air leaks is still subjective and depends on the level of experience of professionals in quantifying them. Therefore, the interpretation of air leaks is related to observer variability.[1,2] Interobserver disagreement may occur, even between experienced observers. When uncertainty resulting from the use of a traditional system persists, the chest tube may be closed and radiographic assessment may be performed. In such cases, the patient remains in the hospital for at least another day, which results in greater use of resources and time.

In recent years, clinical signs, such as blood pressure, HR, SpO_2, and temperature, have been recorded continuously and digitally. Electronic health records and health information technology reduce medical errors because they ensure complete information about the patient's condition.[3] However, to date, air leak information has been obtained subjectively. There is also uncertainty about the amount of fluid. Recent studies on digital drainage systems have presented an objective evaluation of these parameters, but, until now, no such studies have been conducted in children. The objective of the present study was to report our initial experience with a digital drainage system during the postoperative period of pediatric thoracic surgery.

METHODS

This was a prospective, consecutive, observational case-series study performed to evaluate the use of a digital drainage system during the postoperative period of pediatric thoracic surgery. This study is part of a project called *Dreno Digital* and was approved by the Research Ethics Committee of the Federal University of São Paulo/*plataforma Brasil* (Ruling no. 56579/2012; CAAE: 03514312.1.0000.5505).

The inclusion criteria were as follows: being treated at a pediatric thoracic surgery outpatient clinic; being ≤ 14 years of age; and having an indication for pulmonary resection (lobectomy or segmentectomy via muscle-sparing thoracotomy). The exclusion criteria were as follows: renal or hepatic failure; neurological dysfunction; reoperation; emergency operation; preoperative chemotherapy or radiotherapy; and chest wall resection.

The digital drainage system used was a Thopaz® device (Medela AG, Baar, Switzerland). The parameters evaluated were air leak, biosafety, duration of drainage, length of hospital stay, and complications. In children, there are no established data or parameters regarding when the chest tube can be removed; therefore, we defined an air leak flow < 10 mL/min in the last 6 h as the threshold for removal.

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RESULTS

The digital drainage system was used in 11 children in this initial phase. Of those, 4 (36%) were male and 7 (64%) were female. The mean age was 5.9 ± 3.3 years (range, 1.6-13.0 years), with a median of 5 years. The remaining sample data are given in Table 1.

The most common clinical condition was recurrent infection, in 8 patients (72.7%). Pulmonary malformation was the most common diagnosis, in 6 patients (54.5%). Of those 6 patients, 2 had pulmonary sequestration and 4 had cystic adenomatoid malformation. Bronchiectasis was present in 5 patients (45.5%). The procedures performed included pulmonary lobectomy, in 7 patients (63.6%); segmentectomy, in 2 (18.2%); and lobectomy plus segmentectomy, in 2 (18.2%).

Only one chest tube was placed in each patient. The complication rate was 18%, complications occurring in 2 of the 11 patients (atelectasis and pneumonia, respectively). There was no mortality.

Simple tracheal intubation was performed in 10 (91%) of the patients. Only 1 patient underwent selective intubation. All patients were extubated in the operating room, and 7 (64%) stayed in the ICU in the immediate postoperative period.

In-hospital analgesia was provided via an epidural catheter in 8 (72.7%) of the patients, all 8 of whom received a solution of 0.25% bupivacaine and fentanyl (mean, 27.7 ± 16.9 mL; range, 5-55 mL). The mean amount of intravenous or oral dipyrone was 8.4 ± 4.8 g (range, 2.5-18.0 g), whereas the mean amount of intravenous or oral tramadol was 118.3 ± 154.43 mg (range, 0-550 mg). All children underwent pulmonary resection via intercostal nerve-sparing thoracotomy using the intercostal muscle flap technique. None of the patients had rib fractures or required blood transfusion during the postoperative period. The mean intraoperative blood loss was 45.5 ± 35.3 mL (range, 10-100 mL). Cefuroxime was used for antibiotic prophylaxis

None of the patients had subcutaneous emphysema. Routine suction was performed until postoperative day 1 and was continued thereafter if there was no adequate lung expansion, as confirmed by chest X-ray. Only 1 patient required continuous suction until postoperative day 2. Air leak management efficiency was increased because there was no uncertainty about bubbling, regardless of the rater. Air leak flow was quantified objectively, in mL/min, the mean maximum being 92.78 ± 95.83 mL/min (range, 18-338 mL/min) and the median being 89 mL/min. All chest tubes were removed when the air leak flow was < 10 mL/min: 0 mL/min and 1 mL/min, respectively, in 10 patients and 1 patient. None of the patients required further drainage or had a > 4-cm residual pleural cavity.

The information provided by the device was exported to a computer using the ThopEasy® software (Medela AG). We thus obtained more parameters, such as duration of drainage, date, start time, end time, maximum suction pressure, minimum suction pressure, maximum air leak flow, and minimum air leak flow. The data were displayed in chart and graph formats (Figure 1).

DISCUSSION

Biosafety refers to interventions focused on risk protection, prevention, and minimization for health care professionals and patients. It consists of measures adopted to prevent activity-related risks and involves the relationships among technology, risks, the human factor, and the environment. In this study, biosafety measurement was subjective, and biosafety was favorably assessed by the nursing staff because of the optimization of patient care time. The management process of the digital system was improved as compared with that of a traditional system, given that there was no need for replacing the water seal daily, caring for the bottle, clamping the system, providing continuous suction, etc.

The use of digital drainage systems in general thoracic surgery is well known. Such systems are routinely used in adults in several countries, such as Italy and Germany; however, to our knowledge, there have been no reports on their use in pediatric thoracic surgery. This might be explained by the low incidence of prolonged air leak in children. As part of the protocol developed at our institution, we studied the usefulness of such a system also in children. The traditional water-seal drainage systems used in children are the same as those used in adults and have the same limitations regarding air leak.

In a digital system, air leak flow is quantified in mL/min and is also represented in graph format. The suction pressure is controlled by the system itself, which operates independently from the suction system of the hospital, and this provides autonomy and safety for patients and the health care team. In adults, the chest tube can be removed when the air leak flow is > 30 mL/min in the last 6 h, as displayed in the graph on the device screen .[2,4-7] For children, there are no established parameters; therefore, we defined an air leak flow < 10 mL/min in the last 6 h as the threshold for chest tube removal.

Table 1. Postoperative data of the patients included in the sample.

Variable	Mean ± SD	Minimum	Maximum
Length of hospital stay, days	4.9 ± 2.6	3	12
Duration of drainage, days	2.5 ± 0.7	2	4
Operative time, min	166.0 ± 42.5	90	240
Drainage volume, mL	270.4 ± 166.7	135	750

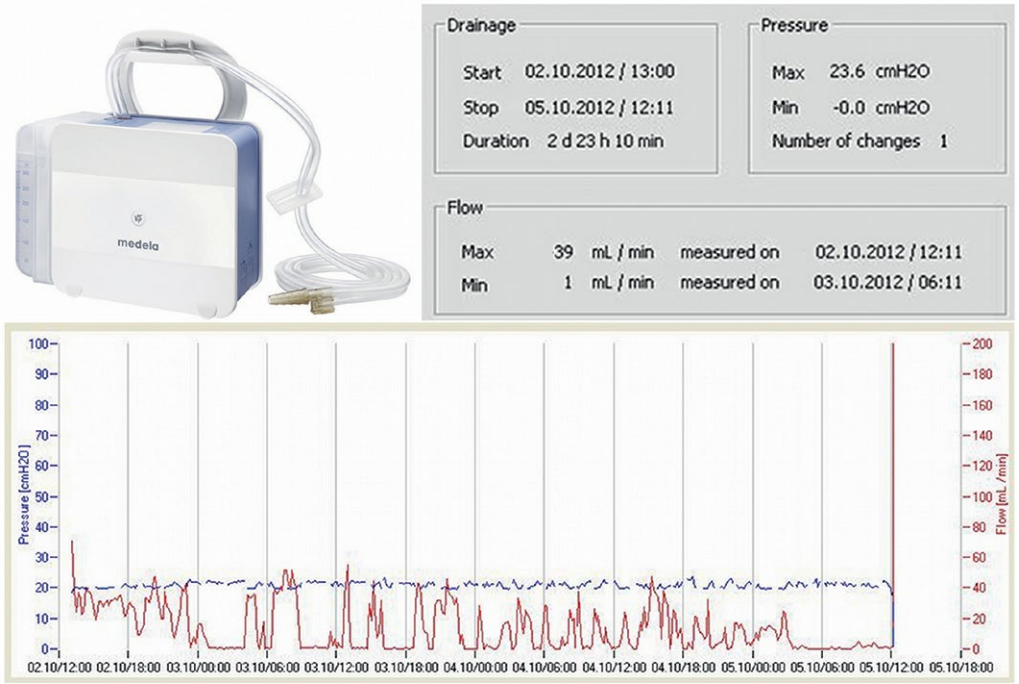

Figure 1. In the upper left, a picture of the digital device used. In the upper right and at the bottom, computer-generated data and a computer-generated graph, respectively. This information constitutes the postoperative data of an 8-year-old child who underwent a left upper lobectomy for cystic adenomatoid malformation. The duration of drainage was three days, the maximum air leak flow was 39 mL/min, and the maximum suction pressure used was 23.6 cmH_2O. Hospital discharge occurred on postoperative day 4.

The system we studied was found to be functional, to be simple to use, and to offer new standards for thoracic drainage in pediatric surgery. It not only measured air leaks but also allowed early mobilization of patients, even for those on continuous suction, which is difficult to accomplish with a traditional system.[6,8]

Despite the lack of data on biosafety and thoracic drainage systems in the literature, subjective assessment by nursing staff was positive, being favored by an increase in practicality and the non-need for replacing the water seal daily. Because of minimal system handling, there is no risk of usual complications, such as lack of a water seal in the bottle, clamping of the system, chest tube disconnection or chest tube obstruction, etc. The system provided objective air leak data. Among the disadvantages is the fact that training is needed so that health care professionals can handle this new digital system and the fact that its cost is higher than that of a traditional system, mainly because of taxes and duties—the so called "*custo Brasil*" (cost of doing business in Brazil). To our knowledge, this is the first study on the use of this digital system in children. The digital drainage system facilitated the decision-making process during the postoperative period, thereby reducing the risk of errors in the interpretation and management of air leaks. Our study presents limited conclusions because it is a case series involving few patients. There is a need for further studies on the use of digital drainage systems in children. Such studies should include devices that already are available in other countries and measure not only air leak but also fluid flow. The use of electronic health records is inevitable.

REFERENCES

1. Costa Jr Ada S, Leão LE, Succi JE, Rymkiewicz E, Folador J, Kazantzis T. Digital drainage system: how far can we go? J Bras Pneumol. 2014;40(5):579-81. https://doi.org/10.1590/S1806-37132014000500015
2. Cerfolio RJ, Bryant AS. The benefits of continuous and digital air leak assessment after elective pulmonary resection: a prospective study. Ann Thorac Surg. 2008;86(2):396-401. https://doi.org/10.1016/j.athoracsur.2008.04.016
3. Ajami S, Bagheri-Tadi T. Barriers for Adopting Electronic Health Records (EHRs) by Physicians. Acta Inform Med. 2013;21(2):129-34. https://doi.org/10.5455/aim.2013.21.129-134
4. Mier JM, Molins L, Fibla JJ. The benefits of digital air leak assessment after pulmonary resection: prospective and comparative study [Article in Spanish]. Cir Esp. 2010,87(6):385-9. https://doi.org/10.1016/j.ciresp.2010.03.012
5. Cerfolio RJ, Varela G, Brunelli A. Digital and smart chest drainage systems to monitor air leaks: the birth of a new era? Thorac Surg Clin. 2010;20(3):413-20. https://doi.org/10.1016/j.thorsurg.2010.03.007
6. Bertolaccini L, Rizzardi G, Filice MJ, Terzi A. "Six Sigma approach" - an objective strategy in digital assessment of postoperative air leaks: a prospective randomized study. Eur J Cardiothorac Surg. 2011;39(5):e128-32. https://doi.org/10.1016/j.ejcts.2010.12.027
7. Pompili C, Detterbeck F, Papagiannopoulos K, Sihoe A, Vachlas K, Maxfield MW, et al. Multicenter international randomized comparison of objective and subjective outcomes between electronic and traditional chest drainage systems. Ann Thorac Surg. 2014;98(2):490-6; discussion 496-7. https://doi.org/10.1016/j.athoracsur.2014.03.043
8. Pompili C, Brunelli A, Salati M, Refai M, Sabbatini A. Impact of the learning curve in the use of a novel electronic chest drainage system after pulmonary lobectomy: a case-matched analysis on the duration of chest tube usage. Interact Cardiovasc Thorac Surg. 2011;13(5):490-3; discussion 493. https://doi.org/10.1510/icvts.2011.280941

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Hard metal lung disease: a case series

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ABSTRACT

Objective: To describe diagnostic and treatment aspects of hard metal lung disease (HMLD) and to review the current literature on the topic. **Methods:** This was a retrospective study based on the medical records of patients treated at the Occupational Respiratory Diseases Clinic of the *Instituto do Coração*, in the city of São Paulo, Brazil, between 2010 and 2013. **Results:** Of 320 patients treated during the study period, 5 (1.56%) were diagnosed with HMLD. All of those 5 patients were male (mean age, 42.0 ± 13.6 years; mean duration of exposure to hard metals, 11.4 ± 8.0 years). Occupational histories were taken, after which the patients underwent clinical evaluation, chest HRCT, pulmonary function tests, bronchoscopy, BAL, and lung biopsy. Restrictive lung disease was found in all subjects. The most common chest HRCT finding was ground glass opacities (in 80%). In 4 patients, BALF revealed multinucleated giant cells. In 3 patients, lung biopsy revealed giant cell interstitial pneumonia. One patient was diagnosed with desquamative interstitial pneumonia associated with cellular bronchiolitis, and another was diagnosed with a hypersensitivity pneumonitis pattern. All patients were withdrawn from exposure and treated with corticosteroid. Clinical improvement occurred in 2 patients, whereas the disease progressed in 3. **Conclusions:** Although HMLD is a rare entity, it should always be included in the differential diagnosis of respiratory dysfunction in workers with a high occupational risk of exposure to hard metal particles. A relevant history (clinical and occupational) accompanied by chest HRCT and BAL findings suggestive of the disease might be sufficient for the diagnosis.

Keywords: Lung diseases, interstitial; Cobalt; Tungsten; Occupational exposure; Hard metal.

INTRODUCTION

Hard metal lung disease (HMLD) is a rare disease caused by exposure to particles of hard metal alloys, whose major components are tungsten carbide (approximately 90%) and cobalt (approximately 10%) or cobalt and diamond.[1,2] Other components , such as tantalum, titanium, nickel, niobium, and chrome, are found in small amounts.

Because they are extremely hard and maintain their physical properties even at high temperatures, hard metals are used in tools for cutting and sharpening metals, drilling wells, polishing diamonds and dental prostheses, etc. Workers are exposed to particles rich in cobalt (in ionized form) and tungsten carbide, which are absorbed by the lungs and gastrointestinal tract, both in cobalt powder production and when using cobalt alloy tools. The pathophysiology of HMLD remains unknown. The proposed mechanism for the pathogenesis of the interstitial disease involves a hypersensitivity reaction to cobalt.[3] In addition, genetic susceptibility[4] may play a role in the pathogenesis of the disease, although this role has yet to be fully understood.

Exposure to cobalt can cause several forms of lung disease, from asthma to various interstitial patterns in the lungs.[1] The most widely known and typical histopathological presentation is giant cell interstitial pneumonia (GIP), described by Liebow[5] in 1968. GIP is characterized by the presence of multinucleated giant cells, which can be "macrophagic" in nature,[1,6] in alveolar spaces. In addition to GIP, other patterns described include usual interstitial pneumonia, hypersensitivity pneumonitis (HP), and desquamative interstitial pneumonia.[1,6] In the present study, we describe diagnostic and treatment aspects of HMLD and review the current literature on the topic.

METHODS

The study subjects were treated at the Occupational Respiratory Diseases Clinic of the Pulmonology Division of the *Instituto do Coração* of the University of São Paulo School of Medicine *Hospital das Clínicas*, in the city of São Paulo, Brazil, between 2010 and 2013. Occupational histories were taken, after which all subjects underwent clinical evaluation, chest HRCT, pulmonary function tests (Elite DX Series, Medical Graphics Corporation, Saint Paul, MN, USA), bronchoscopy, BAL, and lung biopsy. When the lung tissue obtained was considered insufficient for diagnosis, surgical biopsies were performed. We performed elemental analysis of lyophilized lung tissue specimens by

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energy-dispersive X-ray fluorescence spectrometry[7] in 2 patients (EDX 700-HS, Shimadzu Corporation, Analytical Instruments Division, Kyoto, Japan).

RESULTS

During the study period, 320 patients were treated at the facility. Of those, 5 (1.56%) were diagnosed with HMLD. The mean age at diagnosis was 42.0 ± 13.6 years. All of those 5 patients were male and were working at the time of the initial evaluation. The mean duration of exposure was 11.4 ± 8.0 years. One patient reported working as an industrial tool maintenance technician, 2 reported being industrial tool sharpeners, and 2 reported being grinder operators (Table 1). All 5 clinically presented with dyspnea on exertion and cough.

The most common chest HRCT finding was ground glass opacities, in 4 patients (80%; Figure 1). Other findings included peripheral reticular opacities with traction bronchiectasis and bronchiolectasis, in 3 (60%; Figure 2); micronodules, in 2 (40%; Figure 2); and bronchial wall thickening, in 2 (40%; Table 1). Restrictive lung disease, in varying degrees, was found in all subjects, and decreased DLCO was found in 3 (Table 2).

All patients underwent bronchoscopy, BAL, and lung biopsy, with the diagnosis being established by examination of a bronchoscopy specimen in 1 patient and by examination of a surgical biopsy specimen in 4. Large numbers of multinucleated giant cells were found in the BAL fluid of 4 of the 5 patients (Figure 3) and in the biopsy tissue of 3 (Figure 4). Desquamative interstitial pneumonia associated with cellular bronchiolitis was diagnosed in 1 patient; a histological pattern suggestive of chronic HP, with no evidence of other occupational or environmental exposures that could be associated with HP, was identified in 1; the presence of tungsten was identified in 2, whose tissue samples were analyzed by energy-dispersive X-ray fluorescence spectrometry; and the presence of cobalt was identified in 1 of those 2 (Table 1).

Following diagnosis, all patients were withdrawn from their occupational exposure and received systemic corticosteroid therapy. Two patients showed clinical, radiological, and functional improvement, although their lung function did not normalize (Tables 1 and 2). Three patients experienced disease progression despite corticosteroid therapy, 2 of whom additionally received azathioprine. One patient was placed on a lung transplant list, but he died before undergoing transplantation.

DISCUSSION

In the case series presented here, ground-glass opacities were the most common chest HRCT changes. Restrictive lung disease was the most common finding, occurring in all patients. Multinucleated giant cells were detected in the BAL fluid of most patients, and this finding was correlated with the typical histological pattern of GIP. Withdrawal from exposure combined with corticosteroid therapy was successful in 2 patients, and disease progression occurred in 3 patients.

The functional, cytological, histopathological, and imaging findings are similar to those found in other studies.[1,6,8]

HMLD is a rare entity, even in populations at occupational risk. The published literature on cases of HMLD in Brazil is scarce and consists of the reporting of the disease in 4 patients.[9-12] In the literature, data on the prevalence and incidence of HMLD among individuals exposed to hard metals vary. Meyer-Bisch et al.[13] and Kusaka et al.[14] found no cases of HMLD in cross-sectional studies involving 425 and 319 workers, respectively, with a mean duration of exposure to hard metals of 9 and 14 years, respectively. Sprince et al.[15] found only 1 patient with HMLD among 290 hard metal production workers evaluated. The diagnostic imaging methods available at the time might have contributed to the low HMLD detection results observed in those studies.[13-15]

The paucity of cases and the varying latency period suggest that a hypersensitivity mechanism may be involved in the pathophysiology of HMLD. Sabbioni et al.[3] found that 9% of the workers who had contact with hard metals had lung disease, and that the observed prevalence was not correlated with cobalt, tungsten, or tantalum levels, nor was it correlated with age, gender, or duration of occupational exposure, which, in the authors' view, reinforced the hypersensitivity hypothesis. Recurrence of HMLD in unilateral[16,17] or bilateral[6] lung transplant recipients, even after cessation of exposure to hard metals, suggests the hypothesis that immune-mediated mechanisms are involved in the pathophysiology of the disease. In those 3 reported cases of recurrence,[6,16,17] the histological pattern of GIP was found, and no traces of tungsten or cobalt were detected in the transplanted lungs, which, in the authors' view, reinforced this immune-mediated hypothesis.

Genetic susceptibility also contributes to the development of HMLD. Potolicchio et al.[4] demonstrated that HLA-DP-βGlu69 was more prevalent among hard-metal-exposed workers with HMLD than in those without. In that study,[4] 19 (95%) of 20 hard-metal-exposed workers with HMLD exhibited this polymorphism, compared with 17 (48.6%) of 35 hard-metal-exposed workers without the disease.

The individual contribution of the major components of hard metal has also been investigated. In animal models, instillation of tungsten alone did not produce pulmonary inflammation, whereas cobalt alone was able to produce tissue injury. When combined, cobalt and tungsten had a synergistic effect and caused increased tissue inflammation.[18,19]

Moriyama et al.[8] performed electron microprobe analysis of elemental levels in 17 patients with HMLD and concluded that cobalt and tungsten accumulate in

Table 1. Characteristics of the patients with hard metal lung disease.

Characteristic	Case 1	Case 2	Case 3	Case 4	Case 5
Age, years	44	30	30	43	63
Smoking	No	No	No	Former smoker	No
Occupation	Grinder operator	Grinder operator	Industrial tool sharpener	Industrial tool sharpener	Industrial tool maintenance technician
Duration of exposure, years	25	6	8	6	12
Chest HRCT findings	Extensive ground-glass opacities and poorly defined centrilobular micronodules, predominantly in the middle and upper lung fields. Pattern suggestive of subacute HP	Fine reticulation, ground-glass opacities, and traction bronchiolectasis, distributed symmetrically and mainly peripherally, predominantly in the lung bases	Interstitial micronodular infiltrates distributed in a perilymphatic pattern, predominantly in the upper lung fields	Ground-glass opacities, peripheral reticulation, and traction bronchiectasis and bronchiolectasis, predominantly in the lower lung fields	Fine reticulation, ground-glass opacities, traction bronchiectasis and bronchiolectasis, distributed peripherally, and an area of air trapping in the left lower lobe
BAL pattern	Multinucleated giant cells	Multinucleated giant cells	Multinucleated giant cells	Multinucleated giant cells	Lymphocytic
Type of biopsy	Surgical	Surgical	Transbronchial	Surgical	Surgical
Histological pattern of the biopsy specimen	DIP and cellular bronchiolitis	GIP	GIP	GIP	HP
EDS results	Cobalt + Tungsten +	Cobalt - Tungsten +	NA	NA	NA
Treatment	Corticosteroid therapy, azathioprine	Corticosteroid therapy	Corticosteroid therapy	Corticosteroid therapy, azathioprine, placement on a lung transplant list	Corticosteroid therapy
Patient course	Worsening	Improvement	Improvement	Death	Worsening

DIP: desquamative interstitial pneumonia; GIP: giant cell interstitial pneumonia; HP: hypersensitivity pneumonitis; EDS: energy-dispersive X-ray fluorescence spectrometry; and NA: not assessed.

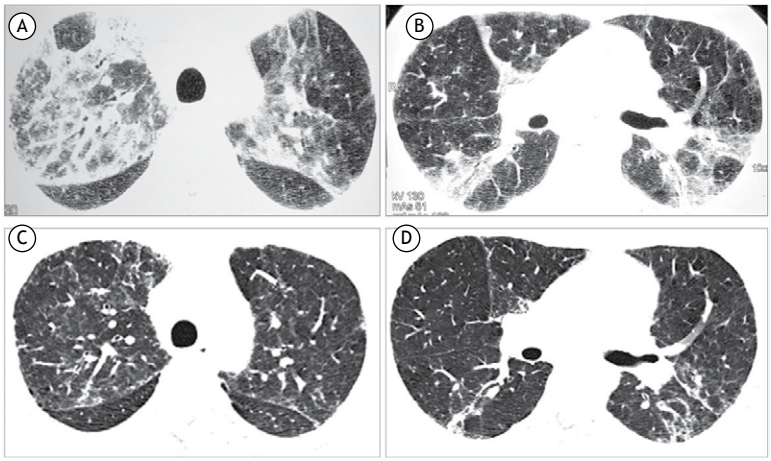

Figure 1. HRCT scans. Case 2, before treatment initiation (Figures A and B): ground-glass opacities and parenchymal consolidations with some air bronchograms in both lungs, predominantly in the middle and upper lung fields, in a pattern similar to that of organizing pneumonia. Case 2, after treatment (Figures C and D): the pulmonary changes were significantly reduced, there now being subtle foci of ground-glass opacification, mild, poorly defined centrilobular nodules, and scattered linear opacities, bilaterally.

centrilobular fibrotic lesions. In that study, immunohistochemistry revealed the presence of tungsten particles within lesions surrounded by CD163+ macrophages and T CD8+ lymphocytes. The authors[8] suggest that such macrophages play an important role in the development of fibrotic lesions.

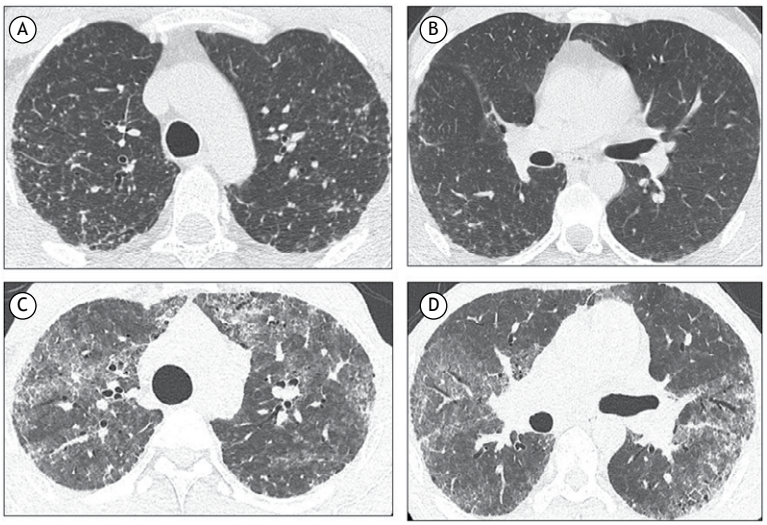

Figure 2. HRCT scans. Case 3 (Figures A and B): micronodular opacities distributed in a perilymphatic pattern, predominantly in the middle and upper lung fields. Case 4 (Figures C and D): ground-glass opacities and foci of parenchymal consolidation, predominantly in the middle and upper lung fields, as well as mild peripheral reticulation with traction bronchiectasis and bronchiolectasis.

Table 2. Course of lung function in the study subjects.[a]

Variable	Case 1		Case 2		Case 3		Case 4		Case 5	
	Baseline	After 14m	Baseline	After 60m	Baseline	After 56m	Baseline	After 30m	Baseline	After 24m
FVC, L	4.17 (79%)	3.74 (67%)	2.85 (63%)	2.88 (59%)	3.47 (63%)	4.12 (76%)	2.22 (49%)	1.76 (39%)	2.81 (83%)	2.33 (61%)
FEV_1, L	3.54 (83%)	3.20 (73%)	2.45 (65%)	2.38 (60%)	2.73 (60%)	3.08 (68%)	2.09 (56%)	1.70 (46%)	2.32 (86%)	1.94 (69%)
FEV_1/FVC	0.85	0.86	0.86	0.83	0.81	0.75	0.94	0.94	0.82	0.83
TLC, L	NA	5.57 (75%)	4.31 (68%)	5.11 (83%)	5.19 (66%)	5.89 (75%)	3.80 (56%)	NA	4.07 (65%)	4.06 (65%)
RV, L	NA	1.84 (91%)	1.56 (96%)	2.09 (142%)	1.47 (79%)	1.83 (98%)	1.54 (77%)	NA	1.29 (54%)	1.67 (76%)
DLCO, mL/min/mmHg	NA	NA	22.76 (72%)	28.89 (106%)	32.44 (93%)	43.25 (107%)	6.15 (20%)	NA	19.39 (67%)	11.29 (39%)

m: months; and NA: not assessed. [a]Percent predicted values calculated for the Brazilian population according to Neder et al.[32]

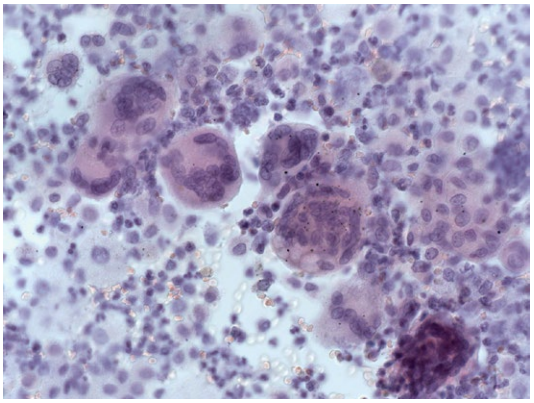

Figure 3. BAL specimen containing macrophages, neutrophils, and lymphocytes, as well as multinucleated giant cells (Papanicolaou stain; magnification, ×400).

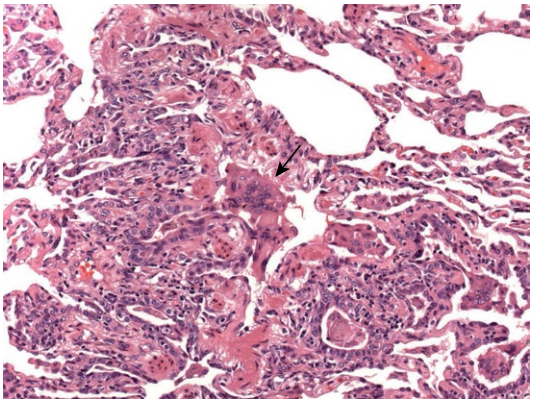

Figure 4. Histological analysis of a lung biopsy specimen. Respiratory bronchiole stripped of its lining epithelium, filled with multinucleated giant cells (arrow), also observed in the adjacent alveoli, which are covered by metaplastic columnar epithelium (H&E; magnification, ×200).

The clinical presentation of HMLD varies widely, as shown in this case series. The initial symptom is usually dyspnea on exertion. Patients who have HMLD develop restrictive lung disease and have a reduction in DLCO, of varying severity.[1]

A relevant clinical and occupational history is essential for the diagnosis of HMLD. Although chest X-ray and HRCT findings are nonspecific, they are important in diagnosis, together with a history of exposure and histopathological changes. The major chest HRCT changes found by Choi et al.[20] were ground-glass opacities and irregular linear opacities, predominantly in the lower lung fields; these changes were also commonly seen in the 5 cases described here.

Unlike in other pneumoconioses, in which, in most cases, relevant occupational history and suggestive chest X-ray findings are sufficient to establish the diagnosis, in HMLD, chest HRCT and a specimen for cytological or histological analysis are required. BAL, which is a minimally invasive method, can confirm the diagnosis without the need for lung biopsy.[1,21]

Forni,[21] in reviewing BAL cytopathological findings described in the literature, concluded that there are two patterns that suggest the diagnosis of HMLD. The first is characterized by significantly increased cellularity, resulting from characteristic multinucleated giant cells, lymphocytosis with a decreased CD4/CD8 ratio, and eosinophilia. To Forni,[21] these findings mirror the histopathological findings of GIP, and, in such cases, a lung tissue biopsy would not be required. The second BAL pattern is that of predominant lymphomononuclear infiltrates, with a decreased CD4/CD8 ratio, rare eosinophils, and giant cells, being similar to the pattern found in HP. In such cases, biopsy is essential to establish the diagnosis.[21]

In the present case series, the BAL patterns coincided with those described by Forni[21] and reinforce the relationship between the presence of multinucleated giant cells in the BAL and the histological diagnosis of GIP.

Naqvi et al.,[1] in a review of 100 patients who had undergone lung biopsy and had a diagnosis of HMLD, reported that 59 of those patients had the pattern of GIP, defined as the presence of typical multinucleated giant cells in the alveolar space. Moriyama et al.[8] highlighted the importance of the presence of centrilobular fibrotic lesions in the histological specimen for the diagnosis of HMLD, even when there are no multinucleated giant cells. Another histopathological pattern that is seen is that of HP.[1,22] Hard-metal-exposed workers often also use cutting oil, which may be contaminated with *Mycobacterium immunogenum*, whose antigens can cause HP.[23]

When the observed histological patterns are inconsistent with GIP, elemental analysis, by a combination of electron microscopy and energy-dispersive X-ray fluorescence spectrometry, is important in establishing the diagnosis.[1] Tungsten is usually found at high levels,[1,8,24] whereas cobalt is usually found at moderate or low levels, since cobalt is highly soluble and is eliminated rapidly.[1,3]

Although some authors have suggested that GIP is a pathognomonic finding of HMLD,[25] there have been several published reports of cases[1,6,8] with a histological pattern of GIP without occupational exposure to hard metals and without tungsten or cobalt being detected in lung tissue. Other authors[8,26] have suggested that such cases correspond to idiopathic GIP. Other reported cases of GIP have been associated with exposure to titanium[27] and to nitrofurantoin.[28]

Treatment of HMLD consists of withdrawal from the occupational exposure, which can stabilize or even improve lung function,[29] and corticosteroid therapy. Because of the scarcity of cases in the literature, there have been no studies comparing corticosteroid therapy and placebo treatment; however, clinical experience is that corticosteroid therapy results in improvement.[9,30] The use of immunosuppressive therapy also is not well established, although immunosuppressants are occasionally used.[9] Lung transplantation is a treatment option in patients with advanced lung disease that progresses despite treatment,[31] despite the possibility of GIP pattern recurrence in the transplanted lung.[6,16,17]

Although HMLD is rare, it should always be included in the differential diagnosis of respiratory dysfunction in hard-metal-exposed workers—such as tool sharpeners, toolmakers, operators of machines (such as milling cutters, grinders, and lathes), operators of diamond-blade cutting discs, and diamond polishers (using polishing discs made of hard metals)—who present with clinical complaints, functional changes, or imaging changes. Data in the literature and our experience with the cases reported here suggest that adequate occupational history taking accompanied by chest HRCT changes and BAL findings (lymphocytosis with a decreased CD4/CD8 ratio and, especially, the presence of large numbers of giant cells) consistent with the disease might be sufficient for the diagnosis, there being no need for an open lung biopsy. Treatment is based on permanent withdrawal from exposure and corticosteroid or immunosuppressive therapy, with varying results.

REFERENCES

1. Naqvi AH, Hunt A, Burnett BR, Abraham JL. Pathologic spectrum and lung dust burden in giant cell interstitial pneumonia (hard metal disease/cobalt pneumonitis): review of 100 cases. Arch Environ Occup Health. 2008;63(2):51-70. https:/doi.org/10.3200/AEOH.63.2.51-70
2. Palmen N. Criteria Document for Swedish Occupational Standards: Cobalt and Cobalt Compounds. Stockholm: Swedish National Institute for Working Life, Swedish Criteria Group for Occupational Standards; 2015. Report No.: NR 2005:12.
3. Sabbioni E, Minoia C, Pietra R, Mosconi G, Forni A, Scansetti G. Metal determinations in biological specimens of diseased and non-diseased hard metal workers. Sci Total Environ. 1994;150(1-3):41-54. https:/doi.org/10.1016/0048-9697(94)90127-9
4. Potolicchio I, Mosconi G, Forni A, Nemery B, Seghizzi P, Sorrentino R. Susceptibility to hard metal lung disease is strongly associated with the presence of glutamate 69 in HLA-DP beta chain. Eur J Immunol. 1997;27(10):2741-3. https:/doi.org/10.1002/eji.1830271039
5. Liebow A. New Concepts and Entities in Pulmonary Disease in the Lung. Baltimore, MD: Williams and Wilkins; 1968. p. 332.
6. Khoor A, Roden AC, Colby TV, Roggli VL, Elrefaei M, Alvarez F et

al. Giant cell interstitial pneumonia in patients without hard metal exposure: analysis of 3 cases and review of the literature. Hum Pathol. 2016;50:176-82. https:/doi.org/10.1016/j.humpath.2015.12.004

7. Carneiro MF, Ribeiro FQ, Fernandes-Filho FN, Lobo DJ, Barbosa F Jr, Rhoden CR, et al. Pollen abortion rates, nitrogen dioxide by passive diffusive tubes and bioaccumulation in tree barks are effective in the characterization of air pollution. Environ Exp Bot. 2011;72(2):272-7. https:/doi.org/10.1016/j.envexpbot.2011.04.001
8. Moriyama H, Kobayashi M, Takada T, Shimizu T, Terada M, Narita J, et al. Two-dimensional analysis of elements and mononuclear cells in hard metal lung disease. Am J Respir Crit Care Med. 2007;176(1):70-7. https:/doi.org/10.1164/rccm.200601-134OC
9. Bezerra PN, Vasconcelos AG, Cavalcante LL, Marques VB, Nogueira TN, Holanda MA. Hard metal lung disease in an oil industry worker. J Bras Pneumol. 2009;35(12):1254-8.
10. Moreira MA, Cardoso Ada R, Silva DG, Queiroz MC, Oliveira AA, Noleto TM. Hard metal pneumoconiosis with spontaneous bilateral pneumothorax. J Bras Pneumol. 2010;36(1):148-151. https:/doi.org/10.1590/S1806-37132010000100020
11. De Capitani EM, Schweller M, Grangeial TA, Corso-Pereira M, Cerqueira EM, Metze K, et al. Pneumonia intersticial descamativa secundária a exposição à poeira de metal duro. Pneumologia Paulista, 2010;24(11):62-3.
12. De Capitani EM, Corso-Pereira M, Saldiva PH. Hard metal subacute pneumopathy: a case report. In: Proceedings of the 8th International Conference on Occupational Lung Diseases; 1992 Sep 14-17; Prague. ILO and Czech Medical Society; 1993.
13. Meyer-Bisch C, Pham QT, Mur JM, Massin N, Moulin JJ, Teculescu D, et al. Respiratory hazards in hard metal workers: a cross sectional study. Br J Ind Med. 1989;46(5):302-9. https:/doi.org/10.1136/oem.46.5.302
14. Kusaka Y, Yokoyama K, Sera Y, Yamamoto S, Sone S, Kyono H, et al. Respiratory diseases in hard metal workers: an occupational hygiene study in a factory. Br J Ind Med. 1986;43(7):474-85. https:/doi.org/10.1136/oem.43.7.474
15. Sprince NL, Chamberlin RI, Hales CA, Weber AL, Kazemi H. Respiratory disease in tungsten carbide production workers. Chest. 1984;86(4):549-57. https:/doi.org/10.1378/chest.86.4.549
16. Frost AE, Keller CA, Brown RW, Noon GP, Short HD, Abraham JL, et al. Giant cell interstitial pneumonitis. Disease recurrence in the transplanted lung. Am Rev Respir Dis. 1993;148(5):1401-4. https:/doi.org/10.1164/ajrccm/148.5.1401
17. Tarabichi Y, Saggar R, Wallace WD, Lynch JP 3rd, Saggar R. Primary disease recurrence after single lung transplantation in a patient with prior hard metal exposure. J Heart Lung Transplant. 2015;34(9):1216-8. https:/doi.org/10.1016/j.healun.2015.05.019
18. Kaplun ZS, Mezencheva NV. Experimental study on the toxic effect of dust in production of sintered metals [Article in German]. J Hyg Epidemiol Microbiol Immunol. 1960;4:390-9.
19. Lasfargues G, Lardot C, Delos M, Lauwerys R, Lison D. The delayed lung responses to single and repeated intratracheal administration of pure cobalt and hard metal powder in the rat. Environ Res. 1995;69(2):108-21. https:/doi.org/10.1006/enrs.1995.1032
20. Choi JW, Lee KS, Chung MP, Han J, Chung MJ, Park JS. Giant cell interstitial pneumonia: high-resolution CT and pathologic findings in four adult patients. Am J Roentgenol. 2005;184(1):268-72. https:/doi.org/10.2214/ajr.184.1.01840268
21. Forni A. Bronchoalveolar lavage in the diagnosis of hard metal disease. Sci Total Environ. 1994;150(1-3):69-76. https:/doi.org/10.1016/0048-9697(94)90131-7
22. Okuno K, Kobayashi K, Kotani Y, Ohnishi H, Ohbayashi C, Nishimura Y. A case of hard metal lung disease resembling a hypersensitive pneumonia in radiological images. Inter Med. 2010;49(12):1185-9. https:/doi.org/10.2169/internalmedicine.49.3049
23. Tillie-Leblond I, Grenouillet F, Reboux G, Roussel S, Chouraki B, Lorthois C, et al. Hypersensitivity pneumonitis and metalworking fluids contaminated by mycobacteria. Eur Respir J. 2011;37(3):640-7. https:/doi.org/10.1183/09031936.00195009
24. Tanaka J, Moriyama H, Terada M, Takada T, Suzuki E, Narita I, et al. An observational study of giant cell interstitial pneumonia and lung fibrosis in hard metal lung disease. BMJ Open. 2014;4(3):e004407. https:/doi.org/10.1136/bmjopen-2013-004407
25. Abraham JL. Lung pathology in 22 cases of giant cell interstitial pneumonia (GIP) suggests GIP is pathognomonic of cobalt (hard metal) disease [abstract]. Chest. 1987;91:312.
26. Blanc PD. Is giant cell interstitial pneumonitis synonymous with hard metal lung disease? Am J Respir Crit Care Med. 2007;176(8): 834; author reply 834-5. https:/doi.org/10.1164/ajrccm.176.8.834
27. Paris C, Pairon JC, Billon-Galland MA, Vanoni-Espiand H, Godbert B, Martinet Y, et al. Giant cell interstitial pneumonia: report of two cases with high titanium concentration in the lung. Am J Respir Crit Care Med. 2011;184(11):1315-7. https:/doi.org/10.1164/ajrccm.184.11.1315a
28. Lee B, Balavenkataraman A, Sanghavi D, Walter K. Recurrent nitrofurantoin-induced giant cell interstitial pneumonia: case report and literature review. Respir Med Case Rep. 2015;14:49-52. https:/doi.org/10.1016/j.rmcr.2015.01.002
29. Terui H, Konno S, Kaga K, Matsuno Y, Hatanaka KC, Kanno H, et al. Two cases of hard metal lung disease showing gradual improvement in pulmonary function after avoiding dust exposure. J Occup Med Toxicol. 2015;10:29. https:/doi.org/10.1186/s12995-015-0070-9
30. Enriquez LS, Mohammed TL, Johnson GL, Lefor MJ, Beasley MB. Hard metal pneumoconiosis: a case of giant-cell interstitial pneumonitis in a machinist. Respir Care. 2007;52(2):196-9.
31. Weill D, Bender C, Corris PA, Dark JH, Davis RD, Keshavjee S, et al. A consensus document for the selection of lung transplant candidates: 2014–an update from the Pulmonary Transplantation Council of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant. 2015;34(1):1-15. https:/doi.org/10.1016/j.healun.2014.06.014
32. Neder JA, Andreoni S, Castelo-Filho A, Nery LE. Reference values for lung function tests. I. Static volumes. Braz J Med Biol Res. 1999;32(6):703-17. https:/doi.org/10.1590/s0100-879x1999000600006

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http://dx.doi.org/10.1590/S1806-37562016000000050

CASE SERIES

Mouthpiece ventilation in Duchenne muscular dystrophy: a rescue strategy for noncompliant patients

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ABSTRACT

Objective: To evaluate mouthpiece ventilation (MPV) in patients with Duchenne muscular dystrophy (DMD) who are noncompliant with noninvasive ventilation (NIV). **Methods:** We evaluated four young patients with DMD who had previously refused to undergo NIV. Each patient was reassessed and encouraged to try MPV. **Results:** The four patients tolerated MPV well and were compliant with NIV at home. MPV proved to be preferable and more comfortable than NIV with any other type of interface. Two of the patients required overnight NIV and eventually agreed to use a nasal mask during the night. **Conclusions:** The advantages of MPV over other types of NIV include fewer speech problems, better appearance, and less impact on the patient, eliminating the risk of skin breakdown, gastric distension, conjunctivitis, and claustrophobia. The use of a mouthpiece interface should be always considered in patients with DMD who need to start NIV, in order to promote a positive approach and a rapid acceptance of NIV. Using MPV during the daytime makes patients feel safe and more likely to use NIV at night. In addition, MPV increases treatment compliance for those who refuse to use other types of interfaces.

Keywords: Muscular dystrophy, Duchenne; Noninvasive ventilation; Patient compliance.

INTRODUCTION

Duchenne muscular dystrophy (DMD) is one of the most common neuromuscular diseases in childhood. The young patient often needs noninvasive mechanical ventilation (NIV) due to the development of respiratory failure, reduction in FVC, or nocturnal hypoventilation symptoms.[1-3] Patients with neuromuscular disease might also function extremely well with minimal symptoms despite significant reductions in FVC and severe nocturnal oxygen desaturation.[4] For this reason and for the poor tolerance of the interface, sometimes the young patient does not accept NIV easily. Poor tolerance of the interface can be caused by various factors, such as excessive pressure of the mask on the face, excessive oral air leakage, anxiety of the patient because he or she is unable to call a family member, claustrophobia, and patient-ventilator dyssynchrony.[5] Thus, the interface plays a crucial role in tolerance and effectiveness of NIV use. Interfaces that cover the nose or the nose and mouth (oronasal interface) are the most commonly used; however, they are more likely to cause skin breakdown, gastric distension, conjunctivitis, and claustrophobia.[6] Sometimes the presence of deep cutaneous lesions precludes the use of NIV. The NIV interface, however, should be comfortable and reasonably airtight. Although there are various types of interfaces nowadays, the physiognomy of the patient often makes the choice of a suitable interface difficult. The most common drawbacks can be avoided by using mouthpiece NIV (MPV) interfaces, and, in recent years, MPV modes have been introduced to some of the portable ventilators available.

METHODS

The Monaldi Hospital Review Board approved the study. Patients were studied in our respiratory department between January of 2015 and April of 2015. We evaluated four young patients with DMD, with a mean of 18.5 years of age (Table 1). Three patients (labeled as patients 1, 2, and 3) showed reductions in FVC (< 50% than the previous control measurement) and progressive decreases in PaO_2. The four patients presented with an FVC ≤ 1 L, and patients 1 and 4 presented with hypercapnia and nocturnal respiratory failure. Patient 1 presented with obstructive sleep-disordered breathing (SDB), and sleep monitoring demonstrated an apnea-hypopnea index = 20 events/h. Patient 4 presented with sleep hypoventilation syndrome; sleep monitoring demonstrated an increase in $PaCO_2$ > 10 mmHg at waking in the morning (when compared with awake supine values) and sustained hypoxemia not related to apnea or hypopnea (SaO_2 < 90% over 30% of the monitoring period during sleep; T90 > 30%), demonstrating SDB.

The patients had previously refused to use NIV due to claustrophobia, fear of being unable to communicate with family members while using it, and annoying leaks. Each patient was reassessed and proposed to try using MPV. All patients initiating NIV/MPV were treated in a

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day hospital. No patient was excluded from MPV as a result of bulbar impairment.

The subjects were submitted to NIV using a mechanical ventilator (Trilogy; Philips Respironics, Murrysville, PA, USA) that has a dedicated particular function designated "kiss trigger" MPV and an arm dedicated to support the mouthpiece in order to facilitate its use and allow the patient to stay on a wheelchair (Figure 1). During the adaptation phase, we presented the mouthpiece interface to the patients and selected the most comfortable position of the support arm according to the postural impairment of the patient. The preferred mode in the initial phase was pressure control, with a support of 8-10 cmH_2O, which was gradually increased until a suitable tidal volume, an optimal SpO_2 (confirmed by blood gas analysis), a stable HR, and good chest expansion (measured by electrical impedance tomography—PulmoVista 500; Dräger Medical GmbH, Lübeck, Germany) were reached. Inspiratory time was set at 1.2 s (for patients 1, 2, and 3), and 1.4 s (for patient 4). For all patients, the expiratory positive airway pressure (EPAP) was set to 0 cmH_2O; the rise time amounted to 3 s (for patients 1, 2, and 3) and 4 s (for patient 4). Respiratory rate (RR) was set to 0 breaths/min. Time of disconnection alarm was set at 15 min (Table 1). All patients tolerated this new ventilation mode well, with good compliance to the interface. All patients accepted the treatment, and they continued NIV at home. At this writing, none of the DMD patients had been unable to retain the mouthpiece as a result of weakness.

In our practice, patients are submitted to chest X-rays prior to treatment. The results for patients 2 and 3 showed dilated bowel loops and upward displacement of the diaphragm (Figure 2).

After an initial phase of adaptation to MPV during daytime hours, thanks to a greater feeling of security, patients 1 and 4 also accepted NIV with a nasal mask during the night. Patient 1 was adapted to spontaneous-timed average volume assured pressure support (ST-AVAPS) ventilation mode; maximum inspiratory positive airway pressure (IPAP) = 14 and 10 cmH_2O; minimum IPAP = 10 cmH_2O; EPAP = 6 cmH_2O; AVAPS rate = 1 cmH_2O/min; tidal volume = 650 mL; trigger flow = 4.0 L; cycle = 25%; rise time = 3 s; RR = 10 breaths/min; and inspiratory time = 1.2 s in a simple circuit configuration. Patient 4 was adapted to assist-control ventilation (ACV) mode; VC = 750 mL; RR = 12 breaths/min; inspiratory time = 1.2 s; decelerated flow; and EPAP = 4 cmH_2O (Table 2).

Oxyhemoglobin saturation was measured using pulse oximetry (PalmSAT 2500A; Nonin Medical, Plymouth, MN, USA), and $PaCO_2$ was measured using a transcutaneous blood gas monitor (Linde MicroGas 7650; Linde Medical Sensors AG, Basel, Switzerland) or arterial blood gases when the transcutaneous monitor was unavailable while the patient was awake. Adequate ventilatory support was assessed using a combination of clinical assessment, normal overnight oximetry, serial daytime measures of $PaCO_2$, and downloaded data from the devices.

RESULTS

All of the patients had previously refused to use NIV, but accepted treatment with MPV. The preferred mode was pressure control (Table 1). IPAP was set between 10 and 14 cmH_2O, which ensured an optimal tidal volume (8-10 mL/kg). No back-up rate was needed during

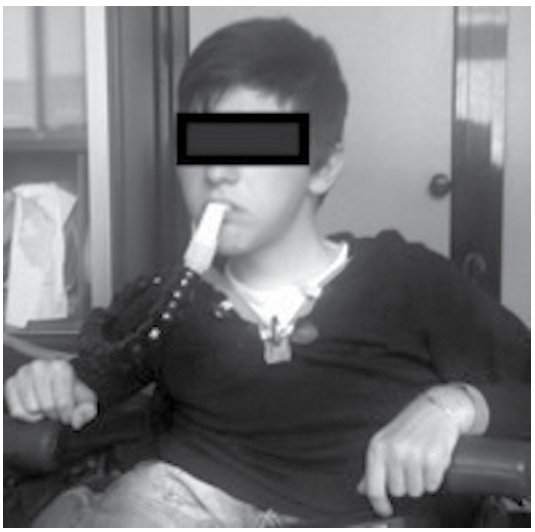

Figure 1. A patient during mouthpiece ventilation.

Table 1. Characteristics of the patients and noninvasive ventilation settings.

Patient	Age, years	FVC, L	PaO_2	$PaCO_2$	SDB	Cause of NIV refusal	Mode	IPAP, cmH_2O	EPAP, cmH_2O	IT, s	RT, s	RR, cycles/min
1	21	1,07	89	47	Yes	Fear and anxiety	MPV/PC	12	0	1,2	3	0
2	16	0,91	69	45	No	Claustrophobia	MPV/PC	14	0	1,2	3	0
3	18	0,96	70	44	No	Skin intolerance	MPV/PC	14	0	1,2	3	0
4	19	1,02	81	51	Yes	Fear and anxiety	MPV/PC	15	0	1,4	4	0

SDB: sleep-disordered breathing; NIV: noninvasive ventilation; IPAP: inspiratory positive airway pressure; EPAP: expiratory positive airway pressure; IT: inspiratory time; RT: rise time; RR: respiratory rate; and MPV/PC: mouthpiece ventilation/pressure control.

daytime, so no air blew into the face of the patients. In this configuration, the equipment could be set without EPAP. Alarms for apnea, minimum pressure, and minimum volume could be easily shut off in order to avoid their unnecessary activation. In most home volume-controlled ventilators, the minimum pressure alarm cannot be deactivated; therefore, it is necessary to set up positive end-expiratory pressure (often at 2 cmH_2O), which, thanks to the resistance to the airflow created from the angle of the mouthpiece, creates a pressure that prevents the continuous activation of the alarms.

Patient 1 presented with sleep apnea syndrome. During night time, he was treated using ST-AVAPS mode, which allowed greater comfort and better fit. The use of EPAP = 6 cmH_2O helped to reduce apnea. A brief expiratory cycle was more physiological. A trigger with an average sensitivity was better tolerated than a more sensitive trigger, which was initially set. The patient had good peak inspiratory flow and a great number of triggered cycles. Patient 2 presented with sleep hypoventilation syndrome and adapted to the ACV mode well, reducing respiratory effort and improving nocturnal breathing pattern.

DISCUSSION

Respiratory disease is a nearly inevitable complication in patients with DMD and represents the underlying cause of death in 70% of the patients with less than 25 years of age.[7] It has been widely demonstrated that mechanical ventilation corrects respiratory failure and can prolong the life of those patients.[8] It is known that NIV improves gas exchange, relieves shortness of breath, allows inspiratory muscles to rest, and reduces the incidence of nosocomial infections. In addition, mortality and hospitalizations due to respiratory failure decrease.[9] In our experience, the selection of an appropriate interface is crucial for successful NIV. Nasal and oronasal masks are the most practical (and most commonly used) for NIV.[10] The main limitations to the use of these interfaces are claustrophobia, discomfort, and skin lesions.[11,12] The application of an oronasal interface can worsen social interaction, since it impairs eating, drinking, and talking. This type of mask changes the patient's perception of himself and may have negative psychological consequences.[13] The preferable and more comfortable alternative is MPV via a 15- or 22-mm mouthpiece device; however, more active participation of the patient is necessary than with the use of traditional masks. We preferred the "kiss trigger" MPV function of the ventilator, because the patient has only to touch it for air delivery. Patients easily trigger the ventilator with mouth pressure. The open-circuit MPV is safe and comfortable to patients confined to wheelchairs. There is a system in which the mouthpiece should be placed close to the mouth by the adjustable arm, and the patient can grab the mouthpiece as desired. It should be removable for talking, eating, or breathing independently. The most significant advantages of MPV when compared with the use of a nasal or an oronasal mask are that the mouthpiece interferes with speech to a lesser degree, improves appearance, reduces the negative impact on the patient, and eliminates the risk of skin breakdown and claustrophobia.[14] Additionally, it is safer than the other interfaces since it permits the use of glossopharyngeal breathing in the event of a sudden ventilator failure or an accidental disconnection from the ventilator.

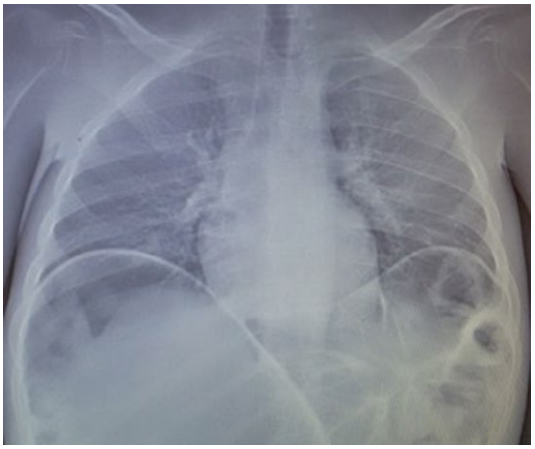

Figure 2. A chest X-ray showing dilated bowel loops and upward displacement of the diaphragm.

A recent comparative study on the performance of different home ventilators showed that MPV and the use of a whisper valve were associated with a reduction in the number of alarms when compared with the other configurations available in the Trilogy (Philips Respironics) ventilator. The authors emphasized that the "kiss trigger" function in that ventilator is not comparable with functions in classical ventilators, since it is based on a flow signal technology that detects an alteration in the flow-by mode generated by the ventilator due to any reason, such as a partial obstruction via the mouth connection.[15]

All of the patients in the present study had previously rejected the application of NIV due to the tightness

Table 2. Mouthpiece ventilation settings for patients 1 and 2.

Patient	Mode	$IPAP_{min}$, cmH_2O	$IPAP_{max}$, cmH_2O	EPAP, cmH_2O	AVAPS rate	V_T, L	TG	Cycle	RT, s	RR, breaths/min	IT, s	Interface
1	ST-AVAPS	10	14	6	1	650	4	25%	3	10	1,2	Nasal
4	AC			4		750					1,2	Nasal

$IPAP_{min}$: minimum inspiratory positive airway pressure; $IPAP_{max}$: maximum inspiratory positive airway pressure; EPAP: expiratory positive airway pressure; AVAPS: average volume assured pressure support; V_T: tidal volume; TG: trigger flow; RT: rise time; RR: respiratory rate; IT: inspiratory time; ST: spontaneous-timed; and AC: assist-control

of the interface and claustrophobia, resulting in poor compliance. The patients who required overnight NIV subsequently accepted the treatment via a nasal mask during the night hours. This was probably due to the fact that the use of MPV during daytime hours made the patients feel safe, gradually being confident enough for using NIV at night. The use of the nasal mask and MPV with that specific ventilator (Trilogy; Philips Respironics) allowed us to treat the patients who had previously refused nasal, oral, or oronasal interfaces.

The use of a mouthpiece interface should be always considered for patients with DMD who need to start NIV; it is useful to promote a positive approach and a rapid acceptance of the new condition. As time goes by, patients with DMD develop constant hypoventilation and need respiratory support 24 h a day; MPV can be valuable, particularly in patients who undergo NIV various hours a day and who present with skin lesions, gastric distension, or eye irritation. The use of a nasal or an oronasal mask may be alternated as well.

REFERENCES

1. Hamada S, Ishikawa Y, Aoyagi T, Ishikawa Y, Minami R, Bach JR. Indicators for ventilator use in Duchenne muscular dystrophy. Respir Med. 2011;105(4):625-9. http://dx.doi.org/10.1016/j.rmed.2010.12.005
2. Toussaint M, Chatwin M, Soudon P. Mechanical ventilation in Duchenne patients with chronic respiratory insufficiency: clinical implications of 20 years published experience. Chron Respir Dis. 2007;4(3):167-77. http://dx.doi.org/10.1177/1479972307080697
3. Nardi J, Prigent H, Garnier B, Lebargy F, Quera-Salva MA, Orlikowski D, et al. Efficiency of invasive mechanical ventilation during sleep in Duchenne muscular dystrophy. Sleep Med. 2012;13(8):1056-65. http://dx.doi.org/10.1016/j.sleep.2012.05.014
4. Jeppesen J, Green A, Steffensen BF, Rahbek J. The Duchenne muscular dystrophy population in Denmark, 1977-2001: prevalence, incidence and survival in relation to the introduction of ventilator use. Neuromuscul Disord 2003;13(10):804-12. http://dx.doi.org/10.1016/S0960-8966(03)00162-7
5. Garuti G, Nicolini A, Grecchi B, Lusuardi M, Winck JC, Bach JR. Open circuit mouthpiece ventilation: Concise clinical review. Rev Port Pneumol. 2014;20(4):211-8. http://dx.doi.org/10.1016/j.rppneu.2014.03.004
6. Pisani L, Carlucci A, Nava S. Interfaces for noninvasive ventilation: technical aspects and efficiency. Minerva Anestesiol. 2012;78(10):1154-61.
7. Bach JR, Martinez D. Duchenne muscular dystrophy: continuous noninvasive ventilatory support prolongs survival. Respir Care. 2011;56(6):744-50. http://dx.doi.org/10.4187/respcare.00831
8. Finder JD, Birnkrant D, Carl J, Farber HJ, Gozal D, Iannaccone ST, et al. Respiratory care of the patient with Duchenne muscular dystrophy: ATS consensus statement. Am J Respir Crit Care Med. 2004;170(4):456-65. http://dx.doi.org/10.1164/rccm.200307-885ST
9. Bach JR, Rajaraman R, Ballanger F, Tzeng AC, Ishikawa Y, Kulessa R, et al. Neuromuscular ventilator insufficiency: effect of home mechanical ventilator use vs oxygen therapy on pneumonia and hospitalization rates. Am J Phys Rehabil. 1998;77(1):8-19. http://dx.doi.org/10.1097/00002060-199801000-00003
10. Hess DR. Noninvasive ventilation in neuromuscular disease: equipment and application. Respir Care. 2006;51(8):896-911; discussion 911-2.
11. Gregoretti C, Confalonieri M, Navalesi P, Squadrone V, Frigerio, P, Beltrame F, et al. Evaluation of patient skin breakdown and comfort with a new face mask for non-invasive ventilation: a multi-center study. Intensive Care Med. 2002;28(3):278-84. http://dx.doi.org/10.1007/s00134-002-1208-7
12. Antón A, Tarrega J, Giner J, Güell R, Sanchis J. Acute physiologic effects of nasal and full-face masks during noninvasive positive-pressure ventilation in patients with acute exacerbations of chronic obstructive pulmonary disease. Respir Care. 2003;48(10):922-5.
13. Sferrazza Papa GF, Di Marco F, Akoumianaki E, Brochard L. Recent advances in interfaces for non-invasive ventilation: from bench studies to practical issues. Minerva Anestesiol. 2012;78(10):1146-53.
14. Benditt JO. Full-time noninvasive ventilation: possible and desirable. Respir Care. 2006; 51(9):1005-12; discussion 1012-5.
15. Khirani S, Ramirez A, Delord V, Leroux K, Lofaso F, Hautot S, et al. Evaluation of ventilators for mouthpiece ventilation in neuromuscular disease. Respir Care. 2014;59(9):1329-37. http://dx.doi.org/10.4187/respcare.03031

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REVIEW ARTICLE

The role of physical exercise in obstructive sleep apnea

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Study carried out in the Laboratório do Sono e Coração, Pronto-Socorro Cardiológico de Pernambuco – PROCAPE – Universidade de Pernambuco, and at the Hospital Metropolitano Sul Dom Helder Câmara, Instituto de Medicina Integral Professor Fernando Figueira – IMIP Hospitalar – Recife (PE) Brasil.

ABSTRACT

Obstructive sleep apnea (OSA) is a common clinical condition, with a variable and underestimated prevalence. OSA is the main condition associated with secondary systemic arterial hypertension, as well as with atrial fibrillation, stroke, and coronary artery disease, greatly increasing cardiovascular morbidity and mortality. Treatment with continuous positive airway pressure is not tolerated by all OSA patients and is often not suitable in cases of mild OSA. Hence, alternative methods to treat OSA and its cardiovascular consequences are needed. In OSA patients, regular physical exercise has beneficial effects other than weight loss, although the mechanisms of those effects remain unclear. In this population, physiological adaptations due to physical exercise include increases in upper airway dilator muscle tone and in slow-wave sleep time; and decreases in fluid accumulation in the neck, systemic inflammatory response, and body weight. The major benefits of exercise programs for OSA patients include reducing the severity of the condition and daytime sleepiness, as well as increasing sleep efficiency and maximum oxygen consumption. There are few studies that evaluated the role of physical exercise alone for OSA treatment, and their protocols are quite diverse. However, aerobic exercise, alone or combined with resistance training, is a common point among the studies. In this review, the major studies and mechanisms involved in OSA treatment by means of physical exercise are presented. In addition to systemic clinical benefits provided by physical exercise, OSA patients involved in a regular, predominantly aerobic, exercise program have shown a reduction in disease severity and in daytime sleepiness, as well as an increase in sleep efficiency and in peak oxygen consumption, regardless of weight loss.

Keywords: Exercise therapy; Sleep apnea, obstructive; Cardiovascular diseases.

INTRODUCTION

Obstructive sleep apnea (OSA) is a very common but underdiagnosed clinical condition and is associated with the development or worsening of a number of clinical conditions.[1-7] In a study conducted by Tufik et al. in the city of São Paulo, Brazil, in 2010,[5] the prevalence of OSA in a general population in the 20- to 80-year age bracket was found to be 32.8%, being 40.6% in males and 26.2% in females.

Epidemiological data suggest that regular physical exercise has beneficial effects other than weight loss in OSA patients; however, the mechanisms of those effects remain unclear.

OSA DEFINITION, CLASSIFICATION, AND RISK FACTORS

OSA is characterized by upper airway obstruction during sleep, resulting in recurrent hypoxia, hypercapnia, and arousals.[8-11] It is diagnosed by polysomnography, which is a test that allows the calculation of the apnea-hypopnea index (AHI), i.e., the ratio of the total number of apneas and hypopneas to total sleep time.[2,8,9] The severity of OSA is determined by the AHI: 5.0-14.9 events/h, mild OSA; 15-30 events/h, moderate OSA; and > 30 events/h, severe OSA.[2,8]

The etiology of OSA is multifactorial, including anatomical changes, neuromuscular factors, and genetic predisposition. The major risk factors for OSA are shown in Chart 1.[8-12]

CLINICAL MANIFESTATIONS OF OSA

Recurrent apnea, hypoxia, and hypercapnia, as well as sleep fragmentation (microarousals), together with increased negative intrathoracic pressure—which results from increased inspiratory muscle work in order to reopen the collapsed airways—result in impaired central nervous system, cardiovascular system, and metabolic function.[8,9,11-13] Excessive daytime sleepiness, nocturia, morning headache, decreased libido, attention deficit, impaired concentration, neurocognitive impairment, irritability, and depression are common in patients with OSA and greatly reduce their work efficiency and quality of life.[10,11]

OSA is associated with a variety of cardiovascular disorders, including systemic arterial hypertension (SAH), myocardial ischemia, cardiac arrhythmia, stroke, and

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Chart 1. Risk factors for obstructive sleep apnea.[8-12]

Snoring	Retrognathia or micrognathia
Male gender	Nasal obstruction
Age > 50 years	Hyperplasia of the tonsils and adenoids
Menopause	Macroglossia
Obesity	Collapse of the soft palate
Increased neck circumference	

increased arterial stiffness.[14] In patients with OSA, the most common cardiovascular comorbidity is SAH, and the relationship between SAH and OSA was first described 30 years ago. The prevalence and severity of SAH increase linearly with the increase in OSA severity. OSA treatment can reduce blood pressure.[8,9,11-13,15]

Recently, OSA has been associated with a systemic inflammatory response, resulting in atherosclerosis, insulin resistance, type 2 diabetes, and lipid profile changes, thus greatly increasing morbidity and mortality in patients with untreated OSA. Figure 1 shows the pathophysiology of the effects of OSA on the cardiovascular system.[10]

THERAPEUTIC STRATEGIES FOR OSA

Continuous positive airway pressure (CPAP) is typically the treatment of choice for OSA. It maintains a positive pharyngeal transmural pressure and increases end-expiratory lung volume, contributing to the maintenance of an open airway.[2,10] The aforementioned benefits were first reported by Sullivan et al. in 1981.[16]

According to the American Academy of Sleep Medicine, CPAP should be the first-line treatment for moderate to severe OSA (AHI > 15 events/h). The clinical decision to prescribe CPAP is based on the possibility of symptom relief and cardiovascular protection. Although CPAP is effective, it might not be tolerated by some patients. Adherence to CPAP therapy is highest in patients who snore heavily and have excessive daytime sleepiness.[2,17-24]

Sleep hygiene and changes in lifestyle habits, including weight loss, discontinuation or replacement of drugs that directly interfere with upper airway muscle function (benzodiazepines, barbiturates, and narcotics), reducing alcohol consumption (especially during the evening), smoking cessation, regular physical activity, and changing body position during sleep (avoiding the supine position) should always be encouraged in the treatment of OSA.[2,17-24]

The use of oral appliances is recommended in order to prevent the oropharynx and base of the tongue from collapsing during sleep. Mandibular repositioning or mandibular advancement splints are currently the most commonly used devices. They are indicated for the treatment of mild OSA and primary snoring. They can also be used in individuals who do not tolerate or would rather not use CPAP. Their use is contraindicated in patients with a predominance of central apneas, in those with active periodontal disease, and in those with temporomandibular joint dysfunction.[2,17-24]

Although surgical procedures were widely used in the treatment of OSA in the recent past, they are no longer used, because of symptom recurrence after a few months. In addition to being used in cases of significant facial changes and in young individuals with significant tonsillar hypertrophy, surgery has been used in order to improve nasal breathing for the use of a CPAP mask.[2,17-24]

EXERCISE-RELATED PHYSIOLOGICAL ADAPTATIONS IN OSA PATIENTS

Recent studies have focused on exercise programs for patients with OSA because they constitute a low-cost, easy-to-use treatment modality and have been shown to be effective in mitigating several harmful consequences of OSA, including cardiovascular disorders, glucose intolerance, and fatigue.[25-27]

The mechanisms whereby physical exercise attenuates OSA have yet to be well defined. It was long believed that the beneficial effects of physical exercise on patients with OSA were related to a reduction in body weight; however, experimental and clinical studies have shown that the benefits of exercise are independent of weight loss.[20,27-29] Several hypotheses have been proposed to explain the beneficial effects of physical exercise on patients with OSA.

Increased upper airway dilator muscle tone

Maintenance of airway patency requires the coordinated activity of upper airway and thoracic respiratory muscles.[30,31] Inspiratory muscle contraction results in a subatmospheric pressure gradient that allows the air to enter the respiratory system and predisposes to pharyngeal collapse. This trend toward pharyngeal collapse is compensated by the activation and contraction of several upper airway dilator muscles, such as the sternohyoid and omohyoid muscles, and pharyngeal lumen regulators, such as the genioglossus and digastric muscles.[32]

The effects of exercise on the characteristics and activity of the aforementioned muscles remain unclear. During physical activity, the respiratory muscles, particularly the diaphragm, work at an increased rate. This leads to metabolic and structural adaptations that improve fatigue resistance. On the basis of the knowledge that exercise increases respiratory muscle recruitment, it seems plausible that endurance exercise might result in increased upper airway muscle activation to increase upper airway diameter, reduce airway resistance, and oppose pharyngeal collapse during sleep.[32]

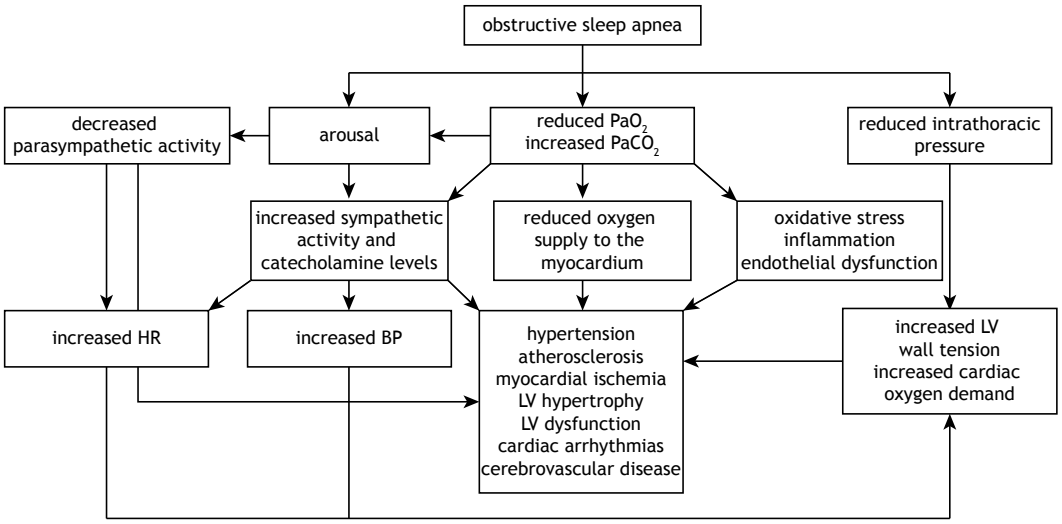

Figure 1. Pathophysiology of the effects of obstructive sleep apnea on the cardiovascular system. Adapted from Bradley & Floras, 2009.[10] BP: blood pressure; and LV: left ventricular.

Haxhiu et al.[33] and Hussain et al.[34] used similar methods for electrically stimulating the gastrocnemius muscle nerve of anesthetized dogs and noted an acute and significant increase in the tone and peak electromyographic activity of the genioglossus muscle, suggesting that greater activation of the lower limb muscles, such as occurs during physical activity, can result in greater activation of the upper airway dilator muscles, thus counterbalancing the increase in transpulmonary pressure gradient resulting from increased respiratory muscle activity.

Subsequently, Vincent et al.[32] evaluated 32 rats, which were divided into three groups: one group of sedentary rats (n = 10); one group of rats undergoing endurance exercise (n = 10); and one group of rats undergoing acute exercise (n = 12). The authors found that a 12-week treadmill exercise protocol (4 days/week, 90 min/day, at approximately 75% of maximal oxygen consumption) increased oxidative capacity, antioxidant activity, and type I muscle fiber content, as well as decreasing lipid peroxidation and type IIb muscle fiber content of the digastric and sternohyoid muscles. No such changes were noted in the genioglossus and omohyoid muscles.

In light of the current literature, the true role of physical exercise in improving upper airway dilator muscle performance in humans remains unclear. In this sense, this physiological effect of exercise on patients with OSA has yet to be confirmed.

Reduced fluid accumulation in the neck

Sedentary lifestyle and decreased ambulation are associated with fluid retention in the legs, given the central role of leg muscles in venous fluid dynamics. During sleep, the recumbent position contributes to fluid displacement to and accumulation in the neck, which increases laryngeal compression. This mechanism can increase the severity of OSA, given that most OSA patients have excessive daytime sleepiness and a sedentary lifestyle.[35-39]

Redolfi et al.[40] evaluated the relationship between overnight rostral fluid shift from the legs and OSA severity in 23 nonobese males. Associations were found between reduced leg fluid volume and increased neck circumference ($r = -0.792$; $p = 0.001$), between increased overnight rostral fluid shift from the legs and increased AHI ($r^2 = 0.643$; $p = 0.001$), and between increased time spent sitting daily and increased rostral fluid shift ($r^2 = 0.346$; $p = 0.003$). This last finding emphasizes the role of sedentary behavior in fluid accumulation in the neck during sleep.

The role that fluid accumulation in the neck plays in the development and worsening of OSA is more evident in patients with hypervolemia, especially those with chronic kidney disease, heart failure, and resistant hypertension, which are clinical conditions that are independently associated with reduced cardiorespiratory efficiency and muscular endurance,[37] resulting in a vicious cycle of sorts in the genesis of OSA (Figure 2).

White et al.[41] evaluated the effect of compression stockings on OSA severity in 22 individuals with leg edema, who were compared with a control group (n = 23). The AHI decreased significantly in the group of patients who wore compression stockings, in association with reduced nocturnal fluid shift from the legs and a significant increase in morning upper-airway cross-sectional area, neck fluid volume having remained unchanged overnight.

The real role of regular physical exercise in improving leg fluid dynamics and, consequently, OSA has yet to be clarified. Mendelson et al.[42] evaluated the effect of physical exercise on OSA and central sleep apnea in 34 individuals with coronary artery disease undergoing 4 weeks of aerobic exercise training, those 34 individuals being compared with a group of controls. All participants underwent polysomnography

at baseline and follow-up, the following being measured before and after sleep: leg fluid volume; neck fluid volume; thoracic fluid volume; and upper-airway cross-sectional area. The AHI decreased significantly in the exercise group, in association with a significant reduction in the overnight change in leg fluid volume and a significant increase in the overnight change in upper-airway cross-sectional area.

In another study, physical activity was found to have improved OSA severity in patients with heart failure; however, patients with fluid overload, as is the case of heart failure patients, are more likely to benefit from exercise than are those without hypervolemia.[39]

Increased slow-wave sleep

Normal sleep is divided into rapid eye movement (REM) sleep and non-rapid eye movement (NREM) sleep. Physiologically, REM sleep accounts for approximately 25% of total sleep time, being characterized by rapid, low-amplitude brain activity; episodes of REM; ventilatory instability; and hypotonic muscles, including those responsible for upper airway patency. Currently, NREM sleep is divided into stages 1, 2, and 3, stage 3 being designated slow-wave sleep and being characterized by a deeper sleep and an increased arousal threshold.[43]

Ratnavadivel et al.[44] evaluated 253 individuals and found that it took those with OSA longer to achieve slow-wave sleep, OSA patients also having decreased slow-wave sleep, increased daytime sleepiness, and an increased AHI. McSharry et al.[45] found increased genioglossus single motor unit activity during slow-wave sleep and proposed that this increased activity makes the airway more stable and resistant to collapse.

The first reports of the effects of exercise on sleep patterns date from 1970. Heinzelmann and Bagley[46] reported that individuals who participated in an 18-month exercise program during which they exercised for 1 h three times a week had a more relaxing and restorative sleep.

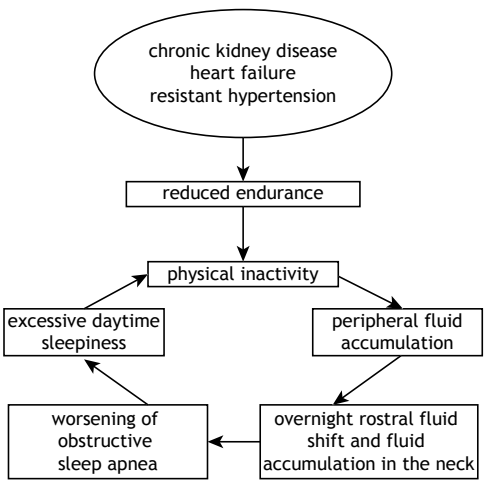

Figure 2. Interrelationship between chronic diseases resulting in hypervolemia and worsening of obstructive sleep apnea.

Exercise increases body temperature and can therefore facilitate the onset of sleep by activating heat-dissipating processes and hypothalamus-controlled sleep-inducing mechanisms. The theories of body energy conservation and organ function restoration indicate that there is a relationship between increased energy expenditure and increased stage 3 NREM sleep.[47]

Previous studies have shown sleep pattern changes in individuals undergoing exercise programs, including increased slow-wave sleep, decreased REM sleep, and increased latency to REM sleep.[48,49]

Ueno et al.[26] evaluated patients with functional class I-III heart failure and OSA, central sleep apnea, or no sleep apnea. The patients underwent a 4-month exercise program consisting of three 60-min sessions per week divided into muscle stretching and cycle ergometry, the intensity of which was set at 10% below the respiratory compensation point obtained by cardiopulmonary exercise testing. The authors found an increase in stage 3 NREM sleep.[26]

Recently, Kredlow et al.[50] performed a meta-analysis of the effects of acute and regular exercise on sleep quality and found that exercise can improve subjective perception and objective parameters of sleep (including total sleep time, sleep efficiency, and duration of slow-wave sleep).

Reduced body weight

Physical exercise can reduce OSA severity by reducing body weight and abdominal fat. Previous data have shown that a 10% reduction in the body mass index (BMI) is associated with a 30% reduction in the AHI.[21,51] Dobrosielski et al.[52] found a reduced AHI associated with a reduced BMI in OSA patients undergoing an aerobic exercise program and following a calorie-restricted diet.

Barnes et al.[53] evaluated 21 OSA patients undergoing a program combining a very-low-energy diet and aerobic and resistance exercise and found a significant reduction in the BMI and Epworth Sleepiness Scale score in those with mild to moderate OSA, but no significant changes in the AHI. These results suggest that there is a need for randomized controlled studies aimed at determining the relationship among physical exercise, body weight reduction, and OSA severity.

Reduced systemic inflammatory response

Adipose tissue, particularly abdominal fat, is rich in inflammatory cytokines. OSA can modulate the expression and release of inflammatory mediators from visceral fat and other tissues. Independently of obesity, OSA patients have been found to have elevated levels of C-reactive protein, TNF, and IL-6, which are associated with sleepiness, fatigue, and various metabolic and cardiovascular complications.[54]

Adiponectin is a protein that is secreted exclusively by white adipose tissue and has anti-inflammatory and antiatherosclerotic effects; in patients with OSA, serum adiponectin concentrations are reduced, increasing their risk of cardiovascular disease.[54]

Chart 2. Characteristics of the exercise programs.

Authors	Participants	Characteristics of the exercise program	Results
Norman et al.[56]	9 patients with mild to moderate OSA	supervised exercise at months 1-4 and only one supervised session at months 5 and 6 duration: 24 weeks • aerobic exercise – 3 days a week; 30-45 min/session – treadmill/cycle ergometer at 60-85% of HRR • resistance exercise: participants were instructed on how to perform resistance exercises that they could incorporate into their routine	reduced AHI and BMI; improved aerobic capacity and quality of life
Barnes et al.[53]	21 patients with mild to severe AHI	supervised exercise at weeks 1-8; from week 9 onward, only one supervised session 12. resistance exercise – duration: 16 weeks – 3 days/week at 80% of maximal resistance – 7 different muscle groups; dumbbells; 8-12 repetitions 13. aerobic exercise – beginning at week 5 of the resistance exercise program – duration: 24 weeks – 5 days/week; 40 min/session – walking, cycling, and jogging at 80% of VO_{2peak}	reduced body weight and daytime sleepiness; improved cardiometabolic outcomes (MAP, cholesterol levels, triglyceride levels, C-reactive protein levels, insulin levels, GGT levels, and VO_{2peak}) and quality of life
Kline et al.[57]	43 patients with moderate OSA	supervised exercise duration: 12 weeks 14. aerobic exercise – 150 min/week; 4 days/week – treadmill/elliptical trainer/cycle ergometer at 60% of HRR 15. resistance exercise – 2 days/week after aerobic training – 8 different muscle groups; dumbbells; 10-12 repetitions	reduced AHI and oxygen desaturation index; no changes in the BMI
Sengul et al.[28]	20 patients with mild to moderate OSA	supervised exercise duration: 12 weeks 16. aerobic exercise – 3 days/week; 60-90 min/session – treadmill/cycle ergometer at 60-70% of VO_{2peak} 17. breathing exercises – 3 days/week; 15-30 min/session	Reduced AHI; improved exercise capacity, sleep quality, and quality of life; no changes in the BMI
Servantes et al.[58]	50 patients with heart failure and OSA	The first 3 sessions were supervised; the remaining sessions were performed at home. duration: 12 weeks; patients divided into two groups group I 18. aerobic exercise – 3 days/week (weeks 1-8) – 4 days/week (weeks 9-12) – 30-45 min/session at AT group II 19. aerobic exercise – 3 days/week (weeks 1-8) – 4 days/week (weeks 9-12) – 30-45 min/session at AT 20. resistance exercise – 3 days/week (weeks 1-8) – 4 days/week (weeks 9-12) – 1 series; 7 different muscle groups; 12-16 repetitions	increased exercise capacity, muscle strength, and muscle resistance; reduced AHI
Ackel-D'elia et al.[60]	32 patients with moderate to severe OSA and ESS score > 9	supervised exercise duration: 2 months • aerobic exercise – 3 days/week; 40 min/session – treadmill at 85% of AT	reduced sleepiness, tension, and fatigue; increased physical functioning and vitality
Schütz et al.[61]	25 patients with moderate to severe OSA	supervised exercise aerobic and resistance exercise duration: 2 months 3 days/week; 60 min/session The exercise protocol was not described.	reduced daytime sleepiness, LDL levels, and triglyceride levels

OSA: obstructive sleep apnea; HRR: heart rate reserve; AHI: apnea-hypopnea index; BMI: body mass index; MAP: mean arterial pressure; VO_{2peak}: peak oxygen consumption; GGT: gamma-glutamyltransferase; AT: anaerobic threshold; and ESS: Epworth Sleepiness Scale.

Studies have shown that regular exercise has an anti-inflammatory effect, especially in obese patients; however, the impact of this treatment modality on the inflammatory response of individuals with OSA remains unclear.[54] In a recent study, Cavagnolli et al.[55] evaluated the effects of a 2-month aerobic exercise program on 20 nonobese adult males, 10 of whom had OSA; the authors found that C-reactive protein levels were similar between the control group and the OSA group, as well as finding a less than significant reduction in C-reactive protein levels and the AHI after the exercise program.

CLINICAL BENEFITS OF EXERCISE IN THE TREATMENT OF OSA

In a recent meta-analysis of five studies, Iftikhar et al.[7] found significant reductions in the AHI and daytime sleepiness, as well as increases in sleep efficiency and peak oxygen consumption (VO_{2peak}), in adult patients with OSA.[28,56-58] The authors[7] found that OSA patients undergoing regular exercise had a 32% reduction in the AHI (a reduction of 6.27 events/h) and a 28% reduction in daytime sleepiness, as well as a 5.8% increase in sleep efficiency and a 17.65% increase in VO_{2peak}, having found no significant reduction in the BMI (VO_{2peak} = −1.37; 95% CI: −2.81 to 0.07; p = 0.06, I^2 = 76.92%). Another important point is that even if exercise has no significant impact on OSA severity, indirect benefits of exercise include decreased blood pressure, improved metabolic profile, and reduced overall cardiovascular risk. More recently, Aiello et al.[59] performed a meta-analysis of nine studies and confirmed the findings of Iftikhar et al.,[7] having found a reduction in the AHI and in daytime sleepiness after exercise as the sole treatment for OSA.

There is a lack of studies evaluating the role of exercise as the sole treatment for OSA. In addition, there are differences across studies regarding exercise protocols; however, aerobic exercise (either in isolation or in combination with resistance exercise) has been used in all studies. The main characteristics of the exercise programs used in seven randomized controlled studies are shown in Chart 2.[28,53,56-58,60,61]

FINAL CONSIDERATIONS

A condition that affects several organ systems, OSA significantly increases morbidity and mortality. The most common therapeutic strategies (i.e., CPAP, oral appliances, and corrective upper airway surgery) are sometimes not tolerated by patients. In this context, physical exercise is a therapeutic alternative for patients with OSA, because it is simple and inexpensive, as well as having systemic benefits.

Exercise-related physiological adaptations in OSA patients include increased upper airway dilator muscle tone, reduced fluid accumulation in the neck, increased slow-wave sleep (stage 3 NREM sleep), reduced body weight, and reduced systemic inflammatory response.

In addition to conferring systemic clinical benefits, regular, predominantly aerobic, exercise results in reduced OSA severity (a reduced AHI), reduced daytime sleepiness, increased sleep efficiency, and increased VO_{2peak}, independently of weight loss. Although these findings are encouraging, further studies are needed in order to clarify the true role of physical exercise in the treatment of OSA and its complications.

REFERENCES

1. Spicuzza L, Caruso D, Di Maria G. Obstructive sleep apnoea syndrome and its management. Ther Adv Chronic Dis. 2015;6(5):273-85. http://dx.doi.org/10.1177/2040622315590318
2. Naughton MT. Sleep disorders in patients with congestive heart failure. Curr Opin Pulm Med. 2003;9(6):453-8. http://dx.doi.org/10.1097/00063198-200311000-00001
3. Lorenzi-Filho G, Genta PR, Pedrosa RP, Drager LF, Martinez D. Cardiovascular consequences of obstructive sleep apnea syndrome [Article in Portuguese]. J Bras Pneumol. 2010;36 Suppl 2:38-42.
4. Punjabi NM. The epidemiology of adult obstructive sleep apnea. Proc Am Thorac Soc. 2008;5(2):136-43. http://dx.doi.org/10.1513/pats.200709-155MG
5. Tufik S, Santos-Silva R, Taddei JA, Bittencourt LR. Obstructive sleep apnea syndrome in the Sao Paulo Epidemiologic Sleep Study. Sleep Med. 2010;11(5):441-6. http://dx.doi.org/10.1016/j.sleep.2009.10.005
6. Pedrosa RP, Drager LF, Gonzaga CC, Sousa MG, de Paula LK, Amaro AC, et al. Obstructive sleep apnea: The most common secondary cause of hypertension associated with resistant hypertension. Hypertension. 2011;58(5):811-7. http://dx.doi.org/10.1161/HYPERTENSIONAHA.111.179788
7. Iftikhar IH, Kline CE, Youngstedt SD. Effects of exercise training on sleep apnea: a meta-analysis. Lung. 2014;192(1):175-84. http://dx.doi.org/10.1007/s00408-013-9511-3
8. Pham LV, Schwartz AR. The pathogenesis of obstructive sleep apnea. J Thorac Dis. 2015;7(8):1358-72.
9. Jordan AS, McSharry DG, Malhotra A. Adult obstructive sleep apnoea. Lancet. 2014;383(9918):736-47. http://dx.doi.org/10.1016/S0140-6736(13)60734-5
10. Bradley TD, Floras JS. Obstructive sleep apnoea and its cardiovascular consequences. Lancet. 2009;373(9657):82-93. http://dx.doi.org/10.1016/S0140-6736(08)61622-0
11. Somers VK, White DP, Amin R, Abraham WT, Costa F, Culebras A, et al. Sleep apnea and cardiovascular disease: an American Heart Association/American College of Cardiology Foundation Scientific Statement from the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council on Cardiovascular Nursing. J Am Coll Cardiol. 2008;52(8):686-717. http://dx.doi.org/10.1016/j.jacc.2008.05.002
12. Stansbury RC, Strollo PJ. Clinical manifestations of sleep apnea. J Thorac Dis. 2015;7(9):E298-310.
13. Lévy P, Ryan S, Oldenburg O, Parati G. Sleep apnoea and the heart. Eur Respir Rev. 2013;22(129):333-52. http://dx.doi.org/10.1183/09059180.00004513
14. Pedrosa RP, Barros IM, Drager LF, Bittencourt MS, Medeiros AK, Carvalho LL, et al. OSA is common and independently associated with hypertension and increased arterial stiffness in consecutive perimenopausal women. Chest. 2014;146(1):66-72. http://dx.doi.org/10.1378/chest.14-0097
15. Pedrosa RP, Drager LF, de Paula LK, Amaro AC, Bortolotto LA, Lorenzi-Filho G. Effects of OSA treatment on BP in patients with resistant hypertension: a randomized trial. Chest. 2013;144(5):1487-94. http://dx.doi.org/10.1378/chest.13-0085
16. Sullivan CE, Issa FG, Berthon-Jones M, Eves L. Reversal of obstructive sleep apnoea by continuous positive airway pressure applied through the nares. Lancet. 1981;1(8225):862-5. http://dx.doi.org/10.1016/S0140-6736(81)92140-1

17. Morgenthaler TI, Kapen S, Lee-Chiong T, Alessi C, Boehlecke B, Brown T, et al. Practice parameters for the medical therapy of obstructive sleep apnea. Sleep. 2006;29(8):1031-5.
18. Sundaram S, Bridgman SA, Lim J, Lasserson TJ. Surgery for obstructive sleep apnoea. Cochrane Database Syst Rev. 2005;(4):CD001004.
19. Smith PL, Gold AR, Meyers DA, Haponik EF, Bleecker ER. Weight loss in mildly to moderately obese patients with obstructive sleep apnea. Ann Intern Med. 1985;103(6 (Pt 1)):850-5. http://dx.doi.org/10.7326/0003-4819-103-6-850
20. Schwartz AR, Gold AR, Schubert N, Stryzak A, Wise RA, Permutt S, et al. Effect of weight loss on upper airway collapsibility in obstructive sleep apnea. Am Rev Respir Dis. 1991;144(3 Pt 1):494-8. http://dx.doi.org/10.1164/ajrccm/144.3_Pt_1.494
21. Peppard PE, Young T, Palta M, Dempsey J, Skatrud J. Longitudinal study of moderate weight change and sleep-disordered breathing. JAMA. 2000;284(23):3015-21. http://dx.doi.org/10.1001/jama.284.23.3015
22. Kushida CA, Morgenthaler TI, Littner MR, Alessi CA, Bailey D, Coleman J Jr, et al. Practice parameters for the treatment of snoring and Obstructive Sleep Apnea with oral appliances: an update for 2005. Sleep. 2006;29(2):240-3.
23. Kushida CA, Littner MR, Hirshkowitz M, Morgenthaler TI, Alessi CA, Bailey D, et al. Practice parameters for the use of continuous and bilevel positive airway pressure devices to treat adult patients with sleep-related breathing disorders. Sleep. 2006;29(3):375-80.
24. Bennett LS. Adult obstructive sleep apnoea syndrome. J R Coll Physicians Lond. 1999;33(5):439-44.
25. Yamamoto U, Mohri M, Shimada K, Origuchi H, Miyata K, Ito K, et al. Six-month aerobic exercise training ameliorates central sleep apnea in patients with chronic heart failure. J Card Fail. 2007;13(10):825-9. http://dx.doi.org/10.1016/j.cardfail.2007.08.001
26. Ueno LM, Drager LF, Rodrigues AC, Rondon MU, Braga AM, Mathias W Jr, et al. Effects of exercise training in patients with chronic heart failure and sleep apnea. Sleep. 2009;32(5):637-47.
27. Quan SF, O'Connor GT, Quan JS, Redline S, Resnick HE, Shahar E, et al. Association of physical activity with sleep-disordered breathing. Sleep Breath. 2007;11(3):149-57. http://dx.doi.org/10.1007/s11325-006-0095-5
28. Sengul YS, Ozalevli S, Oztura I, Itil O, Baklan B. The effect of exercise on obstructive sleep apnea: a randomized and controlled trial. Sleep Breath. 2011;15(1):49-56. http://dx.doi.org/10.1007/s11325-009-0311-1
29. Awad KM, Malhotra A, Barnet JH, Quan SF, Peppard PE. Exercise is associated with a reduced incidence of sleep-disordered breathing. Am J Med. 2012;125(5):485-90. http://dx.doi.org/10.1016/j.amjmed.2011.11.025
30. Giebelhaus V, Strohl KP, Lormes W, Lehmann M, Netzer N. Physical Exercise as an Adjunct Therapy in Sleep Apnea-An Open Trial. Sleep Breath. 2000;4(4):173-176.
31. Fregosi RF, Ludlow CL. Activation of upper airway muscles during breathing and swallowing. J Appl Physiol (1985). 2014;116(3):291-301. http://dx.doi.org/10.1152/japplphysiol.00670.2013
32. Vincent HK, Shanely RA, Stewart DJ, Demirel HA, Hamilton KL, Ray AD, et al. Adaptation of upper airway muscles to chronic endurance exercise. Am J Respir Crit Care Med. 2002;166(3):287-93. http://dx.doi.org/10.1164/rccm.2104120
33. Haxhiu MA, van Lunteren E, Mitra J, Cherniack NS, Strohl KP. Comparison of the responses of the diaphragm and upper airway muscles to central stimulation of the sciatic nerve. Respir Physiol. 1984;58(1):65-76. http://dx.doi.org/10.1016/0034-5687(84)90045-8
34. Hussain SN, Ward ME, Gatensby AG, Roussos C, Deschamps A. Respiratory muscle activation by limb muscle afferent stimulation in anesthetized dogs. Respir Physiol. 1991;84(2):185-98. http://dx.doi.org/10.1016/0034-5687(91)90116-Z
35. Shiota S, Ryan CM, Chiu KL, Ruttanaumpawan P, Haight J, Arzt M, et al. Alterations in upper airway cross-sectional area in response to lower body positive pressure in healthy subjects. Thorax. 2007;62(10):868-72. http://dx.doi.org/10.1136/thx.2006.071183
36. Redolfi S, Arnulf I, Pottier M, Lajou J, Koskas I, Bradley TD, et al. Attenuation of obstructive sleep apnea by compression stockings in subjects with venous insufficiency. Am J Respir Crit Care Med. 2011;184(9):1062-6. http://dx.doi.org/10.1164/rccm.201102-0350OC
37. Redolfi S, Arnulf I, Pottier M, Bradley TD, Similowski T. Effects of venous compression of the legs on overnight rostral fluid shift and obstructive sleep apnea. Respir Physiol Neurobiol. 2011;175(3):390-3. http://dx.doi.org/10.1016/j.resp.2011.01.001
38. White LH, Bradley TD. Role of nocturnal rostral fluid shift in the pathogenesis of obstructive and central sleep apnoea. J Physiol. 2013;591(5):1179-93. http://dx.doi.org/10.1113/jphysiol.2012.245159
39. Mirrakhimov AE. Physical exercise related improvement in obstructive sleep apnea. Look for the rostral fluid shift. Med Hypotheses. 2013;80(2):125-8. http://dx.doi.org/10.1016/j.mehy.2012.11.007
40. Redolfi S, Yumino D, Ruttanaumpawan P, Yau B, Su MC, Lam J, et al. Relationship between overnight rostral fluid shift and Obstructive Sleep Apnea in nonobese men. Am J Respir Crit Care Med. 2009;179(3):241-6. http://dx.doi.org/10.1164/rccm.200807-1076OC
41. White LH, Lyons OD, Yadollahi A, Ryan CM, Bradley TD. Effect of below-the-knee compression stockings on severity of obstructive sleep apnea. Sleep Med. 2015;16(2):258-64. http://dx.doi.org/10.1016/j.sleep.2014.12.005
42. Mendelson M, Lyons OD, Yadollahi A, Inami T, Oh P, Bradley TD. Effects of exercise training on sleep apnoea in patients with coronary artery disease: a randomised trial. Eur Respir J. 2016;48(1):142-50. http://dx.doi.org/10.1183/13993003.01897-2015
43. Beltrami FG, Nguyen X, Pichereau C, Maury E, Fleury B, Fagondes S. Sleep in the intensive care unit. J Bras Pneumol. 2015;41(6):539-46. http://dx.doi.org/10.1590/S1806-37562015000000056
44. Ratnavadivel R, Chau N, Stadler D, Yeo A, McEvoy RD, Catcheside PG. Marked reduction in obstructive sleep apnea severity in slow wave sleep. J Clin Sleep Med. 2009;5(6):519-24.
45. McSharry DG, Saboisky JP, Deyoung P, Matteis P, Jordan AS, Trinder J, et al. A mechanism for upper airway stability during slow wave sleep. Sleep. 2013;36(4):555-63. http://dx.doi.org/10.5665/sleep.2544
46. Heinzelmann F, Bagley RW. Response to physical activity programs and their effects on health behavior. Public Health Rep. 1970;85(10):905-11. http://dx.doi.org/10.2307/4594000
47. Martins PJ, Mello MT, Tufik S. Exercício e Sono. Rev Bras Med Esporte. 2001;7(1):28-36.
48. Youngstedt SD, O'Connor PJ, Crabbe JB, Dishman RK. The influence of acute exercise on sleep following high caffeine intake. Physiol Behav. 2000;68(4):563-70. http://dx.doi.org/10.1016/S0031-9384(99)00213-9
49. Youngstedt SD, O'Connor PJ, Dishman RK. The effects of acute exercise on sleep: a quantitative synthesis. Sleep. 1997;20(3):203-14.
50. Kredlow MA, Capozzoli MC, Hearon BA, Calkins AW, Otto MW. The effects of physical activity on sleep: a meta-analytic review. J Behav Med. 2015;38(3):427-49. http://dx.doi.org/10.1007/s10865-015-9617-6
51. Newman AB, Foster G, Givelber R, Nieto FJ, Redline S, Young T. Progression and regression of sleep-disordered breathing with changes in weight: the Sleep Heart Health Study. Arch Intern Med. 2005;165(20):2408-13. http://dx.doi.org/10.1001/archinte.165.20.2408
52. Dobrosielski DA, Patil S, Schwartz AR, Bandeen-Roche K, Stewart KJ. Effects of exercise and weight loss in older adults with obstructive sleep apnea. Med Sci Sports Exerc. 2015;47(1):20-6. http://dx.doi.org/10.1249/MSS.0000000000000387
53. Barnes M, Goldsworthy UR, Cary BA, Hill CJ. A diet and exercise program to improve clinical outcomes in patients with obstructive sleep apnea – a feasibility study. J Clin Sleep Med. 2009;5(5):409-15.
54. Alves Eda S, Ackel-D'Elia C, Luz GP, Cunha TC, Carneiro G, Tufik S, et al. Does physical exercise reduce excessive daytime sleepiness by improving inflammatory profiles in obstructive sleep apnea patients? Sleep Breath. 2013;17(2):505-10. http://dx.doi.org/10.1007/s11325-012-0729-8
55. Cavagnolli DA, Esteves AM, Ackel-D'Elia C, Maeda MY, de Faria AP, Tufik S, et al. Aerobic exercise does not change C-reactive protein levels in non-obese patients with obstructive sleep apnoea. Eur J Sport Sci. 2014;14 Suppl 1:S142-7.
56. Norman JF, Von Essen SG, Fuchs RH, McElligott M. Exercise training effect on obstructive sleep apnea syndrome. Sleep Res Online. 2000;3(3):121-9.
57. Kline CE, Crowley EP, Ewing GB, Burch JB, Blair SN, Durstine JL, et al. The effect of exercise training on obstructive sleep apnea and sleep quality: a randomized controlled trial. Sleep. 2011;34(12):1631-40. http://dx.doi.org/10.5665/sleep.1422
58. Servantes DM, Pelcerman A, Salvetti XM, Salles AF, de Albuquerque

PF, de Salles FC, et al. Effects of home-based exercise training for patients with chronic heart failure and sleep apnoea: a randomized comparison of two different programmes. Clin Rehabil. 2012;26(1):45-57. http://dx.doi.org/10.1177/0269215511403941

59. Aiello KD, Caughey WG, Nelluri B, Sharma A, Mookadam F, Mookadam M. Effect of exercise training on sleep apnea: A systematic review and meta-analysis. Respir Med. 2016;116:85-92. http://dx.doi.org/10.1016/j.rmed.2016.05.015
60. Ackel-D'Elia C, da Silva AC, Silva RS, Truksinas E, Sousa BS, Tufik S, et al., Effects of exercise training associated with continuous positive airway pressure treatment in patients with obstructive sleep apnea syndrome. Sleep Breath. 2012;16(3):723-35. http://dx.doi.org/10.1007/s11325-011-0567-0
61. Schütz TC, Cunha TC, Moura-Guimaraes T, Luz GP, Ackel-D'Elia C, Alves Eda S, et al. Comparison of the effects of continuous positive airway pressure, oral appliance and exercise training in obstructive sleep apnea syndrome. Clinics (Sao Paulo). 2013;68(8):1168-74. http://dx.doi.org/10.6061/clinics/2013(08)17

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An uncommon tomographic association: amiodarone pulmonary toxicity and adenocarcinoma

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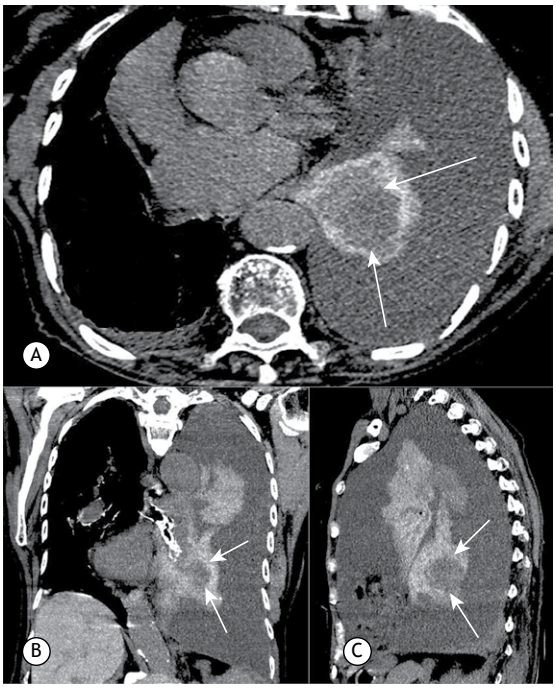

Figure 1. Axial (in A), coronal (in B), and sagittal (in C) chest CT scans showing left pleural effusion and a high-density collapsed lung containing a round hypodense mass (arrows). Note also small right pleural effusion and liver hyperdensity (the liver is denser than the heart).

A 73-year-old woman, a current smoker, presented with progressive dyspnea. She had a history of ventricular tachyarrhythmia treated with amiodarone. A chest X-ray demonstrated diffuse opacification of the left hemithorax. Chest CT showed left pleural effusion and a high-density collapsed lung containing a round hypodense mass (arrows). There was also small right pleural effusion and liver hyperdensity (the liver was denser than the heart; Figure 1). Percutaneous fine-needle aspiration biopsy of the mass revealed adenocarcinoma. The histopathological findings of the dense pulmonary parenchyma were compatible with amiodarone-induced pulmonary toxicity (APT). The patient died one month after the examination. Amiodarone is associated with a wide range of adverse effects, including APT.[1-3] The diagnosis of APT can be suggested on the basis of a combination of clinical, radiological, and pathological findings, and is confirmed by improvement after discontinuation of amiodarone therapy.[3] The high iodine content of the medication enables the detection of amiodarone deposits in the lung by CT as high-attenuation parenchymal opacities. The association of dense lung consolidations with high liver density is characteristic of amiodarone impregnation.[2,3] In the case described here, the dense pulmonary parenchyma caused by amiodarone impregnation allowed the tomographic identification of the tumor.

REFERENCES

1. Hudzik B, Polonski L. Amiodarone-induced pulmonary toxicity. CMAJ. 2012;184(15):E819. http://dx.doi.org/10.1503/cmaj.111763
2. Hochhegger B, Soares Souza A Jr, Zanetti G, Marchiori E. An enlarged heart with hyperdense consolidation. Neth J Med. 2013;71(6):317, 321.
3. Jarand J, Lee A, Leigh R. Amiodaronoma: an unusual form of amiodarone-induced pulmonary toxicity. CMAJ. 2007;176(10):1411-3. http://dx.doi.org/10.1503/cmaj.061102

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Pulmonary fat embolism of neoplastic origin

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TO THE EDITOR:

We report the case of a 67-year-old female patient who had hypertension and diabetes and had recently been diagnosed with a right renal mass. Abdominal CT and magnetic resonance imaging (MRI) showed that the renal mass, which measured approximately 7.5 cm along its longest axis, was predominantly exophytic, was located in the upper half of the right kidney, and had areas suggestive of intratumoral fat; in addition, the signal of the lesion extended to the ipsilateral renal vein and the inferior vena cava (Figure 1A). Histopathological examination of a CT-guided percutaneous biopsy sample revealed the presence of clear cells and oxyphilic cells that were probably malignant, with a moderately elevated proliferative index; a diagnosis of malignant primary renal neoplasm was therefore made.

Shortly thereafter, the patient presented to the emergency room with respiratory complaints. A CT scan of the chest revealed the presence of negative (fat) density in a branch of the left pulmonary artery (Figure 1B). A chest CT angiography was subsequently performed and confirmed the presence of pulmonary fat embolism (Figures 1C and 1D). Therefore, a diagnosis of pulmonary embolism secondary to renal cell carcinoma was made.

It is important to emphasize that the diagnosis of pulmonary tumor embolism was based on CT and MRI findings. Abdominal CT showed that the embolus had negative density values, which are characteristic of fat. Contrast-enhanced MRI of the thorax was also performed, showing a signal drop in the thrombus on the fat-saturated and out-of-phase T1-weighted images, thus confirming the presence of pulmonary fat embolism. The same was found for the renal tumor and its extensions to the ipsilateral renal vein and the inferior vena cava.

An imaging finding of fat in a renal tumor is highly suggestive of angiomyolipoma. Fat is rarely associated

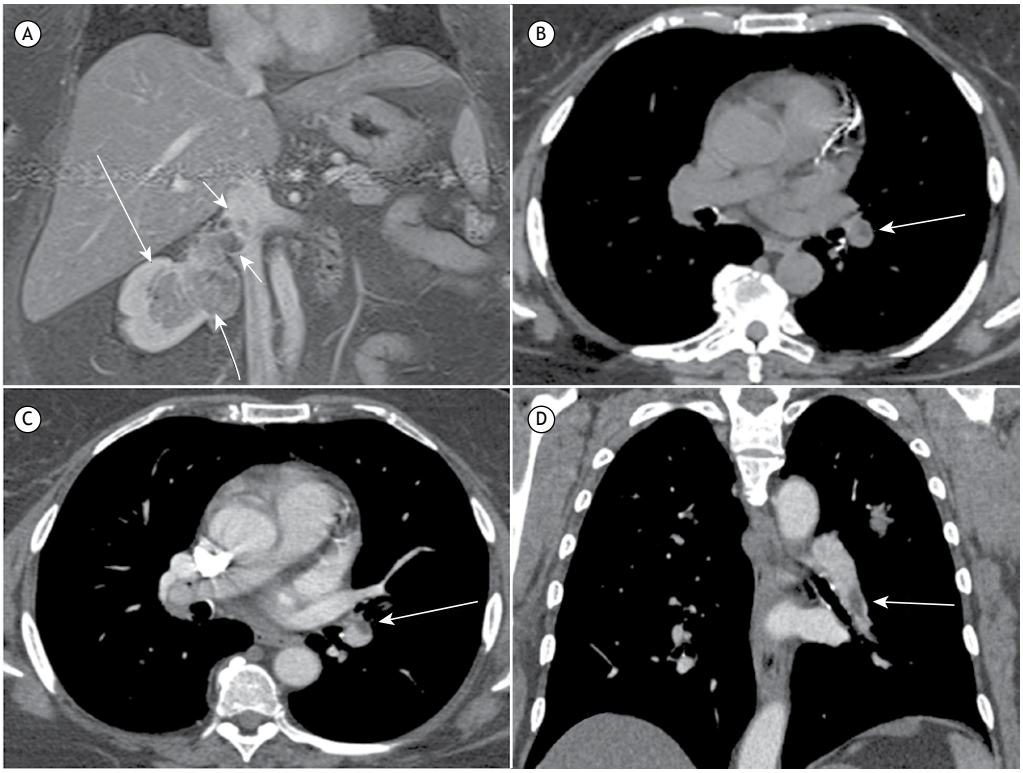

Figure 1. In A, coronal contrast-enhanced fat-saturated T1-weighted magnetic resonance image showing a renal tumor in the renal sinus (arrows), invading the right renal vein and extending into the inferior vena cava (arrowheads). In B, axial CT scan without contrast enhancement, showing a filling defect with fat density in a branch of the left pulmonary artery (arrow). Axial and coronal CT angiography scans of the chest in C and D, respectively, showing a fatty embolus partially obstructing the pulmonary artery branch to the left lower lobe (arrows). Density values for the tumor embolus ranged from −30 to −60 Hounsfield units.

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with other renal neoplasms, such as renal cell carcinomas.[1] Cases of pulmonary embolism secondary to renal tumors have been reported in the literature, most of which were cases of pulmonary fat embolism secondary to angiomyolipoma.[2-4] To our knowledge, there has been only one reported case of pulmonary embolism secondary to renal cell carcinoma,[5] albeit without fatty emboli. Therefore, in addition to the known association between renal angiomyolipoma and fatty emboli in the pulmonary arteries, there is an association between renal cell carcinoma and fatty emboli, as demonstrated by the case reported herein. Renal cell carcinoma is the most common type of kidney cancer, with metastatic disease at diagnosis in 20-25% of cases.[5] The association between renal tumors and pulmonary fat embolism is of note because, given the signal intensity and density characteristics on MRI and CT, respectively—which are relatively specific to fat—a presumptive diagnosis can be made without contrast-enhanced imaging, as was the case here.

In conclusion, it is important to evaluate fat density thrombi in the pulmonary vessels of patients with renal neoplasms with or without respiratory symptoms for a diagnosis of pulmonary tumor embolism.

REFERENCES

1. Hammadeh MY, Thomas K, Philp T, Singh M. Renal cell carcinoma containing fat mimicking angiomyolipoma: demonstration with CT scan and histopathology. Eur Radiol. 1998;8(2):228-9. https://doi.org/10.1007/s003300050367
2. Harris K, Hatem E, Maroun R, Seminara D, Maniatis T. A renal angiomyolipoma with extension to the renal vein and asymptomatic fat pulmonary embolus. Ther Adv Respir Dis. 2014;8(4):133-5. https://doi.org/10.1177/1753465814538690
3. Hamidi N, Suer E, Gokce MI, Alacayir I, Atasoy C, Kankaya D, et al. An Unusual Manifestation of Renal Angiomyolipoma: Pulmonary Fat Embolism. Urology. 2015;86(3):e13-5. https://doi.org/10.1016/j.urology.2015.05.016
4. Yarmish G, DiPoce J. Case 199: Aggressive angiomyolipoma with renal vein thrombosis and pulmonary fat embolus. Radiology. 2013;269(2):615-8. https://doi.org/10.1148/radiol.13121187
5. Lim NK, Aik OT, Meng LL, Htun TH, Razack AH. Superior vena caval syndrome secondary to metastatic renal cell carcinoma. J Coll Physicians Surg Pak. 2014;24 Suppl 1:S68-70.

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Abstracts

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

Chapter in a Book

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

Official Publications

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

Theses

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

Electronic publications

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

Homepages/URLs

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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VENT (US + OUS)[4]	6 meses	24.7%	28 metros	- 8.4 pontos

1. Eberhardt R. et al. A Multicenter, Prospective, Randomized, Controlled Trial of Endobronchial Valve Therapy vs Standard of Care in Homogeneous Emphysema (IMPACT), Abstract; ERJ. 2016; 2. Klooster K. et al. N Engl J Med. 2015; 373: 2325-36 + Supplementary Appendix; 3. Zoumot Z. et al. Lancet. 2015; 386 (9998): 1066-73 + Supplementary Appendix; 4. Scuirba F.C. et al. N Engl J Med. 2010; 363(13): 1233-44/ Herth F. J. et al. Eur. Respir. J. 2012; 39(6): 1334-42/ Ad hoc analysis on le at Pulmonx.

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1. Lindberg A, Szalai Z, Pullerits T, et al. Fast onset of effect of budesonide/formoterol versus salmeterol/fluticasone and salbutamol in patients with chronic obstructive pulmonary disease and reversible airway obstruction. Respirology 2007 Sep;12(5): 732-9. **2**. Tashkin DP, Rennard SI, Martin P, et al. Efficacy and safety of budesonide+/formoterol in one pressurized metered dose inhaler in patients with moderate to very severe chronic obstructive pulmonary disease. Results of a 6-month randomized clinical trial. Drugs 2008;68(14): 1975-2000. **3**. Rennard SI, Tashkin DP, McElhattan J, et al. Efficacy and tolerability of budesonide/formoterol in one hydrofluoroalkane pressurized metered-dose inhaler in patients with chronic obstructive pulmonary disease: results from a 1-year randomized controlled clinical trial [supplementary material]. Drugs. 2009;69(5):549-65. doi: 10.2165/00003495-200969050-00004. **4**. Hampel F C, Martin P. Mezzanotte W S. Early bronchodilatory effects of budesonide/formoterol pMDI compared with fluticasone/salmeterol DPI and albuterol pMDI: 2 randomized controlled trials in adults with persistent asthma previously treated with inhaled corticosteroids. Journal of Asthma 2008; 45: 265-272. **5**. Bula do produto.

SYMBICORT® SPRAY 6/100 mcg/inalação e **SYMBICORT® SPRAY** 6/200 mcg/inalação (fumarato de formoterol di-hidratado/budesonida) suspensão aerossol. **Indicações: SYMBICORT® SPRAY** está indicado no tratamento da asma nos casos em que o uso de uma associação (corticosteroide inalatório com um beta-2 agonista de ação prolongada) é apropriado e no tratamento regular de pacientes adultos com Doença Pulmonar Obstrutiva Crônica (DPOC) de moderada a grave, com sintomas frequentes e histórico de exacerbações. **Contraindicações: Hipersensibilidade à budesonida, ao formoterol ou a outros componentes da fórmula. Cuidados e Advertências: Advertências:** É recomendado que a dose seja titulada quando o tratamento de longo prazo é descontinuado e este não deve ser interrompido abruptamente. Para minimizar o risco de candidíase orofaríngea, o paciente deve ser instruído a lavar a boca com água após administrar as inalações de **SYMBICORT® SPRAY**. Uma deterioração súbita e progressiva do controle da asma é um risco potencial e o paciente deve procurar suporte médico. Pacientes que necessitaram de terapia corticosteroide de alta dose emergencial ou tratamento prolongado de altas doses recomendadas de corticosteroides inalatórios podem exibir sinais e sintomas de insuficiência adrenal quando expostos a situações de estresse grave. Administração de corticosteroide sistêmico adicional deve ser considerada durante situações de estresse ou cirurgia eletiva. **SYMBICORT® SPRAY** deve ser administrado com cautela em pacientes com graves alterações cardiovasculares (incluindo anomalias do ritmo cardíaco), diabetes mellitus, hipocalemia não tratada ou tireotoxicose. Pacientes com prolongamento do intervalo QTc devem ser cuidadosamente observados (para maiores informações vide bula completa do produto). Estudos clínicos e meta-análises indicaram que o tratamento da DPOC com corticosteroides pode levar a um risco aumentado de pneumonia. No entanto, o risco absoluto para a budesonida é pequeno. Não foi estabelecida uma relação causal com os produtos contendo budesonida. Gravidez: categoria C de risco de gravidez. Este medicamento não deve ser utilizado por mulheres grávidas sem orientação médica ou do cirurgião-dentista. A administração de **SYMBICORT® SPRAY** em mulheres lactantes deve ser apenas considerada se os benefícios esperados para a mãe superarem qualquer possível risco para a criança (para maiores informações vide bula completa do produto). **Interações medicamentosas:** o metabolismo da budesonida é mediado principalmente pela CYP3A4, uma subfamília do citocromo P450. Portanto, inibidores desta enzima, como o cetoconazol ou suco de grapefruit (pomelo), podem aumentar a exposição sistêmica à budesonida. A cimetidina apresenta um leve efeito inibidor sobre o metabolismo hepático da budesonida. Fármacos como a procainamida, fenotiazina, agentes antihistamínicos (terfenadina), inibidor da monoaminooxidase (MAO) e antidepressivos tricíclicos foram relacionados com um intervalo QTc prolongado e um aumento do risco de arritmia ventricular. Os bloqueadores beta-adrenérgicos (incluindo os colírios oftálmicos) podem atenuar ou inibir o efeito do formoterol (para maiores informações vide bula completa do produto). **Reações adversas**: as reações adversas que foram associadas à budesonida ou ao formoterol são apresentadas a seguir. Comum: palpitações, candidíase na orofaringe, cefaléia, tremor, leve irritação na garganta, tosse, rouquidão. Incomum: taquicardia, náusea, câibras musculares, tontura, agitação, ansiedade, nervosismo e perturbações do sono (para outras reações adversas, vide bula completa do produto). Posologia: a dose de **SYMBICORT® SPRAY** deve ser individualizada conforme a gravidade da doença. Quando for obtido o controle da asma, a dose deve ser titulada para a menor dose que permita manter um controle eficaz dos sintomas. ASMA: **SYMBICORT® SPRAY** 6/100 mcg/inalação: Adultos (a partir de 18 anos de idade): 2 inalações uma ou duas vezes ao dia. Em alguns casos, uma dose máxima de 4 inalações duas vezes ao dia pode ser requerida como dose temporária de manutenção durante a piora da asma. Adolescentes (12-17 anos): 2 inalações uma ou duas vezes ao dia. Durante a piora da asma a dose pode temporariamente ser aumentada para o máximo de 4 inalações duas vezes ao dia. Crianças (6-11 anos): 2 inalações duas vezes ao dia. Dose máxima diária: 4 inalações. **SYMBICORT® SPRAY** 6/200 mcg/inalação: Adultos (a partir de 18 anos de idade): 2 inalações uma ou duas vezes ao dia. Em alguns casos, uma dose máxima de 4 inalações duas vezes ao dia pode ser requerida como dose temporária de manutenção durante a piora da asma. Adolescentes (12-17 anos): 2 inalações uma ou duas vezes ao dia. Durante a piora da asma a dose pode temporariamente ser aumentada para o máximo de 4 inalações duas vezes ao dia. DPOC: **SYMBICORT® SPRAY** 6/200 mcg/inalação: Adultos (a partir de 18 anos de idade): 2 inalações duas vezes ao dia. Dose máxima diária: 4 inalações. Não foram estabelecidas a segurança e eficácia de **SYMBICORT® SPRAY** 6/100 mcg/inalação para o tratamento de DPOC. Instruções de Uso: vide bula completa do produto. **Superdose**: A superdosagem de formoterol irá provavelmente provocar efeitos típicos dos agonistas beta-2-adrenérgicos: tremor, cefaléia, palpitações e taquicardia. Poderá igualmente ocorrer hipotensão, acidose metabólica, hipocalemia e hiperglicemia. Pode ser indicado um tratamento de suporte e sintomático. A administração de uma dose de 90 mcg durante três horas em pacientes com obstrução brônquica aguda e quando administrada três vezes ao dia como um total de 54 mcg/dia por 3 dias para a estabilidade asmática não suscitou quaisquer problemas de segurança. Não é esperado que uma superdosagem aguda da budesonida, mesmo em doses excessivas, constitua um problema clínico. Quando utilizado cronicamente em doses excessivas, podem ocorrer efeitos glicocorticosteroides sistêmicos (para informações de superdosagem grave vide bula completa do produto). **Apresentações**: **SYMBICORT® SPRAY** 6/100 mcg/inalação: Suspensão aerossol 6/100 mcg/inalação em embalagem com 1 tubo contendo 120 doses. **SYMBICORT® SPRAY** 6/200 mcg/inalação: Suspensão aerossol 6/200 mcg/inalação em embalagem com 1 tubo contendo 120 doses. USO ADULTO E PEDIÁTRICO (vide posologia e bula completa). VIA INALATÓRIA. VENDA SOB PRESCRIÇÃO MÉDICA. SE PERSISTIREM OS SINTOMAS, O MÉDICO DEVERÁ SER CONSULTADO. Para maiores informações, consulte a bula completa do produto. Tel. SAC: 0800-0145578. www.astrazeneca.com.br **SYMBICORT® SPRAY**. MS – 1.1618.0250 (SYM_SPR002_min).

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