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The importance of the World Symposium on Pulmonary Hypertension

Carlos Jardim[1,a], Daniel Waetge[2]

More than 50 years ago, an epidemic of pulmonary hypertension in Austria, Germany, and Switzerland mobilized the medical community in search of answers. After evaluating the available data, the community observed a relationship between the use of an anorexic agent (aminorex) and the development of pulmonary hypertension caused by precapillary arteriopathy with plexiform lesions.[1]

The World Health Organization organized the first World Symposium on Pulmonary Hypertension, which was held in Geneva, Switzerland, in 1973. The aim of the meeting was to aggregate and, more importantly, to share the existing knowledge on pulmonary hypertension, convening specialists from various areas—including clinicians, pathologists, and epidemiologists. The official recognition of this disease was fundamental to the organization of various research groups in search of new information to better understand and address the burden of this condition.

The recommendation for an international registry on pulmonary hypertension arose from this first world symposium. Systematic, prospective data collection could offer fundamental information to understand the natural history of this condition and allow the international community to seek or propose new interventions to improve patient survival, which was known to be short at the time. The first international registry was published only in the beginning of the 1990s and brought valuable information, including the first survival equation.[2] Hemodynamic data, such as cardiac index, right atrial pressure, and mean pulmonary artery pressure, were shown to be relevant in terms of survival. However, after the first world symposium in 1973 and the publication of the United States registry in 1991,[2] there were few advances in the understanding and treatment of patients with pulmonary arterial hypertension. The most relevant advances in that period were studies on anticoagulation and the use of calcium channel blockers, as well as the advent and establishment of lung transplantation. However, none of those interventions represented a paradigm shift in the treatment of patients with such limited survival.

A study on the use of intravenous epoprostenol in patients with pulmonary arterial hypertension was published in 1996.[3] The results were extremely encouraging and, for the first time, showed that it is possible to reduce mortality in this patient population. At the time, research groups from various regions of the world had gathered and analyzed data not only for patients with pulmonary arterial hypertension but also for those with other forms of compromised pulmonary circulation. The group dedicated to the study and treatment of chronic thromboembolic pulmonary hypertension was noteworthy for establishing and systematizing the pulmonary artery thromboendarterectomy procedure.

The second World Symposium on Pulmonary Hypertension was held in Evian, France, in 1998. With the advent of a new drug that shifted the treatment paradigm, the critical analysis of epidemiological data, and the incorporation of surgical procedures, as well as other factors, the great contribution of this second world symposium was the proposal of a classification table for pulmonary hypertension, so that researchers and physicians from various regions of the world could organize their research and provide proper care for their patients. The classification table considered common factors that could be grouped: clinical presentation, physiopathology, pathology findings, and treatment response. Therefore, the classification system was at the time divided into five groups[4]: pulmonary arterial hypertension; pulmonary venous hypertension; pulmonary hypertension associated with respiratory system diseases or hypoxia; pulmonary hypertension caused by thrombotic or embolic disease; and pulmonary hypertension caused by diseases that directly affect the pulmonary vessels. Each group comprised subgroups defined by specific situations or clinical presentations.

This classification proposal abandoned the then-current simplistic classification between primary and secondary pulmonary hypertension, defined by the presence or absence of known causes or risk factors. The proposal was a significant advance, because it demonstrated, although with limitations, the complexity of pulmonary hypertension. Undoubtedly the second world symposium represented the capacity of the international community to get organized and draw attention to a highly relevant health topic, especially regarding morbidity and survival.

The first study on the use of an endothelin receptor antagonist in patients with pulmonary arterial hypertension was published in 2002[5]; it was the first oral medication shown to be effective in significantly improving the distance covered in the six-minute walk test (primary outcome), in addition to having a positive impact on other disease markers. At the time, the main pathophysiological pathways of pulmonary hypertension had already been identified as those related to prostacyclins, the nitric oxide metabolism, and endothelin.

With an additional pathophysiological pathway as a target of treatment and the growing number of publications in

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the area, the third World Symposium on Pulmonary Hypertension was held in 2003. The classification system was once again adjusted; however, the structure of five groups was maintained, following the same precepts. In addition, the therapeutic options were updated and a new treatment algorithm was introduced. This symposium also featured clearly organized task forces focused on specific areas, especially pathology, genetics, and clinical trials.

In the following years, world symposia were held every five years. In 2008, the fourth world symposium was held in Dana Point, California. At that symposium, the clinical classification of pulmonary hypertension was adjusted and the treatment algorithm was updated, incorporating drugs, as well as designating levels of evidence and grades of recommendation for each pharmacological intervention. The use of calcium channel blockers, as well as drugs said to be specific, was established, and the implications of the response criteria[6,7] were incorporated. Additional epidemiological data had been collected, and one of the most important contributions of the fourth symposium was establishing the need for clinical trials that use the time to clinical worsening as the primary outcome, rather than the surrogate outcomes for severity employed in studies performed in a relatively short time period. Those data were particularly important for testing new pharmacological intervention strategies in a situation in which many patients were already medicated at the time of their inclusion in a new study.

The fifth world symposium was held in 2013, in Nice, France. The classification table was updated; new strategies and drugs were also incorporated into the treatment algorithm. From the perspective of physiopathology, the right ventricle assumed a central role, as did the task force on pathology. From the beginning of the 2000s, hemodynamics and the evaluation of the right ventricle by imaging methods began to play an important role in the diagnosis and monitoring of patients with pulmonary hypertension.[8,9] Data from new registries for various parts of the world were also discussed, producing relevant epidemiological information in terms of age at diagnosis, survival, and risk stratification.[10] In the following years, clinical studies based on the precepts established by the world symposium task forces were able to explore the effects of treatment strategies on aspects of morbidity, mortality, hospitalization, and quality of life.[11,12]

Lastly, a few months ago, the sixth world symposium was once again held in Nice, France. We cannot yet say what alterations and suggestions were made by the task forces, because they have not yet been published in their final form. However, we can say that pulmonary hypertension gained global relevance,[13,14] beyond the issue of its rarer and more fatal presentation. Undoubtedly, the data will reflect the advances in the international community over the last five years.

The world symposia are both cause and consequence of the advances in pulmonary hypertension science. The meeting and the discussions, which also occur throughout the period of preparation for the event, order and illuminate the paths for this highly important area of knowledge, especially for those that face this disease; that is, patients and the community.

REFERENCES

1. Gurtner HP. Aminorex and pulmonary hypertension. A review. Cor Vasa. 1985;27(2-3):160-71.
2. D'Alonzo GE, Barst RJ, Ayres SM, Bergofsky EH, Brundage BH, Detre KM, et al., Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. Ann Intern Med. 1991;115(5):343-9. https://doi.org/10.7326/0003-4819-115-5-343
3. Barst RJ, Rubin LJ, Long WA, McGoon MD, Rich S, Badesch DB, et al., A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. N Engl J Med. 1996;334(5):296-301. https://doi.org/10.1056/NEJM199602013340504
4. Simonneau G, Galiè N, Rubin LJ, Langleben D, Seeger W, Domenighetti G, et al., Clinical classification of pulmonary hypertension. J Am Coll Cardiol. 2004;43(12 Suppl S):5S-12S. https://doi.org/10.1016/j.jacc.2004.02.037
5. Rubin LJ, Badesch DB, Barst RJ, Galie N, Black CM, Keogh A, et al., Bosentan therapy for pulmonary arterial hypertension. N Engl J Med. 2002; 346(12):896-903. https://doi.org/10.1056/NEJMoa012212
6. Sitbon O, Humbert M, Jaïs X, Ioos V, Hamid AM, Provencher S, et al., Long-term response to calcium channel blockers in idiopathic pulmonary arterial hypertension. Circulation. 2005;111(23):3105-11. https://doi.org/10.1161/CIRCULATIONAHA.104.488486
7. Costa EL, Jardim C, Bogossian HB, Amato MB, Carvalho CR, Souza R. Acute vasodilator test in pulmonary arterial hypertension: evaluation of two response criteria. Vascul Pharmacol. 2005;43(3):143-7. https://doi.org/10.1016/j.vph.2005.05.004
8. Vonk-Noordegraaf A, Souza R. Cardiac magnetic resonance imaging: what can it add to our knowledge of the right ventricle in pulmonary arterial hypertension? Am J Cardiol. 2012;110(6 Suppl):25S-31S. https://doi.org/10.1016/j.amjcard.2012.06.013
9. Vonk-Noordegraaf A, Haddad F, Chin KM, Forfia PR, Kawut SM, Lumens J, et al., Right heart adaptation to pulmonary arterial hypertension: physiology and pathobiology. J Am Coll Cardiol. 2013;62(25 Suppl):D22-33. https://doi.org/10.1016/j.jacc.2013.10.027
10. McGoon MD, Benza RL, Escribano-Subias P, Jiang X, Miller DP, Peacock AJ, et al., Pulmonary arterial hypertension: epidemiology and registries. J Am Coll Cardiol. 2013;62(25 Suppl):D51-9. https://doi.org/10.1016/j.jacc.2013.10.023
11. McLaughlin VV, Hoeper MM, Channick RN, Chin KM, Delcroix M, Gaine S, et al., Pulmonary Arterial Hypertension-Related Morbidity Is Prognostic for Mortality. J Am Coll Cardiol. 2018;71(7):752-763. https://doi.org/10.1016/j.jacc.2017.12.010
12. Channick RN, Delcroix M, Ghofrani HA, Hunsche E, Jansa P, Le Brun FO, et al., Effect of macitentan on hospitalizations: results from the SERAPHIN trial. JACC Heart Fail. 2015;3(1):1-8. https://doi.org/10.1016/j.jchf.2014.07.013
13. Hoeper MM, Humbert M, Souza R, Idrees M, Kawut SM, Sliwa-Hahnle K, et al., A global view of pulmonary hypertension. Lancet Respir Med. 2016;4(4):306-22. https://doi.org/10.1016/S2213-2600(15)00543-3
14. Humbert M, Khaltaev N, Bousquet J, Souza R. Pulmonary hypertension: from an orphan disease to a public health problem. Chest. 2007;132(2):365-7. https://doi.org/10.1378/chest.07-0903

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Cost analysis in the ICU from the standpoint of physical therapy

Liria Yuri Yamauchi[1,a]

The study conducted by Rotta et al.,[1] published in the current issue of the JBP, analyzed costs by means of an instrument designed in the early 1990s, the Omega score. The first question that comes to mind is "why did they use this instrument?" This question arises for obvious reasons, since time has a clear influence on the economy and on the costs of certain procedures, which can also undergo changes due to modernization. However, in analyzing the topic "cost analysis in the ICU" more closely, we encounter a highly complex theme. In 2002, a report by the American Thoracic Society listed several issues related to cost analysis in intensive care,[2] such as the lack of accurate data for cost analysis; the complexity of the cases; the fact that there is no standardized approach for measuring or valuing costs across countries; the fact that the most commonly used outcomes in ICU studies (e.g., ICU mortality) are not ideal for cost-effective analyses, while preferred outcomes for cost-effective analyses (e.g., long-term quality-adjusted survival) are rarely evaluated; and the burden of critical illness on family members, which is not easily captured in a cost-effective analysis. Complementary to these issues is the reflection made by Khan[3]: on many occasions, the option with the lowest cost is not the preferred one. For instance, early death may be relatively more economical. In contrast, a costly intervention that saves lives may be acceptable to society if the benefits considered are greater than the increase in costs. This reinforces the notion that cost analysis also depends on several factors, mainly the perspective adopted.

As mentioned by Rotta et al.,[1] the Omega score was developed in France in 1992 and has not been validated for use in or adapted to the currency of Brazil. In addition, the cost of the procedures, as well as the procedures themselves, may have changed over time. As mentioned elsewhere,[2] the lack of standardization for measuring costs across countries is an obstacle to the accuracy of the analyses made. This can be considered a possible measurement bias and underscores the need for instruments that are more accurate in estimating costs in the ICU. However, it is necessary to consider the current scarcity of validated instruments for cost analysis in the ICU.

Although the logarithmic transformation of data in the linear regression analysis presented by Rotta et al.[1] might be statistically acceptable, it limits direct analysis of the results. For instance, we observed that length of ICU stay and severity as measured by the Acute Physiology and Chronic Health Evaluation II were independently associated with increased costs, and that 24-h physical therapy showed an inverse association. However, logarithmic transformation does not allow a direct interpretation of this information on the basis of β values. Assessing values in French francs also limits the interpretation of results. A study published by Montuclard et al.[4] used the Omega score with correction for conversion to euro. At that time, one U.S. dollar was equivalent to one euro, which facilitated the interpretation of costs. The issue of temporality once again appears to influence cost analysis, as a result of changes in the economy.

An important consideration regarding the adoption of 24-hour shifts for physical therapy by hospitals would be indirect reduction of costs. As stated by Bürge et al.,[5] although adding physical therapy to usual care increases fixed costs, its effects can reduce the costs associated with lost productivity, medication use, or treatments by other health care professionals. An indirect reduction in costs could support the finding of Rotta et al.,[1] who estimated that, despite the increase in the costs associated with the team, hospitalization costs decreased. Their study[1] reiterates the importance of standardized approaches for cost analysis in the ICU. In the future, broader-perspective analyses assessing the impact that interventions in the ICU have on the daily lives of patients and their families will be needed in order to foster public policies aimed at critically ill patients.

REFERENCES

1. Rotta BP, Silva JM, Fu C, Goulardins JB, Pires-Neto RC, Tanaka C. Relationship between availability of physiotherapy services and ICU costs. J Bras Pneumol. 2018;44(3):184-9.
2. Understanding costs and cost-effectiveness in critical care: report from the second American Thoracic Society Workshop on outcomes research. Am J Respir Crit Care Med. 2002,165(4):540-50. https://doi.org/10.1164/ajrccm.165.4.16541
3. Kahn JM. Understanding economic outcomes in critical care. Curr Opin Crit Care. 2006;12(5):399-404. https://doi.org/10.1097/01.ccx.0000244117.08753.38
4. Montuclard L, Garrouste-Orgeas M, Timsit JF, Misset B, De Jonghe B, Carlet J. Outcome, functional autonomy, and quality of life of elderly patients with a long-term intensive care unit stay. Crit Care Med. 2000;28(10):3389-95. https://doi.org/10.1097/00003246-200010000-00002
5. Bürge E, Monnin D, Berchtold A, Allet L. Cost-effectiveness of physical therapy only and of usual care for various health conditions: systematic review. Phys Ther. 2016;96(6):774-86. https://doi.org/10.2522/ptj.20140333

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Reference values for assessing the arms: are we seeing a light at the end of the tunnel?

Luciana Dias Chiavegato[1,2,a]

Although the systemic changes caused by COPD are well known, respiratory mechanics changes, constant dyspnea, and, therefore, exercise limitation are of note.[1,2] However, for a long time, the major focus of therapeutic care was on the legs.[2,3]

Even considering that the legs have an impact on exercise and on such elementary activities as walking, arm activities, especially those involving unsupported arm elevation above the shoulders, result in increased metabolic demand and increased activity of muscles such as thesternocleidomastoid muscle.[4,5] This might culminate in thoracoabdominal asynchrony, as well as in diaphragm and accessory muscle asynchrony, impairing ventilation.[4-7]

When it comes to patients with COPD, this asynchrony tends to be even more evident, especially during unsupported arm activities, and these patients may often present with dynamic hyperinflation and exercise-related dyspnea.[6-8]

Although, in the case of the legs, activities can be more objectively measured by using accelerometers placed at the hip or legs, information regarding how much and how patients move their arms is still considered limited.[8,9]

Since an important systematic review of 41 studies that was conducted by Janaudis-Ferreira et al.,[10] some tests for measuring endurance and functional capacity during unsupported arm exercise, such as the unsupported upper limb exercise test and the six-minute pegboard and ring test (6PBRT),[11] have been recommended.

The 6PBRT was developed by Zhan et al.[11] and is a very simple, inexpensive test that simulates well activities of daily living. During the 6PBRT, the patient has to move 20 rings (10 rings for each arm) from lower wooden pegs to upper wooden pegs, and, once all rings have been moved, he or she has to move them back. The 6PBRT result is expressed as the total number of rings that a subject is able to move back and forth between the sets of pegs in six minutes.

Given that the 6PBRT has been validated[11] and found to be reproducible in healthy subjects,[12] it has become necessary and interesting, both from the standpoint of clinical practice and research, to determine reference values for this test.

Pursuing this track, Lima et al.,[13] in a very elegant and well-designed study, conducted 6PBRTs on 104 healthy subjects in order to establish, for the first time, reference values for this test in a healthy population. In the study, the subject distribution by age decade (from age 30 to 80-plus) is good and there is an appropriate male-to-female ratio, which causes the proposed equation to have good external validity, allowing it to be generalized to any gender and age group. Although the study took into consideration arm length, upper arm circumference, and forearm circumference, as well as the level of physical activity, only age appears to have influenced the results obtained in the 6PBRT.

Fatigue and dyspnea are often observed during the performance of unsupported arm activities by patients with COPD, limiting them in their activities of daily living. In view of the fact that arm training has been so well incorporated by pulmonary rehabilitation programs,[14] determination of values that can guide us regarding the functioning and endurance of the arms is very important and promising.

REFERENCES

1. EF. Metabolic and ventilatory response pattern to arm elevation in patients with COPD and healthy age-matched subjects. Eur Respir J. 1995;8(8):1345-51. https://doi.org/10.1183/09031936.95.08081345
2. McKeough ZJ, Alison JA, Bye PT. Arm exercise capacity and dyspnea ratings in subjects with chronic obstructive pulmonary disease. J Cardiopulm Rehabil. 2003;23(3):218-25. https://doi.org/10.1097/00008483-200305000-00010
3. Hamilton AL, Killian KJ, Summers E, Jones NL. Symptom intensity and subjective limitation to exercise in patients with cardiorespiratory disorders. Chest. 1996;110(5):1255-63. https://doi.org/10.1378/chest.110.5.1255
4. Dolmage TE, Maestro L, Avendano MA, Goldstein RS. The ventilatory response to arm elevation of patients with chronic obstructive pulmonary disease. Chest. 1993;104(4):1097-100. https://doi.org/10.1378/chest.104.4.1097
5. Miranda EF, Malaguti C, Corso SD. Peripheral muscle dysfunction in COPD: lower limbs versus upper limbs. J Bras Pneumol. 2011;37(3):380-8. https://doi.org/10.1590/S1806-37132011000300016
6. Celli BR, Rassulo J, Make BJ. Dyssynchronous breathing during arm but not leg exercise in patients with chronic airflow obstruction. N Engl J Med. 1986;314(23):1485-90. https://doi.org/10.1056/NEJM198606053142305
7. Lima VP, Iamonti VC, Velloso M, Janaudis-Ferreira T. Physiological Responses to Arm Activity in Individuals With Chronic Obstructive Pulmonary Disease Compared With Healthy Controls: A SYSTEMATIC REVIEW. J Cardiopulm Rehabil Prev. 2016;36(6):402-412. https://doi.org/10.1097/HCR.0000000000000190
8. Robles P, Araujo T, Brooks D, Zabjek K, Janaudis-Ferreira T, Marzolini S, et al. Does limb partitioning and positioning affect acute cardiorespiratory responses during strength exercises in patients with COPD? Respirology. 2017;22(7):1336-1342. https://doi.org/10.1111/resp.13056

1. Programa de Mestrado e Doutorado em Fisioterapia, Universidade Cidade de São Paulo, São Paulo (SP) Brasil.
2. Programa de Residência Multiprofissional com Concentração em Distúrbios Respiratórios Clínicos e Cirúrgicos, Universidade Federal de São Paulo, São Paulo (SP) Brasil.
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9. Frykholm E, Lima VP, Janaudis-Ferreira T, Nyberg A. Physiological responses to arm versus leg activity in patients with chronic obstructive pulmonary disease: a systematic review protocol. BMJ Open. 2018;8(2):e019942. https://doi.org/10.1136/bmjopen-2017-019942
10. Janaudis-Ferreira T, Beauchamp MK, Goldstein RS, Brooks D. How should we measure arm exercise capacity in patients with COPD? A systematic review. Chest. 2012;141(1):111-120. https://doi.org/10.1378/chest.11-0475
11. Zhan S, Cerny FJ, Gibbons WJ, Mador MJ, Wu WY. Development of an unsupported arm exercise test in patients with chronic obstructive pulmonary disease. J Cardiopulm Rehabil. 2006;26(3):180-7; discussion 188-90. https://doi.org/10.1097/00008483-200605000-00013
12. Lima VP, Velloso M, Almeida FD, Carmona B, Ribeiro-Samora GA, Janaudis-Ferreira T. Test-retest reliability of the unsupported upper-limb exercise test (UULEX) and 6-min peg board ring test (6PBRT) in healthy adult individuals. Physiother Theory Pract. 2018 Jan 19:1-7. [Epub ahead of print] https://doi.org/10.1080/09593985.2018.1425786
13. Lima VP, Almeida FD, Janaudis-Ferreira T, Carmona B, Ribeiro-Samora GA, Velloso M. Reference values for the six-minute pegboard and ring test in healthy adults in Brazil. J Bras Pneumol. 2018;44(3):190-4.
14. McKeough ZJ, Velloso M, Lima VP, Alison JA. Upper limb exercise training for COPD. Cochrane Database Syst Rev. 2016;11:CD011434. https://doi.org/10.1002/14651858.CD011434.pub2

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Opening windows of opportunity for smoking cessation treatment

Maria Vera Cruz de Oliveira Castellano[1,a]

Smoking is the direct or indirect cause of more than 50 diseases, collectively known as "smoking-related" diseases. Therefore, it is not surprising that there are a large number of active smokers among patients hospitalized in Brazil.

Smoking control is one of the public health investments with the highest positive return in terms of its effects on the indicators of morbidity and mortality. In Brazil, the rates of active smoking in the adult population have been decreasing because of the implementation of public policies, due in large part to the persistent efforts of several entities, especially the *Sociedade Brasileira de Pneumologia e Tisiologia* (SBPT, Brazilian Thoracic Society). The SBPT, through its Committee on Smoking, is constantly engaging in advocacy, working with organizations that create legislation regarding the subject, as well as working with the media and fulfilling their social obligation. In this context, we can highlight instruction in smoking cessation treatment, a recent conquest and long-standing goal of the SBPT, now widely available, that will provide tools for all pulmonologists to treat their smoking patients, hospitalized or not.[1]

The minimal approach, which can be performed by every health professional, reportedly produces a cessation rate of 1-3%.[2] That approach should be routinely applied to smokers admitted to the hospital. Hospitalized smokers are often highly motivated to quit smoking, showing symptoms of nicotine withdrawal, and are open to undergoing the procedures offered in order to prevent relapse after discharge. However, few such patients undergo smoking cessation treatment and most of those who do relapse shortly after discharge from the hospital.[3,4]

The ideal would be to put in place in-hospital protocols to train all staff members to speak to speak to patients in the same way, thus intensifying the approach and increasing the chances of smoking cessation, although that is not always feasible.

In view of these considerations, Campos et al.,[5] in this issue of the JBP, describe a timely study in which they proposed an easily accessed tool for approaching hospitalized smokers. The authors compared the efficacy of two cognitive behavioral therapy-based interventions and analyzed the factors related to relapse using the Brief Questionnaire of Smoking Urges, an instrument that evaluates craving from a multidimensional perspective. The overall abstinence rate at six months after hospital discharge was 40.7%, demonstrating the impact of the program. The intensive intervention, performed by a trained professional, involved a 40-min smoking cessation treatment session, comprising a 10-min oral intervention and the presentation of a 30-min educational video produced by a pulmonologist, a cardiologist, and a psychiatrist. After discharge, the participants were contacted by telephone at three time points. At 6 months, a lower relapse rate and a higher smoking abstinence rate were observed in the intensive intervention group. The proposed intervention can be reproduced at other hospitals, without excessive cost.

The recommended practice is to offer counseling during hospitalization to all smokers and to schedule a follow-up interview, in person or by telephone, for a date at least 30 days after hospital discharge. In a meta-analysis of 50 studies, Rigotti et al.[6] concluded that intensive approaches with follow-up after discharge were the most effective. Relapses occur mainly during the first month after discharge, and close monitoring is therefore important during this period. Characterizing the intensity of the craving and other factors that increase the risk of relapse, such as dependence on alcohol or other drugs, allows us to individualize the treatment of those at a higher risk of relapse.

By proposing the educational video presentation strategy, Campos et al.[5] contribute to efforts to devise a more appropriate approach to hospitalized smokers. Video is a resource that, like other digital media and social networks, plays a fundamental role as a vehicle for interventions on smoking, especially for hospitalized smokers, who are more motivated and have more time available to use videos.[7]

For institutions that do not have a specialized smoking cessation team or protocols in place, video is an instrument that can increase smoking cessation rates. Although pregnant women and psychiatric patients were excluded from the study sample, they are populations that should be included in the approaches performed during hospitalization: the first because of the consequences for the health of the infant; and the second in order to reduce the high rate of mortality due to smoking-related diseases.

Although the study protocol did not include the use of medications, Campos et al.[5] and the current guidelines[3,4] recommend the use of nicotine replacement therapy to reduce cravings and to increase abstinence rates after discharge from the hospital.

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Smoking cessation treatment should be attempted at every opportunity, and hospitalization is, without a doubt, a unique window of opportunity. Let us continue to open these and all other windows necessary for the treatment of smoking, a chronic disease that is a preventable cause of a panoply of other diseases.

REFERENCES

1. Sociedade Brasileira de Pneumologia e Tisiologia (SBPT) [homepage on the Internet]. Brasília: SBPT; [cited 2018 May 21]. SBPT lança curso de tratamento do tabagismo; [about 2 screens]. Available from: https://sbpt.org.br/portal/sbpt-lanca-curso-de-tratamento-do-tabagismo/
2. Stead LF, Buitrago D, Preciado N, Sanchez G, Hartmann-Boyce J, Lancaster T. Physician advice for smoking cessation. Cochrane Database Syst Rev 2013;(5):CD000165. https://doi.org/10.1002/14651858.CD000165.pub4
3. Reichert J, Araújo AJ, Gonçalves CM, Godoy I, Chatkin JM, Sales MP, et al. Smoking cessation guidelines–2008. J Bras Pneumol. 2008;34(10):845-80. https://doi.org/10.1590/S1806-37132008001000014
4. Jiménez Ruiz CA, de Granda Orive JI, Solano Reina S, Riesco Miranda JA, de Higes Martinez E, Pascual Lledó JF, et al. Guidelines for the Treatment of Smoking in Hospitalized Patients. Arch Bronconeumol. 2017;53(7):387-394. https://doi.org/10.1016/j.arbres.2016.11.004
5. Campos ACF, Nani ASF, Fonseca VAS, Silva EN, Castro MCS, Martins WA. Comparison of two smoking cessation interventions for inpatients. J Bras Pneumol. 2018;44(3):195-201.
6. Rigotti NA, Clair C, Munafò MR, Stead LF. Interventions for smoking cessation in hospitalised patients. Cochrane Database Syst Rev. 2012;(5):CD001837. https://doi.org/10.1002/14651858.CD001837.pub3
7. Nguyen Thanh V, Guignard R, Lancrenon S, Bertrand C, Delva C, Berlin I, et al. Effectiveness of a fully automated internet-based smoking cessation program: a randomized controlled trial (STAMP). Nicotine Tob. Res. 2018 Jan 23. [Epub ahead of print] https://doi.org/10.1093/ntr/nty016

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Vascular reperfusion in pulmonary thromboembolism: certainties and uncertainties

Veronica Moreira Amado[1,a]

Pulmonary thromboembolism (PTE) is the leading cause of death in patients with venous thromboembolism. Between 2001 and 2009, the incidence of PTE increased from 29 to 78 cases per year; this increase is partly due to an increase in the number and quality of imaging tests, particularly chest CT angiography, as well as to incidental findings of pulmonary embolism on routine examinations for other diseases, such as cancer.[1,2] Despite technological advances, the diagnosis of PTE remains a challenge; autopsy studies have shown that the prevalence of PTE cases undiagnosed in life is 84.6%.[3]

In patients with PTE, pulmonary vascular obstruction and the consequent increase in pulmonary vascular resistance result in a sudden increase in right ventricular (RV) afterload. The increase in RV afterload is primarily dependent on the magnitude of the embolic load and on the extent to which the pulmonary circulation can use adaptation mechanisms such as vascular recruitment and distension in order to compensate for the obstruction. Previous cardiovascular conditions play a role in the extent to which the right ventricle can adapt to the increase in afterload. Acute RV failure is a marker of pulmonary embolism severity, given that reduced cardiac output can result in hemodynamic instability and, eventually, death.[4,5]

In low-risk and low intermediate-risk patients, the treatment of PTE consists of anticoagulation; given that RV function is preserved in such patients, there is no urgent need to clear the obstructed vascular bed. Oral anticoagulants with direct anti-factor Xa and antithrombin activity constitute an alternative to conventional treatment with anti-vitamin K anticoagulants, the effects of which should be monitored periodically; in addition, anti-vitamin K anticoagulants have high drug-drug and food-drug interaction potential.[5,6]

The need for rapid clearance of the pulmonary vascular bed in patients with PTE and hemodynamic instability is well established in the literature, thrombolytic therapy being the treatment of choice in such cases.[5,7] However, there is controversy in the literature regarding the use of thrombolytics in patients with RV dysfunction without hemodynamic instability and with a high intermediate risk of death.[8,9] Treatment with thrombolytics has been found to have no beneficial effects on mortality in such patients, despite the fact that reperfusion occurs more rapidly; there is an increased risk of severe bleeding, intracranial bleeding occurring in 2%.[8] For years, attempts were made to identify a subgroup of patients at an increased risk of hemodynamic instability and benefiting from thrombolysis as initial therapy despite the risk of bleeding. Despite the use of algorithms employing biomarkers and imaging tests to assess RV function, no such subgroup was identified.[10] Therefore, in high intermediate-risk patients, thrombolysis should be prescribed on a case-by-case basis, depending on the clinical setting and on patient progression. In recent years, it has been proposed that expert panels be convened in order to discuss high-risk and high intermediate-risk PTE cases and make decisions regarding treatment optimization.[11]

In the current issue of the JBP, there is a good review of indications for reperfusion, as well as reperfusion modalities, in patients with PTE.[12] Conventional thrombolysis remains the most widely used drug therapy for achieving reperfusion. However, treatment options such as low-dose, peripherally administered thrombolytic therapy or in situ thrombolysis to reduce the risk of bleeding have shown good results; nevertheless, further studies are needed in order to define their therapeutic role. Invasive approaches such as surgical embolectomy and catheter-based embolectomy have gained prominence in recent years, having been used primarily in patients with hemodynamic instability (in whom thrombolytics are contraindicated) but also in those receiving thrombolytic therapy and requiring rescue therapy for failed reperfusion.

The diagnosis and treatment of PTE remain challenging. Nevertheless, recent advances in treatment options have contributed to improving the prognosis of patients with PTE.

REFERENCES

1. Heit JA. Epidemiology of venous thromboembolism. Nat Rev Cardiol. 2015;12(8):464-74. https://doi.org/10.1038/nrcardio.2015.83
2. Ferreira EV, Gazzana MB, Sarmento MB, Guazzelli PA, Hoffmeister MC, Guerra VA, et al. Alternative diagnoses based on CT angiography of the chest in patients with suspected pulmonary thromboembolism. J Bras Pneumol. 2016;42(1):35-41. https://doi.org/10.1590/S1806-37562016000000105
3. Yoo HH, Mendes FG, Alem CE, Fabro AT, Corrente JE, Queluz TT. Clinicopathological findings in pulmonary thromboembolism: a 24-year autopsy study. J Bras Pneumol. 2004;30(5):426-32.
4. Laporte S, Mismetti P, Décousus H, Uresandi F, Otero R, Lobo JL, et al. Clinical predictors for fatal pulmonary embolism in 15,520 patients with venous thromboembolism: findings from the Registro Informatizado de la Enfermedad TromboEmbolica venosa (RIETE) Registry. Circulation. 2008;117(13):1711-6. https://doi.org/10.1161/CIRCULATIONAHA.107.726232
5. Konstantinides SV, Torbicki A, Agnelli G, Danchin N, Fitzmaurice D, Galiè N, et al. 2014 ESC Guidelines on the diagnosis and management of acute pulmonary embolism. Eur Heart J. 2014;35(43):3033-69, 3069a-3069k.
6. Fernandes CJ, Alves Junior JL, Gavilanes F, Prada LF, Morinaga LK, Souza R. New anticoagulants for the treatment of venous

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thromboembolism. J Bras Pneumol. 2016;42(2):146-54. https://doi.org/10.1590/S1806-37562016042020068

7. Stein PD, Matta F. Thrombolytic therapy in unstable patients with acute pulmonary embolism: saves lives but underused. Am J Med. 2012;125(5):465-70. https://doi.org/10.1016/j.amjmed.2011.10.015
8. Meyer G, Vicaut E, Danays T, Agnelli G, Becattini C, Beyer-Westendorf J, et al. Fibrinolysis for patients with intermediate-risk pulmonary embolism. N Engl J Med. 2014;370(15):1402-11. https://doi.org/10.1056/NEJMoa1302097
9. Goldhaber SZ. PEITHO Long-Term Outcomes Study: Data Disrupt Dogma. J Am Coll Cardiol. 2017;69(12):1545-1548. https://doi.org/10.1016/j.jacc.2017.01.027
10. Kostrubiec M, Pruszczyk P, Bochowicz A, Pacho R, Szulc M, Kaczynska A, et al. Biomarker-based risk assessment model in acute pulmonary embolism. Eur Heart J. 2005;26(20):2166-72. https://doi.org/10.1093/eurheartj/ehi336
11. Kabrhel C, Rosovsky R, Channick R, Jaff MR, Weinberg I, Sundt T, et al. A Multidisciplinary Pulmonary Embolism Response Team: Initial 30-Month Experience With a Novel Approach to Delivery of Care to Patients With Submassive and Massive Pulmonary Embolism. Chest. 2016;150(2):384-93. https://doi.org/10.1016/j.chest.2016.03.011
12. Fernandes CJCS, Jardim CVP, Alver JL Jr, Oleas FAG, Morinaga LTK, Souza R. Reperfusion in acute pulmonary thromboembolism. J Bras Pulmonol. 2018;44(3):237-243.

J Bras Pneumol. 2018;44(3):182-182
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Unilateral hyperlucent lung

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

A seven-year-old girl presented to the emergency room with a 24-h history of dyspnea and dry cough. Physical examination revealed wheezing with no other abnormalities. Chest CT showed hypoattenuation in the left lung (Figure 1).

In most cases, unilateral hyperlucent lung is first identified on a chest X-ray. The initial difficulty is to define whether the change is pulmonary or extrapulmonary. In this type of evaluation, chest CT is superior to chest X-ray because it eliminates the superimposition of thoracic structures. Extrapulmonary causes include technical factors; chest wall changes such as mastectomy, scoliosis, and Poland syndrome; and pleural changes (pneumothorax). Pulmonary causes can be congenital (congenital lobar emphysema, bronchial atresia, or cystic adenomatoid malformation) or acquired (e.g., Swyer-James syndrome, massive thromboembolism, and partial bronchial obstruction). It is important to note that most of the etiologies seen in children, even congenital ones, can also be seen in adults, because they usually have a benign course, patients remaining asymptomatic into adulthood.

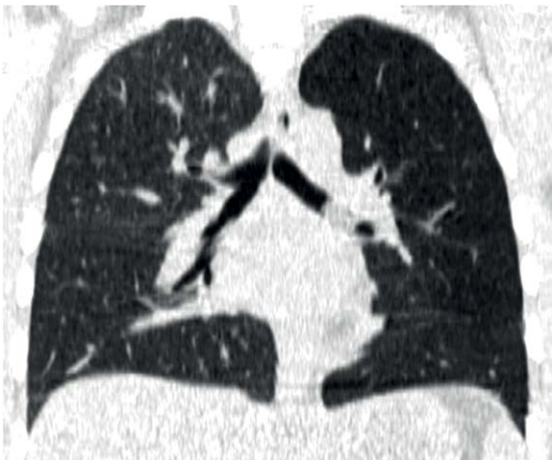

Figure 1. Chest CT scan with coronal reconstruction showing diffuse hypoattenuation in the left lung. Also note the opacity with soft-tissue density within the left main bronchus.

The most important cause of unilateral hyperlucency/pulmonary hypoattenuation, because of its clinical implications, is partial bronchial obstruction, creating a check-valve mechanism. In children, the main cause is obstruction by foreign body aspiration (FBA)[1], whereas the main cause in adults is obstruction by neoplastic processes, particularly bronchial cancer.[2] The compromised lung may be with normal or hyperinflation. Hypoattenuation occurs only in cases of partial obstruction. When the obstruction is total, the tendency is for atelectasis to develop. Bronchoscopy plays a key role in the study of these patients.

In our patient, the acute clinical analysis and the presence of wheezing with no history of asthma led us to suspect FBA. On CT, we observed not only hypoattenuation on the left but also a foreign body inside the left main bronchus.

The diagnosis of FBA in a child is not always easy. In most cases, the parents do not witness the accident and the suspicion must be made based on the clinical history, physical examination, and complementary diagnostic methods. However, some patients are asymptomatic and show no alterations on physical examination; in addition, most aspirated foreign bodies are radiolucent. The diagnosis of FBA should be made early, because a delay in its recognition and treatment can result in permanent sequelae or fatal damage. Many patients are treated for weeks to months for recurrent respiratory diseases until FBA is suspected. In conclusion, the presence of acute respiratory symptoms associated with pulmonary hypoattenuation or atelectasis in children should be considered a indicator of FBA, prompting an early request for bronchoscopy, because it is a method that can be both diagnostic and therapeutic.

REFERENCES

1. Barbosa AJ, Zanetti GR, Marchiori E. Bronchial foreign body in children. The importance of correct diagnosis. Radiol Bras. 2016;49(5):340-342.
2. Marchiori E, Hochhegger B, Zanetti G. Opaque hemithorax. J Bras Pneumol 2017;43(3):161-161.

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Internal and external validity: can you apply research study results to your patients?

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

CLINICAL SCENARIO

In a multicenter study in France, investigators conducted a randomized controlled trial to test the effect of prone vs. supine positioning ventilation on mortality among patients with early, severe ARDS. They showed that prolonged prone-positioning ventilation decreased 28-day mortality [hazard ratio (HR) = 0.39; 95% CI: 0.25-0.63].[1]

STUDY VALIDITY

The validity of a research study refers to how well the results among the study participants represent true findings among similar individuals outside the study. This concept of validity applies to all types of clinical studies, including those about prevalence, associations, interventions, and diagnosis. The validity of a research study includes two domains: internal and external validity.

Internal validity is defined as the extent to which the observed results represent the truth in the population we are studying and, thus, are not due to methodological errors. In our example, if the authors can support that the study has internal validity, they can conclude that prone positioning reduces mortality among patients with severe ARDS. The internal validity of a study can be threatened by many factors, including errors in measurement or in the selection of participants in the study, and researchers should think about and avoid these errors.

Once the internal validity of the study is established, the researcher can proceed to make a judgment regarding its external validity by asking whether the study results apply to similar patients in a different setting or not (Figure 1). In the example, we would want to evaluate if the results of the clinical trial apply to ARDS patients in other ICUs. If the patients have early, severe ARDS, probably yes, but the study results may not apply to patients with mild ARDS**.** External validity refers to the extent to which the results of a study are generalizable to patients in our daily practice, especially for the population that the sample is thought to represent.

Lack of internal validity implies that the results of the study deviate from the truth, and, therefore, we cannot draw any conclusions; hence, if the results of a trial are not internally valid, external validity is irrelevant.[2] Lack of external validity implies that the results of the trial may not apply to patients who differ from the study population and, consequently, could lead to low adoption of the treatment tested in the trial by other clinicians.

INCREASING VALIDITY OF RESEARCH STUDIES

To increase internal validity, investigators should ensure careful study planning and adequate quality control and implementation strategies—including adequate recruitment strategies, data collection, data analysis, and sample size. External validity can be increased by using broad inclusion criteria that result in a study population that more closely resembles real-life patients, and, in the case of clinical trials, by choosing interventions that are feasible to apply.[2]

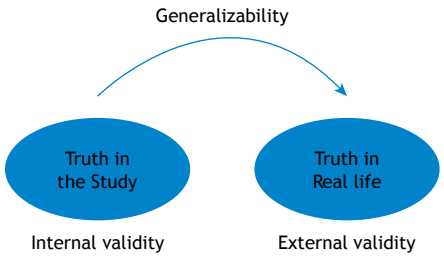

Figure 1. Internal and external validity.

REFERENCES

1. Guérin C, Reignier J, Richard JC, Beuret P, Gacouin A, Boulain T, et al. Prone positioning in severe acute respiratory distress syndrome. N Engl J Med. 2013;368(23):2159-68. https://doi.org/10.1056/NEJMoa1214103
2. Akobeng AK. Assessing the validity of clinical trials. J Pediatr Gastroenterol Nutr. 2008;47(3):277-82. https://doi.org/10.1097/MPG.0b013e31816c749f

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ORIGINAL ARTICLE

Relationship between availability of physiotherapy services and ICU costs

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ABSTRACT

Objective: To determine whether 24-h availability of physiotherapy services decreases ICU costs in comparison with the standard 12 h/day availability among patients admitted to the ICU for the first time. **Methods:** This was an observational prevalence study involving 815 patients ≥ 18 years of age who had been on invasive mechanical ventilation (IMV) for ≥ 24 h and were discharged from an ICU to a ward at a tertiary teaching hospital in Brazil. The patients were divided into two groups according to h/day availability of physiotherapy services in the ICU: 24 h (PT-24; n = 332); and 12 h (PT-12; n = 483). The data collected included the reasons for hospital and ICU admissions; Acute Physiology and Chronic Health Evaluation II (APACHE II) score; IMV duration, ICU length of stay (ICU-LOS); and Omega score. **Results:** The severity of illness was similar in both groups. Round-the-clock availability of physiotherapy services was associated with shorter IMV durations and ICU-LOS, as well as with lower total, medical, and staff costs, in comparison with the standard 12 h/day availability. **Conclusions:** In the population studied, total costs and staff costs were lower in the PT-24 group than in the PT-12 group. The h/day availability of physiotherapy services was found to be a significant predictor of ICU costs.

Keywords: Intensive care units; Respiration, artificial; Respiratory therapy; Hospital costs.

INTRODUCTION

The ICU is considered the most costly hospital department. For example, in Germany, it has been estimated that the ICU accounts for 20% of all hospital costs.[1] Because critical care is a crucial hospital service, the factors that impact ICU costs have been widely studied. The total cost per patient in the ICU depends largely on the severity of illness and the ICU length of stay (ICU-LOS).[2-4] However, there have been very few studies looking into cost of ICU in Brazil. Nangino et al.[5] calculated the financial impact of nosocomial infections in the ICU at a charitable hospital in the Brazilian state of Minas Gerais. The authors reported longer ICU-LOS, higher per-patient ICU expenditures, and higher per-day ICU expenditures for patients with infection than for those without. Nevertheless, it is important to consider the heterogeneity among countries, and even within a country, in terms of the allocation of resources, distribution of critical care services, personnel costs, drug prices, culture, and the ethical standards of the society in relation to health care.[6]

Prolonged ICU-LOS has been associated with a longer duration of invasive mechanical ventilation (IMV).[7] Approximately 33% of patients admitted to the ICU require IMV,[8,9] which has been associated with higher mortality,[10] a higher incidence of hospital-associated pneumonia,[11] and ICU-acquired muscle weakness.[12] The use of IMV is also associated with higher costs,[13] accounting for 12% of all hospital costs.[14] Therefore, it seems that strategies to improve the weaning process and reduce IMV duration would reduce costs[11] and improve long-term patient outcomes.[15]

The aim of physiotherapy in the ICU is to enhance the overall functional capacity of patients, as well as to restore respiratory and physical independence, thereby decreasing the risk of bed rest-associated complications.[15] However, it is important to understand that the role of physiotherapists in the ICU varies considerably among countries and depends on such factors as staffing levels, training, and expertise.[16] In Brazil, physiotherapists are in charge of respiratory care and employ mobilization techniques. Respiratory care includes lung expansion, bronchial hygiene, assisted cough, suction, oxygen delivery, implementing/monitoring noninvasive mechanical ventilation, adjusting/monitoring IMV, participating in the weaning process, and extubation.[17] Mobilization techniques consist in the following[18]: general exercises, such as passive, assisted, active, and resistive maneuvers;

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transference training; positioning the patient when sitting; and providing ambulation therapy as soon as possible.

Although growing interest in reducing costs for patients requiring long-term mechanical ventilation has led to the development of various models of care delivery, none of those models have been tested in scientifically rigorous studies.[19,20] Brazilian law requires that ICU teams include one physiotherapist for every 10 patients for at least 18 h/day.[17,21] However, financial pressures, coupled with increasing expectations from regulators, payers, and consumers are changing health care delivery systems. Integrated, outcome-based systems of care delivery are needed.[19] During the process of adapting to the law, ICU patients at our hospital were seen by a physiotherapist on a 12 h/day shift basis. Our hospital has chosen to implement a 24 h/day, rather than an 18 h/day, physiotherapy schedule, in order to facilitate the organization of routines and to match the hours of public transportation. Therefore, the current study aimed to investigate the benefits and costs of this change, comparing ICUs with 24-h availability of physiotherapy services and those with 12-h availability of physiotherapy services in terms of the costs incurred for patients admitted to the ICU for the first time.

METHODS

Procedures

This observational prevalence study was conducted at the *Hospital das Clínicas* of the University of São Paulo School of Medicine, in the city of São Paulo, Brazil. The hospital has 125 ICU beds distributed among 11 ICUs. Three ICUs with a total of 53 beds were provided with physiotherapy services for 24 h/day (PT-24 group), and eight ICUs with a total of 72 beds were provided with physiotherapy services for 12 h/day (PT-12 group).

All patients received physiotherapy in the ICU from the local staff, which comprised professionals certified to treat critically ill patients. Each physiotherapist treated an average of 10 patients during each 6-h shift. Physiotherapy sessions averaged 30 min in length, depending on the needs of the patient. During the data collection period, the physiotherapists continued their normal routine in the ICU, and no new treatment protocols were introduced.

Data were collected from December 1, 2009, to September 31, 2011. The study was approved by the local research ethics committee (Protocol no. 1159/07). The requirement for written consent was waived, because the study analysis was based on secondary data.

For the patients who met the inclusion criteria listed below, data were collected from patient charts. To facilitate access to clinical information, we collected data for the period from ICU admission until 48 h after discharge to a ward. All data were collected by four trained researchers.

Participants

The study included clinical and surgical patients who were between 18 and 90 years of age at their first admission to the ICU, had been on IMV for ≥ 24 h, and were subsequently discharged to a ward. In the case of surgical patients, we included only those who received IMV exclusively because of surgery. Mechanically ventilated patients were specifically chosen because this group is the most common target for ICU-LOS reductions, given the many available interventions that can shorten the duration of mechanical ventilation use.

Surgical patients with a history of neuromuscular disease, neurodegenerative disease, high spinal cord injury, or tetanus were excluded because of the possibility of prolonged mechanical ventilation. Burn patients were excluded because they were admitted exclusively to a PT-12 ICU and underwent multiple surgical procedures for resurfacing, making it impossible to draw comparison with patients who underwent other types of surgical procedures. Patients who had been referred from another facility were excluded, because of the difficulties of accessing the data of interest. We also excluded patients who were on IMV prior to surgery, not only because such patients represent a minority but also because they present multiple complications. Patients who remained in the ICU for more than three months were also excluded, as were obstetric patients, patients who were transferred out of the ICU to other institutions, patients who died in the ICU, and patients for whom the medical records were incomplete. Patients were included in the study only once, even if they were readmitted to the ICU after discharge.

Measures

The following information were collected from the medical records: age; gender; Acute Physiology and Chronic Health Evaluation II (APACHE II) score; IMV duration; ICU-LOS; number of respiratory and motor physiotherapy sessions during the ICU stay; and Omega score.[22]

The Omega system was created by the French Intensive Care Society.[22] The Omega score reflects the workload required for each indicated procedure. The Omega system, which is similar to the Therapeutic Intervention Scoring System,[23] has been shown to be highly accurate for estimating workloads and costs.[22] The Omega system evaluates 47 diagnostic or therapeutic procedures, divided into three categories. Omega 1 includes general procedures (e.g., intubation, vasoactive drug administration, and chest tubes), which are recorded only once during the ICU stay. Omega 2 includes diagnostic procedures and transport out of the unit (e.g., for radiography or endoscopy), which are recorded each time they are performed. Omega 3 includes procedures related to mechanical ventilation and monitoring, which are recorded daily throughout the ICU stay. The procedures listed in Omega 3 are closely related to physiotherapy practices in ICUs in Brazil. The total Omega score is obtained by calculating the sum of the scores for Omega 1, 2, and

3.[22] After calculating the Omega score, we converted the estimated cost to French francs (FF), using the regression equations reported by Sznajder et al.[22] Those authors developed three regression equations to estimate the costs in FF:

Direct costs = 211.68 × *total Omega score* + 1,191.5

Medical costs = 124.4 × *total Omega score*

Nursing staff costs = 67 × *total Omega score*

Statistical analysis

The statistical analysis was performed using the Statistical Package for the Social Sciences, version 15.0 (SPSS Inc., Chicago, IL, USA) and the program R for Windows, version 3.2.3 (R Development Core Team—www.r-project.org). The descriptive analyses of the continuous variables were presented as the mean ± standard deviation, median (interquartile range), or absolute and relative frequency, as appropriate according to the distribution of the data. Normality tests revealed nonparametric distributions for most of the variables in both groups (PT-12 and PT-24). Therefore, the Mann-Whitney U test was used in order to compare the difference between the two groups.

Standard multiple linear regression analysis was performed in order to develop a model for predicting ICU costs based on the h/day availability of physiotherapy services in the ICU (PT-12 = 0; PT-24 = 1); APACHE II score; surgical procedure[4] (no = 0; yes = 1); and ICU-LOS, in days.[2-4] Those variables were selected on the basis of clinical criteria. Prior to interpreting the results of the multiple regression analysis, we evaluated some assumptions. Stem-and-leaf plots and box plots indicated that the variables in regression were not normally distributed, which required logarithmic transformation of the variables. The level of significance was set at $p < 0.05$.

RESULTS

We evaluated a total of 10,654 records of patients admitted to the ICU during the study period (Figure 1). Of those 10,654 patients, 815 met the inclusion criteria: 483 in the PT-12 group and 332 in the PT-24 group.

The general characteristics of the patients are shown in Table 1. The h/day availability of physiotherapy services was not determined by the type of ICU (surgical or clinical). The proportions of surgical patients in the PT-12 and PT-24 groups are also presented in Table 1. In both groups, males predominated. There was no statistical difference between the groups in terms of the severity of illness, as determined by the APACHE II score, at ICU admission ($p = 0.65$). However, the patients in the PT-24 group were significantly older than were those in the PT-12 group ($p < 0.001$). In addition, the duration of IMV was significantly shorter in the PT-24 group than in the PT-12 group ($p < 0.001$), as was the ICU-LOS ($p = 0.013$).

Table 2 presents the ICU costs calculated for the PT-12 and PT-24 groups. The Omega 3 score was significantly lower in the PT-24 group than in the PT-12 group ($p=0.005$), as were the total Omega score, total costs, medical costs, and staff costs ($p = 0.010$ for all).

Standardized regression coefficients (β) and squared semipartial correlations (sr^2) for each predictor in the multiple linear regression model are shown in Table 3. The h/day availability of physiotherapy services in the ICU, APACHE II score, and ICU-LOS were all found to be significant predictors of ICU costs. The model was able to account for 72% of the variance in ICU costs ($p = 0.05$; $R^2 = 0.72$): ICU costs(y) = 4.800 + 0.010*(APACHE II score) + 0.045*(ICU-LOS) − 0.070*(h/day availability of physiotherapy services).

DISCUSSION

Our findings suggest that the estimated cost per patient in a first admission to the ICU is reduced when physiotherapy services are available around the clock rather than for only 12 h per day. That conclusion is based on the lower Omega 3 and total Omega scores, as well as the lower direct, medical, and nursing staff costs associated with the PT-24

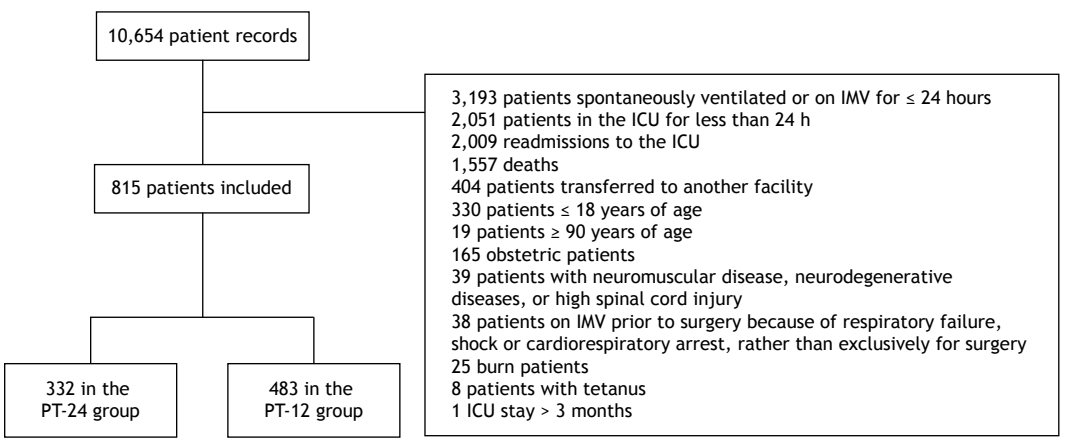

Figure 1. Flowchart of the selection process. PT-24: ICUs provided with physiotherapy services for 24 h/day; and PT-12: ICUs provided with physiotherapy services for 12 h/day.

Table 1. General characteristics of the patients.

Variable	General	PT-12	PT-24	p
N or n (%)	815 (100)	483 (59.3)	332 (40.7)	< 0.001
Age (years), mean ± SD	50.0 ± 17.9	46.7 ± 17.4	54.8 ± 17.4	< 0.001
Male gender, n (%)	510 (62.6)	316 (65.4)	194 (58.4)	0.053
APACHE II score, median (IQR)	14.0 (11.0-20.0)	14.0 (11.0-19.0)	15 (10.7-20.0)	0.650
Surgical patients, n (%)	556 (68.2)	297 (61.5)	259 (78.0)	< 0.001
IMV duration (days), median (IQR)	6.0 (3.0-12.0)	6.0 (4.0-12.5)	5.0 (3.0-9.2)	< 0.001
ICU-LOS (days), median (IQR)	14.0 (8.0-23.0)	15.0 (9.0-24.0)	13.00(8.0-22.0)	0.013

PT-12: ICUs provided with physiotherapy services for 12 h/day; PT-24: ICUs provided with physiotherapy services for 24 h/day; IQR: interquartile range; APACHE II: Acute Physiology and Chronic Health Evaluation II; IMV: invasive mechanical ventilation; and ICU-LOS: intensive care unit length of stay.

Table 2. Omega scores and estimated ICU costs for the two groups evaluated.[a]

Variable	PT-12	PT-24	p
Omega 1 score	37.0 (30.0-45.0)	38.0 (31.7-45.2)	0.070
Omega 2 score	46.0 (24.2-79.0)	40.0 (20.0-75.5)	0.265
Omega 3 score	228.0 (132.0-417.5)	192.0 (99.5-382.5)	0.005
Total Omega score	330.0 (199.5-526.5)	281.5 (167.7-494.5)	0.010
Direct costs (FF)	71,045.9 (43,421.7-112,641.0)	60,779.4 (36,700.8-105,867.3)	0.010
Medical costs (FF)	41,052.0 (24,817.8-65,496.6)	35,018.6 (20,868.1-61,515.8)	0.010
Staff costs (FF)	22,110.0 (13,366.5-35,275.5)	18,860.5 (11,239.2-33,131.5)	0.010

PT-12: ICUs provided with physiotherapy services for 12 h/day; PT-24: ICUs provided with physiotherapy services for 24 h/day; and FF, French francs. [a]Values presented as median (interquartile range).

Table 3. Independent variables for predicting ICU costs in the multiple linear regression model.

Variable	β	sr^2	p	95% CI	
				Lower	Upper
APACHE II score (points)	0.010	0.002	< 0.001	0.006	0.014
Surgery (no = 0; yes = 1)	0.019	0.031	0.530	−0.042	0.082
ICU-LOS (days)	0.045	0.001	< 0.001	0.044	0.048
PT availability (12 h/day = 0; 24 h/day = 1)	−0.070	0.029	0.017	−0.127	−0.013

APACHE II: Acute Physiology and Chronic Health Evaluation II; ICU-LOS, intensive care unit length of stay; and PT, physiotherapy.

condition.[24] We also demonstrated that IMV duration and ICU-LOS were shorter in the PT-24 group. In addition, APACHE II scores, ICU-LOS, and the h/day availability of physiotherapy services were found to be significant predictors of ICU costs. In particular, the relationship between the h/day availability of physiotherapy services and ICU costs was inversely proportional, meaning that the more physiotherapy patients receive during their first ICU stay, the lower are the hospital costs. However, higher APACHE II scores and prolonged ICU-LOS were found to translate to higher hospitalization costs. To our knowledge, this is the first study to examine ICU costs based on the h/day availability of physiotherapy services.

Although the Omega score has not been validated for use in Brazil (i.e., with Brazilian currency), it was chosen because it is easy to use and reflects the workloads associated with caring for critically ill patients.[25] In addition, the Omega 3 score is based on procedures that are closely related to those employed by physiotherapists working in ICUs in Brazil. The need for cost calibration is inherent to all methods used to estimate costs in critical care,[25] such as the Therapeutic Intervention Scoring System[23] and activity-based costing.[26] When comparing results for different countries, factors such as the exchange rate must be considered, and the measurements must reflect purchasing power—comparing costs and resources rather than expenses.[27]

The Omega 3 score evaluates procedures such as mechanical ventilation and continuous surveillance in the ICU. In the current study, the Omega 3 score was lower in the PT-24 group than in the PT-12 group, because of the shorter IMV duration and ICU-LOS in the former. In Brazil, the role of the physiotherapist in the ICU includes implementing and monitoring noninvasive mechanical ventilation; adjusting and monitoring IMV; participating in the weaning process; and extubation. In the current study, round-the-clock ICU availability of physiotherapy services was found to accelerate weaning and to improve IMV management, thereby decreasing the IMV duration, in comparison with ICU availability of physiotherapy services for only 12 h per day. In addition, it is well known that IMV duration is an independent predictor of hospital and ICU costs.[13] Our results are in line with those of a similar study, comparing 24 h/day and 6 h/day availability of physiotherapy services for ICU patients in Brazil.[28] That study showed that round-the-clock availability of physiotherapy services reduces the ICU-LOS, IMV duration, pulmonary infection

rate, and mortality rate. However, the authors of that study did not include a cost analysis of physiotherapy services, as some other authors have done.[29]

As previously mentioned, the total Omega score is the sum of the Omega 1, Omega 2, and Omega 3 scores. Because there were no differences between our two groups in terms of the Omega 1 or Omega 2 score, differences in the Omega 3 scores account for the difference in the total Omega score. The regressions postulated by Sznajder et al.[22] are based on the use of the total Omega score to calculate the total, medical, and staff costs. It is important to note that the Omega system does not include the workload of the physiotherapist. In our study, both groups were given access to a physiotherapist from the multidisciplinary team for either 12 h/day or 24 h/day. Therefore, it should also be noted that providing round-the-clock physiotherapy services contributed to reducing the overall workload of the team, as reflected in the significant differences between the two groups in terms of medical and staff costs.

Despite our positive results, there are still conflicting data in the literature regarding the impacts that respiratory care and chest physiotherapy have on clinical outcomes and cost analyses. One previous report showed that chest physiotherapy delivered twice a day to patients who had been on IMV for at least 48 h was independently associated with a reduction in the incidence of ventilator-associated pneumonia.[29] In a study conducted in Spain, Varela et al.[30] also reported that providing chest physiotherapy for pulmonary lobectomy patients on the ward can shorten hospital stays, resulting in savings equivalent to FF 41,084.69. However, studies conducted in other countries, such as Australia and England, have shown that, among critically ill patients admitted to medical or surgical ICUs, physiotherapy has no effect on the frequency of ventilator-associated pneumonia,[31] mortality, ICU-LOS,[29,30,32] or IMV duration.[29,31,33]

It is particularly challenging to perform outcome studies of physiotherapy in the ICU. The population admitted to the ICU is quite diverse, and the combination of patient characteristics, socioeconomic profile, clinical conditions, and ICU setting can alter outcomes in the critical care area. The most well-accepted recommendations regarding physiotherapy in ICU are related to the weaning process.[31] For example, the European Respiratory Society and the European Society of Intensive Care Medicine recommend the active participation of a physiotherapist in the weaning process,[32,34] because it can optimize weaning from IMV, as was shown in the current study.

The lack of agreement across studies could be related to the complexity of patient health conditions and the diversity of the health care systems in different settings and countries. For example, our hospital is a referral center for South America and a tertiary teaching hospital. Consequently, patients who present to our hospital have multiple comorbidities, are severely ill, and have a prolonged ICU-LOS. We found that, in addition to reducing IMV duration and ICU-LOS, greater availability of physiotherapy services was a significant predictor of reduced ICU costs, as were lower APACHE II scores and shorter ICU-LOS.

Despite the importance of the results, our study has some limitations that should be considered. First, the Omega system has not been validated for use in Brazil, and conversion to the local currency to estimate the financial savings for Brazilian hospitals cannot occur without a cost calibration. Therefore, the interpretation of these data should consider the cost variation between the two dates, 1992 (when the Omega system was devised) and 2011 (when the data collection process for the current study was finalized), based on inflation indices (e.g., consumer price indices), which represent the evolution of the cost of living. Inflation over that period in France was 37.92%. In 1992, 6.9 FF would have been equal to 1 euro. Second, the study was not designed to examine quality improvements (pre- and post-intervention). We compared different ICUs at the same time during the transition to 24-h physiotherapy shifts at our hospital. As a result, the data were not collected from standardized groups. Third, because the study was conducted at a general hospital, heterogeneous diagnoses could have interfered with our results. Nevertheless, the role of the physiotherapist and the clinical routine are the same in all units; we considered it more important to differentiate between clinical and surgical patients than to determine patient diagnoses. It is also worth noting that the severity of illness was similar in both of the groups in our sample. In addition, we excluded all patients with a higher probability of prolonged ICU-LOS; however, the literature indicates that mechanical ventilation weaning times are longer in such patients, due to previous disease, rather than to respiratory failure (the reason for intubation).[7,10] Another limitation is related to the potential lack of external validity of our findings, given the extensive list of exclusion criteria. Finally, some authors have questioned the use of log transformation and its implications for data analysis, arguing that the results of standard statistical tests performed on log-transformed data are often not relevant for the original, non-transformed data.[35,36] However, log transformation is one of the most popular methods of transforming skewed data in order to approximate normality. If the original data follow a log-normal or approximately log-normal distribution, which was the case in our study, then the log-transformed data follow a normal or near normal distribution (the log transformation does in fact reduce or eliminate skewness).[34,37]

In the population studied, ICUs with round-the-clock availability of physiotherapy services presented lower IMV durations and ICU-LOS, as well as lower total, medical, and staff costs, in comparison with ICUs in which physiotherapy services were available for the standard 12 h/day. Providing ICU patients with 24-h access to physiotherapy services was found to be a significant predictor of lower ICU costs.

REFERENCES

1. Chalfin DB. Cost-effectiveness analysis in health care. Hosp Cost Manag Account. 1995;7(4):1-8.
2. Teres D, Rapoport J, Lemeshow S, Kim S, Akhras K. Effects of severity of illness on resource use by survivors and nonsurvivors of severe sepsis at intensive care unit admission. Crit Care Med. 2002;30(11):2413-9. https://doi.org/10.1097/00003246-200211000-00002
3. Moerer O, Schmid A, Hofmann M, Herklotz A, Reinhart K, Werdan K, et al. Direct costs of severe sepsis in three German intensive care units based on retrospective electronic patient record analysis of resource use. Intensive Care Med. 2002;28(10):1440-6. https://doi.org/10.1007/s00134-002-1429-9
4. Jacobs P, Edbrooke D, Hibbert C, Fassbender K, Corcoran M. Descriptive patient data as an explanation for the variation in average daily costs in intensive care. Anaesthesia. 2001;56(7):643-7. https://doi.org/10.1046/j.1365-2044.2001.02052.x
5. Nangino GO, Oliveira CD, Correia PC, Machado NM, Dias AT. Financial impact of nosocomial infections in the intensive care units of a charitable hospital in Minas Gerais, Brazil. Rev Bras Ter Intensiva. 2012;24(4):357-61. https://doi.org/10.1590/S0103-507X2012000400011
6. Jayaram R, Ramakrishnan N. Cost of intensive care in India. Indian J Crit Care Med. 2008;12(2):55-61. https://doi.org/10.4103/0972-5229.42558
7. Kramer AA, Zimmerman JE. A predictive model for the early identification of patients at risk for a prolonged intensive care unit length of stay. BMC Med Inform Decis Mak. 2010;10:27. https://doi.org/10.1186/1472-6947-10-27
8. Esteban A, Anzueto A, Frutos F, Alía I, Brochard L, Stewart TE, et al. Characteristics and outcomes in adult patients receiving mechanical ventilation: a 28-day international study. JAMA. 2002;287(3):345-55. https://doi.org/10.1001/jama.287.3.345
9. Hebert PC, Blajchman MA, Cook DJ, Yetisir E, Wells G, Marshall J, et al. Do blood transfusions improve outcomes related to mechanical ventilation? Chest. 2001;119(6):1850-7. https://doi.org/10.1378/chest.119.6.1850
10. Seneff MG, Zimmerman JE, Knaus WA, Wagner DP, Draper EA. Predicting the duration of mechanical ventilation. The importance of disease and patient characteristics. Chest. 1996;110(2):469-79. https://doi.org/10.1378/chest.110.2.469
11. Kollef MH. What is ventilator-associated pneumonia and why is it important? Respir Care. 2005;50(6):714-21; discussion 721-4.
12. De Jonghe B, Sharshar T, Lefaucheur JP, Authier FJ, Durand-Zaleski I, Boussarsar M, et al. Paresis acquired in the intensive care unit: a prospective multicenter study. JAMA. 2002;288(22):2859-67. https://doi.org/10.1001/jama.288.22.2859
13. Dasta JF, McLaughlin TP, Mody SH, Piech CT. Daily cost of an intensive care unit day: the contribution of mechanical ventilation. Crit Care Med. 2005;33(6):1266-71. https://doi.org/10.1097/01.CCM.0000164543.14619.00
14. Wunsch H, Linde-Zwirble WT, Angus DC, Hartman ME, Milbrandt EB, Kahn JM. The epidemiology of mechanical ventilation use in the United States. Crit Care Med. 2010;38(10):1947-53. https://doi.org/10.1097/CCM.0b013e3181ef4460
15. Hall JB. Creating the animated intensive care unit. Crit Care Med. 2010;38(10 Suppl):S668-75. https://doi.org/10.1097/CCM.0b013e3181f203aa
16. Stiller K. Physiotherapy in intensive care: towards an evidence-based practice. Chest. 2000;118(6):1801-13. https://doi.org/10.1378/chest.118.6.1801
17. Jones AY, Hutchinson RC, Oh TE. Chest physiotherapy practice in intensive care units in Australia, the UK and Hong Kong. Physiother Theory Pract. 1992;8(1):39-47. https://doi.org/10.3109/09593989209108078
18. Pires-Neto RC, Lima NP, Cardim GM, Park M, Denehy L. Early mobilization practice in a single Brazilian intensive care unit. J Crit Care. 2015;30(5):896-900. https://doi.org/10.1016/j.jcrc.2015.05.004
19. Hopkins RO, Spuhler VJ, Thomsen GE. Transforming ICU culture to facilitate early mobility. Crit Care Clin. 2007,23(1): 81-96. https://doi.org/10.1016/j.ccc.2006.11.004
20. Burns SM, Daly B, Tice P. Being led down the critical pathway: a perspective on the importance of care managers vs critical pathways for patients requiring prolonged mechanical ventilation. Crit Care Nurse. 1997,17(6):70-5.
21. Brasil. Ministério da Saúde. Agência Nacional de Vigilância Sanitária [homepage on the Internet] Brasília: o Ministério; [cited 2015 Jun 20]. Resolução no. 7; 2010 Feb 24. [about 10 screens]. Available from: http://bvsms.saude.gov.br/bvs/saudelegis/anvisa/2010/res0007_24_02_2010.html
22. Sznajder M, Leleu G, Buonamico G, Auvert B, Aegerter P, Merlière Y, et al. Estimation of direct cost and resource allocation in intensive care: correlation with Omega system. Intensive Care Med. 1998;24(6):582-9. https://doi.org/10.1007/s001340050619
23. Keene AR, Cullen DJ. Therapeutic Intervention Scoring System: update 1983. Crit Care Med. 1983;11(1):1-3. https://doi.org/10.1097/00003246-198301000-00001
24. Guccione A, Morena A, Pezzi A, Iapichino G. The assessment of nursing workload. Minerva Anestesiol [Article in Italian]. 2004;70(5):411-6.
25. Understanding costs and cost-effectiveness in critical care: report from the Second American Thoracic Society workshop on outcomes research. Am J Respir Crit Care Med. 2002;165(4):540-50. https://doi.org/10.1164/ajrccm.165.4.16541
26. Edbrooke DL, Stevens VG, Hibbert CL, Mann AJ, Wilson AJ. A new method of accurately identifying costs of individual patients in intensive care: the initial results. Intensive Care Med. 1997;23(6):645-50. https://doi.org/10.1007/s001340050388
27. Edbrooke N, Negrini D, Edbrooke D. International comparisons of health care costs: are they important in intensive care and how should they be achieved? In: Vincent JL, editor. Yearbook of Intensive Care & Emergency Medicine. London: Springer Verlag; 2004.
28. Castro AA, Calil SR, Freitas SA, Oliveira AB, Porto EF. Chest physiotherapy effectiveness to reduce hospitalization and mechanical ventilation length of stay, pulmonary infection rate and mortality in ICU patients. Respir Med. 2013;107(1):68-74. https://doi.org/10.1016/j.rmed.2012.09.016
29. Ntoumenopoulos G, Presneill JJ, McElholum M, Cade JF. Chest physiotherapy for the prevention of ventilator-associated pneumonia. Intensive Care Med. 2002; 28(7):850-6. https://doi.org/10.1007/s00134-002-1342-2
30. Varela G, Ballesteros E, Jiménez MF, Novoa N, Aranda JL. Cost-effectiveness analysis of prophylactic respiratory physiotherapy in pulmonary lobectomy. Eur J Cardiothorac Surg. 2006;29(2):216-20. https://doi.org/10.1016/j.ejcts.2005.11.002
31. Patman S, Jenkins S, Stiller K. Physiotherapy does not prevent, or hasten recovery from, ventilator-associated pneumonia in patients with acquired brain injury. Intensive Care Med. 2009;35(2):258-65. https://doi.org/10.1007/s00134-008-1278-2
32. Templeton M, Palazzo MG. Chest physiotherapy prolongs duration of ventilation in the critically ill ventilated for more than 48 hours. Intensive Care Med. 2007;33(11):1938-45. https://doi.org/10.1007/s00134-007-0762-4
33. Clini E, Ambrosino N. Early physiotherapy in the respiratory intensive care unit. Resp Med. 2005;99(9):1096-104. https://doi.org/10.1016/j.rmed.2005.02.024
34. Gosselink R, Bott J, Johnson M, Dean E, Nava S, Norrenberg M, et al. Physiotherapy for adult patients with critical illness: recommendations of the European Respiratory Society and European Society of Intensive Care Medicine Task Force on Physiotherapy for Critically Ill Patients. Intensive Care Med. 2008;34(7):1188-99. https://doi.org/10.1007/s00134-008-1026-7
35. Feng C, Wang H, Lu N, Chen T, He H, Lu Y, TU XM. Log-transformation and its implications for data analysis. Shanghai Arch Psychiatry. 2014;26(2):105-9.
36. Norris AE, Aroian KJ. To transform or not transform skewed data for psychometric analysis: that is the question! Nurs Res. 2004;53(1):67-71. https://doi.org/10.1097/00006199-200401000-00011
37. Bland JM, Altman DG, Rohlf FJ. In defence of logarithmic transformations. Statist Med. 2013;32(21):3766-8. https://doi.org/10.1002/sim.5772

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Reference values for the six-minute pegboard and ring test in healthy adults in Brazil

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ABSTRACT

Objective: To determine reference values for the six-minute pegboard and ring test (6PBRT) in healthy adults in Brazil, correlating the results with arm length, circumference of the upper arm/forearm of the dominant arm, and the level of physical activity. **Methods:** The participants (all volunteers) performed two 6PBRTs, 30 min apart. They were instructed to move as many rings as possible in six minutes. The best test result was selected for data analysis. **Results:** The sample comprised 104 individuals, all over 30 years of age. Reference values were reported by age bracket. We found that age correlated with 6PBRT results. The number of rings moved was higher in the 30- to 39-year age group than in the > 80-year age group (430.25 ± 77.00 vs. 265.00 ± 65.75), and the difference was significant ($p < 0.05$). The 6PBRT results showed a weak, positive correlation with the level of physical activity ($r = 0.358$; $p < 0.05$) but did not correlate significantly with any other variable studied. **Conclusions:** In this study, we were able to determine reference values for the 6PBRT in healthy adults in Brazil. There was a correlation between 6PBRT results and age.

Keywords: Upper extremity; Physical endurance; Exercise tolerance; Exercise test.

INTRODUCTION

Arm activities, whether supported or unsupported, are common when performing activities of daily living (ADLs), such as combing hair, shaving, brushing teeth, doing the dishes, or putting groceries on shelves. Previous studies have demonstrated that simple arm raising movements result in increased metabolic demand in healthy individuals[1] and can also increase activation of the sternocleidomastoid muscle, resulting in respiratory muscle asynchrony in activities such as combing hair.[2] However, individuals who already have a chronic disease, such as COPD, heart disease, etc., can experience increased demand during arm activities, especially during unsupported arm activities.[3-5] As such, various tests have been developed to evaluate strength, endurance, and exercise capacity in this population.[6-8] One of the tests that mimics ADLs is the six-minute pegboard and ring test (6PBRT),[7] which, with the purpose of better adaptation to Portuguese and greater dissemination of the test, was translated as "Teste de Argolas de seis minutos". The 6PBRT is a simple, inexpensive test that evaluates both arm function and endurance.[9] It is time-limited (six minutes), validated, and reproducible, not only for individuals with COPD[7] but also for healthy adults.[10] Various studies have used the 6PBRT as a way to evaluate individuals with COPD[11,12] or as a way to compare them with healthy individuals[7]; however, to date, no 6PBRT reference values have been determined for healthy individuals in Brazil. Knowledge of reference values for a test in healthy individuals is very important, because it will enable quantification of arm impairment in subjects with a disease and comparison of results, as well as assessment of the results of therapeutic interventions, especially in rehabilitation programs.

Given the above, the objective of the present study was to determine reference values for the 6PBRT in healthy adults in Brazil, correlating the results with arm length, upper arm circumference of the dominant arm, forearm circumference of the dominant arm, and the level of physical activity.

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METHODS

This was a prospective cross-sectional study of a convenience sample of healthy adults recruited within the internal and external community of the Federal University of Minas Gerais, located in the city of Belo Horizonte, Brazil, using data obtained between 2014 and 2016. The inclusion criteria were as follows: being 30 years of age or older; being either male or female; having no history of chronic disease; having no limitation of shoulder or arm movement that could compromise performance on the test; and having no history of symptomatic heart or lung disease. The exclusion criteria were as follows: having recently undergone a surgical procedure that prevented performance of the proposed protocol; and having a body mass index < 18.5 kg/m^2 or > 40 kg/m^2.

The study was conducted in the Federal University of Minas Gerais Laboratory for Research on and Evaluation of Cardiorespiratory Performance and was approved by the local research ethics committee (CAAE no. 47887415.6.0000.5149). All participants gave written informed consent.

Initial evaluation

Anthropometric and demographic data were collected before the start of the test session.

Upper arm circumference of the dominant arm and forearm circumference of the dominant arm

Upper arm circumference of the dominant arm and forearm circumference of the dominant arm were measured with a tape measure. The participants were asked to extend their dominant arm (defined as the arm used for signing the consent form), with the palm upward.[13] Upper arm circumference was measured midway between the acromion and olecranon, and forearm circumference was measured near the olecranon, at its point of largest diameter, with the arm relaxed at the side of the body.[14]

Pulmonary function testing

Spirometry was performed with a Koko® spirometer (PDS Instrumentation Inc., Louisville, CO, USA), in accordance with the Brazilian Thoracic Association criteria for acceptability, reproducibility, and quality,[15] the set of values predicted for the Brazilian population being used as a reference.[16]

Human Activity Profile (HAP) questionnaire

The HAP, which has been validated and cross-culturally adapted for use in Brazil,[17] is a 94-item questionnaire addressing common ADLs that are scored according to the energy expenditure required to perform them. The items with lower values represent activities requiring less energy expenditure, and those with higher values represent activities requiring greater energy expenditure. The level of physical activity of individuals is classified by calculating the adjusted activity score (AAS), resulting in their being classified as inactive or debilitated (AAS < 53 points), moderately active (AAS between 53 and 74 points), or active (AAS > 74 points).[17]

6PBRT

The 6PBRT was performed as described by Zhan et al.[7] The participants (all volunteers) remained seated in front of a wooden board on which there were four pegs (two upper pegs and two lower pegs) and 10 rings were hanging on each of the lower pegs (Figure 1). The lower pegs were positioned at the shoulder height of the participants, and the upper pegs were positioned 20 cm above the lower pegs. The participants were instructed to move as many rings as possible from the lower pegs to the upper pegs, and vice-versa, during a six-minute period. Blood pressure, HR, and SpO_2, as well as sensation of dyspnea and arm fatigue (as assessed by the modified Borg scale), were measured before and after each test. The participants performed two 6PBRTs, the second being performed after a 30-min interval or after the variables of interest had returned to their baseline values. Rest was allowed during the test, but the stopwatch was not stopped. If a participant needed to rest, he/she was instructed to resume the test as soon as possible (Figure 1). The outcome of the 6PBRT is the number of rings moved by the end of the test. Standardized phrases of encouragement were offered once every minute during the test.

Figure 1. In A, a volunteer starting to move the rings from the lower to the upper pegs. In B, the same volunteer hanging the rings on the upper pegs.

Statistical analysis

Data were tested for normality with the Shapiro-Wilk test, and the results were described as mean and standard deviation or as median and interquartile range. The lower limit of the 95% CI was adopted as the lower limit of acceptability for the reference values.[18] The association of performance on the 6PBRT with age, gender, arm length, upper arm circumference of the dominant arm, forearm circumference of the dominant arm, and level of physical activity was assessed with Pearson's correlation test. On the basis of correlation analyses, we selected the variables that would be included in the multiple linear regression model. The criterion for inclusion was based on a p value of < 0.05, and the criterion for exclusion was based on a p value of > 0.10. Multiple linear regression was performed in a stepwise fashion. The final model was determined by the adjusted coefficient of determination (R^2) and by statistical significance. The existence of multicollinearity was analyzed using variance inflation factors > 0.2 and tolerance < 5, and the distribution of residuals was examined for normality using quantile-quantile plots. Statistical analysis was performed with the Statistical Package for the Social Sciences, version 17.0 (SPSS Inc., Chicago, IL, USA), and the level of significance was set at α = 5%.

Sample size calculation

According to Horn & Pesce,[18] sample sizes between 40 and 120 are robust when parametric statistical methods are used to determine reference values.

RESULTS

The study sample was a convenience sample of 104 individuals. There was no sample loss since all participants were able to perform the proposed test. None of the participants needed to interrupt the test, and, in all of them, the variables measured returned to baseline values within 30 min after the end of the test (on average, after 15 min); therefore, the interval between the tests was 30 min for all participants. In each age group, the male/female ratio was controlled, being standardized to 1:1. The mean age of the participants was 56.44 ± 15.72 years, 52% being male and 98% being right-handed. The mean body mass index was 26.76 ± 3.84 kg/m^2. In the sample as a whole, the mean number of rings moved was 376.19 ± 79.33 rings. All volunteers had normal pulmonary function. The anthropometric and demographic characteristics of the volunteers are presented in Table 1. Reference values for the 6PBRT were established for each age group (ρ = −0.58; p < 0.05; Table 2), given that gender did not influence performance (ρ = 0.06; p = 0.503). The participants in the younger age groups performed better on the 6PBRT than did those in the older age groups (Tables 2 and 3), with a correlation of r = −0.583 (p < 0.05).

The sample was classified as active by the HAP (80.65 ± 11.21 points), and 69.2% of the participants considered themselves active, performing physical activities 3-5 times a week. The 6PBRT results showed a weak, positive correlation with the level of physical activity (r = 0.358; p < 0.05) but did not correlate with arm length (r = 0.105; p = 0.238); upper arm circumference (r = −0.053; p = 0.553); or forearm circumference (r = −0.007; p = 0.938; Table 3).

The regression equation that enabled the construction of Table 3 with the reference values was as follows:

$$6PBRT = 676.34 - (4.223 \times age); R^2 = 0.34.$$

DISCUSSION

The present study presents reference values for the 6PBRT in healthy individuals ≥ 30 years of age in

Table 1. Descriptive analysis for the sample as a whole (N = 104).[a]

Variable	Result
Age, years	56.44 ± 15.72
BMI, kg/m^2	26.76 ± 3.84
Dominant arm length, cm	70.63 ± 5.34
Upper arm circumference of the dominant arm, cm	28.31 ± 3.24
Forearm circumference of the dominant arm, cm	25.22 ± 2.82
AAS	80.78 ± 11.29
FVC, % of predicted	94.52 ± 14.07
FEV_1, % of predicted	93.12 ± 14.59
FEV_1/FVC, %	96.73 ± 8.23

BMI: body mass index; and AAS: adjusted activity score (on the Human Activity Profile questionnaire). [a]Values presented as mean ± SD.

Table 2. Descriptive statistics for performance (number of rings moved) on the six-minute pegboard and ring test, by age group.

Age group	n	Mean	SD	95% CI
30-39	20	430.25	77.11	394.16-466.34
40-49	20	414.85	61.40	386.11-443.59
50-59	20	382.70	59.38	359.36-428.44
60-69	17	373.76	59.41	343.22-404.31
70-79	19	320.74	65.75	289.05-352.43
>80	08	265.00	47.38	225.39-304.61

Table 3. Correlation of the final six-minute pegboard and ring test score with dominant arm length, upper arm circumference of the dominant arm, forearm circumference of the dominant arm, level of physical activity, and age.

Variable	r*	p
Dominant arm length	0.105	NS
Upper arm circumference of the dominant arm	−0.053	NS
Forearm circumference of the dominant arm	−0.007	NS
Level of physical activity	0.358	0.000
Age	−0.583	0.000

NS: not significant. *Pearson's correlation coefficient.

Brazil. In addition, factors impacting the performance of this population on the 6PBRT were analyzed. These findings will be useful for clinical application, enabling comparison of results between healthy individuals and individuals with different health conditions.

The present study demonstrated that only age was a determinant of performance on the 6PBRT in both genders, younger individuals performing better on the test than did older individuals.

Arm length, upper arm circumference of the dominant arm, and forearm circumference of the dominant arm did not influence 6PBRT results. To our knowledge, this is the first study aimed at determining reference values for the 6PBRT in healthy adults and elderly individuals in Brazil.

The number of rings moved was higher among younger participants (30-49 years of age) than among older participants (≥ 80 years). It is well established in the literature that aging affects muscle mass, strength, endurance, and motor coordination, including in healthy, physically active individuals.[18,19] This may explain the findings of the present study, given that these variables are components of functional capacity. Another important point, demonstrated by Nyberg et al.,[9] is that 6PBRT results correlate better with endurance than with arm muscle strength in individuals with COPD. According to the authors, this can be explained by the fact that the 6PBRT consists of small amplitude movements during which the individuals keep their shoulders flexed at 90°, throughout the test. Although the 6PBRT is less intense from a cardiorespiratory standpoint (unloaded test of short duration), it requires greater motor coordination.

Although gender is a predictor of performance on some functional tests,[20,21] the present study found no such association. The lack of association between gender and 6PBRT results can be explained by the fact that the 6PBRT involves motor coordination, endurance, and manual dexterity rather than strength, which is one of the factors that most differentiates men from women in terms of physical capacity.[22,23]

The 6PBRT results showed a week correlation with the level of physical activity as assessed by the HAP, which corroborates the findings of Ohara et al.[24] This can be explained by the fact that the 6PBRT does not lead to a significant cardiorespiratory demand. Among patients with COPD, 6PBRT results correlate with arm ALD.[11] Physical exercise is known to improve muscle flexibility, as well as to increase endurance and motor coordination,[24-27] but this was not observed here, because we conducted a cross-sectional study and there was no physical training followed by determination of whether there was improvement in performance on the 6PBRT.

Arm length, upper arm circumference of the dominant arm, and forearm circumference of the dominant arm did not correlate with the participant's performance on the 6PBRT, which shows that a better performance on the test does not depend on having long or short arms or having larger or smaller upper arm and forearm circumference. Janaudis-Ferreira et al.[28] evaluated the relationship of shoulder and elbow flexion strength with the total 6PBRT score and found a moderate to strong correlation between shoulder flexion strength and the 6PBRT ($r = 0.41$; $p = 0.016$) and between elbow flexion strength and the 6PBRT ($r = 0.81$; $p < 0.0001$), which demonstrates that the muscles of these joints have an important relationship with 6PBRT results. These findings allow us to infer that, if there were an increase in upper arm and forearm circumference due to increased muscle mass, there would be an improvement in performance on the test; however, the present study did not assess arm muscle strength, which makes this comparison difficult.

One of the limitations of the present study is the small number of individuals older than 80 years, which compromises the generalizability of our findings to that age group. This is due to the fact that the population selected for the study should be healthy, without symptomatic disease or any disease that would limit their ability to perform the 6PBRT, which made us exclude some individuals (n = 10). However, the criteria for robustness and reliability in statistical analysis, such as the estimated sample size and achievement of the required number of individuals for each age group,[29] were met. Another limitation is that we used convenience sampling, which may compromise the external validity of the study. However, this sampling method has been used in benchmark studies.[20,21]

In conclusion, the present study was able to determine reference values for the 6PBRT in healthy adults in Brazil. There was a correlation between 6PBRT results and age, given that the older the individuals, the worse they performed on the test. In view of these findings, we can consider using the 6PBRT in the assessment of arm function both in clinical practice and for research purposes. Since the 6PBRT is simple and easy to perform, its use can be extended to conditions leading to limitation of arm function.

REFERENCES

1. Couser JI Jr, Martinez FJ, Celli BR. Respiratory response and ventilatory muscle recruitment during arm elevation in normal subjects. Chest. 1992;101(2):336-40. https://doi.org/10.1378/chest.101.2.336
2. Panka GF, Oliveira MM, França DC, Parreira VF, Britto RR, Velloso M. Ventilatory and muscular assessment in healthy subjects during an activity of daily living with unsupported arm elevation. Rev Bras Fisioter. 2010;14(4):337-44. https://doi.org/10.1590/S1413-35552010005000013
3. Holland AE, Hill CJ, Nehez E, Ntoumenopoulos G. Does unsupported upper limb exercise training improve symptoms and quality of life for patients with chronic obstructive pulmonary disease? J Cardiopulm Rehabil. 2004;24(6):422-7. https://doi.org/10.1097/00008483-200411000-00010
4. de Souza GF, Castro AA, Velloso M, Silva CR, Jardim JR. Lactic acid levels in patients with chronic obstructive pulmonary disease

accomplishing unsupported arm exercises. Chron Respir Dis. 2010;7(2):75-82. https://doi.org/10.1177/1479972310361833

5. Miles DS, Cox MH, Bomze JP. Cardiovascular responses to upper body exercise in normals and cardiac patients. Med Sci Sports Exerc. 1989;21(5 Suppl):S126-31. https://doi.org/10.1249/00005768-198910001-00003
6. Takahashi T, Jenkins SC, Strauss GR, Watson CP, Lake FR. A new unsupported upper limb exercise test for patients with chronic obstructive pulmonary disease. J Cardiopulm Rehabil. 2003;23(6):430-7. https://doi.org/10.1097/00008483-200311000-00007
7. Zhan S, Cerny FJ, Gibbons WJ, Mador MJ. Development of an unsupported arm exercise test in patients with chronic obstructive pulmonary disease. J Cardiopulm Rehabil. 2006;26(3):180-7. discussion 188-90.
8. Janaudis-Ferreira T, Beauchamp MK, Goldstein RS, Brooks D. How should we measure arm exercise capacity in patients with COPD? A systematic review. Chest. 2012;141(1):111-120. https://doi.org/10.1378/chest.11-0475
9. Nyberg A, Törnberg A, Wadell K. Correlation between limb muscle endurance, strength, and functional capacity in people with chronic obstructive pulmonary disease. Physiother Can. 2016;68(1):46-53. https://doi.org/10.3138/ptc.2014-93
10. Lima VP, Velloso M, Almeida FD, Carmona B, Ribeiro-Samora GA, Janaudis-Ferreira T. Test-retest reliability of the unsupported upper limb exercise test (UULEX) and six-minute peg board ring test (6PBRT) in healthy adult individuals. Physiother Theory Pract. 2018;34. Epub 2018 Jan 19. https://doi.org/10.1080/09593985.2018.1425786
11. Takeda K, Kawasaki Y, Yoshida K, Nishida Y, Harada T, Yamaguchi K, et al. The 6-minute pegboard and ring test is correlated with upper extremity activity of daily living in chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis. 2013;8:347-51. https://doi.org/10.2147/COPD.S45081
12. Cancelliero-Gaiad KM, Ike D, Soave L, Gomes EL, Dias FD, Costa D. Correlation between functional capacity and health-related quality of life in COPD: a case series. Fisioter Mov. 2014;27(4):505-14. https://doi.org/10.1590/0103-5150.027.004.AO02
13. McArdle WD. Fisiologia do Exercício–Nutrição, Energia e Desempenho Humano. 7ed. Rio de Janeiro: Guanabara Koogan; 2011.
14. Sagun G, Oguz A, Karagoz E, Filizer A, Tamer G, Mesci B. Application of alternative anthropometric measurements to predict metabolic syndrome. Clinics. 2014;69(5):347-53. https://doi.org/10.6061/clinics/2014(05)09
15. I Consenso de Espirometria. J Bras Pneumol. 1996;22(3):164.
16. Duarte AA, Pereira CA, Rodrigues SC. Validation of new brazilian predicted values for forced spirometry in caucasians and comparison with predicted values obtained using other reference equations. J Bras Pneumol. 2007;33(5):527-35. https://doi.org/10.1590/S1806-37132007000500007
17. Souza AC, Magalhães Lde C, Teixeira-Salmela LF. Cross-cultural adaptation and analysis of the psychometric properties in the Brazilian version of the Human Activity Profile [Article in Portuguese]. Cad Saude Publica. 2006;22(12):2623-36. https://doi.org/10.1590/S0102-311X2006001200012
18. Horn PS, Pesce AJ. Reference intervals: an update. Clin Chim Acta. 2003;334(1-2):5-23. https://doi.org/10.1016/S0009-8981(03)00133-5
19. Hoogendam YY, van der Lijn F, Vernooij MW, Hofman A, Niessen WJ, van der Lugt A, et al. Older age relates to worsening of fine motor skills: a population-based study of middle-aged and elderly persons. Front Aging Neurosci. 2014;6:259. https://doi.org/10.3389/fnagi.2014.00259
20. Hughes VA, Frontera WR, Wood M, Evans WJ, Dallal GE, Roubenoff R, et al. Longitudinal muscle strength changes in older adults influence of muscle mass, physical activity, and health. J Gerontol A Biol Sci Med Sci. 2001;56(5):B209-17. https://doi.org/10.1093/gerona/56.5.B209
21. Britto RR, Probst VS, de Andrade AF, Samora GA, Hernandes NA., Marinho PE, et al. Reference equations for the six-minute walk distance based on a Brazilian multicenter study. Brazilian J Phys Ther. 2013;17(6):556-63. https://doi.org/10.1590/S1413-35552012005000122
22. Dourado VZ, Guerra RL, Tanni SE, Antunes LC, Godoy I. Reference values for the incremental shuttle walk test in healthy subjects: from the walk distance to physiological responses. J Bras Pneumol. 2013;39(2):190-7. https://doi.org/10.1590/S1806-37132013000200010
23. Miller AE, MacDougall JD, Tarnopolsky MA, Sale DG. Gender differences in strength and muscle fiber characteristics. Eur J Appl Physiol Occup Physiol. 1993;66(3):254-62. https://doi.org/10.1007/BF00235103
24. Ohara DG, Melo CS, Reis IM, Jamami M. Functional capacity assessment of upper limbs in healthy young adult subjects. Fisio Ter. 2017;30(1):159-67. https://doi.org/10.1590/1980-5918.030.001.ao17
25. Miller MS, Callahan DM, Toth MJ. Skeletal muscle myofilament adaptations to aging, disease and disuse and their effects on whole muscle performance in older adult humans. Front Physiol. 2014;5:369. https://doi.org/10.3389/fphys.2014.00369
26. Cartee GD, Hepple RT, Bamman MM, Zierath JR. Exercise Promotes Healthy Aging of Skeletal Muscle. Cell Metab. 2016;23(6):1034-1047. https://doi.org/10.1016/j.cmet.2016.05.007
27. Hübner L, Voelcker-Rehage C. Does physical activity benefit motor performance and learning of upper extremity tasks in older adults?--A systematic review. Eur Rev Aging Phys Act. 2017;14:15. https://doi.org/10.1186/s11556-017-0181-7
28. Janaudis-Ferreira T, Hill K, Goldstein RS, Wadell K, Brooks D. Relationship and responsiveness of three upper-limb tests in patients with chronic obstructive pulmonary disease. Physiother Can. 2013;65(1):40-3. https://doi.org/10.3138/ptc.2011-49
29. Portney LG, Watkins MP. Foundations of Clinical Research: Applications to Practice, 3rd ed. New Jersey: Prentice Hall; 2009.

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ORIGINAL ARTICLE

Comparison of two smoking cessation interventions for inpatients

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ABSTRACT

Objective: This study aimed to compare the effectiveness of two cognitive behavioral therapy-based smoking cessation interventions initiated during hospitalization and to evaluate the factors related to relapse after discharge. **Methods:** This was a prospective randomized study involving 90 smokers hospitalized in a university hospital. We collected data related to sociodemographic characteristics, reasons for admission, smoking-related diseases, smoking history, the degree of nicotine dependence (ND), and the level of craving. Patients were divided into two treatment **groups:** brief intervention (BrInter, n = 45); and intensive intervention with presentation of an educational video (InInterV, n=45). To assess relapse, all patients were assessed by telephone interview in the first, third, and sixth months after discharge. Abstinence was confirmed by measurement of exhaled carbon monoxide (eCO). **Results:** Of the 90 patients evaluated, 55 (61.1%) were male. The mean age was 51.1 ± 12.2 years. The degree of ND was elevated in 39 (43.4%), and withdrawal symptoms were present in 53 (58.9%). The mean eCO at baseline was 4.8 ± 4.5 ppm. The eCO correlated positively with the degree of ND ($r = 0.244$; $p = 0.02$) and negatively with the number of smoke-free days ($r = -0.284$; $p = 0.006$). There were no differences between the groups in terms of the variables related to socioeconomic status, smoking history, or hospitalization. Of the 81 patients evaluated at 6 months, 33 (40.7%) remained abstinent (9 and 24 BrInter and InInterV group patients, respectively; $p = 0.001$), and 48 (59.3%) had relapsed (31 and 17 BrInter and InInterV group patients, respectively; $p= 0.001$). Moderate or intense craving was a significant independent risk factor for relapse, with a relative risk of 4.0 (95% **CI:** 1.5-10.7; $p < 0.00001$). **Conclusions:** The inclusion of an educational video proved effective in reducing relapse rates. Craving is a significant risk factor for relapse.

Keywords: Smoking cessation; Tobacco use disorder; Inpatients; Hospitalization.

INTRODUCTION

Tobacco-related diseases constitute one of the main causes of hospital admission.[1-3] When smoking patients are hospitalized, it is recommended that they be given counseling and treatment for nicotine dependence, during hospitalization and for at least four weeks after discharge.[4] However, very few hospitals treat nicotine-dependent patients during hospitalization. Due to smoking restrictions on hospital premises, such patients feel forced to quit smoking regardless of their level of motivation to do so. Therefore, hospitalization provides a unique opportunity to approach those patients who wish to quit smoking.[5] Various studies[3,6-8] have shown that, despite the fact that smoking is not allowed in hospitals, 25% of nicotine-dependent patients smoke during hospitalization; 55% of smoking patients report withdrawal symptoms during hospitalization; only 6% of such patients receive nicotine replacement therapy (NRT); and 63% of patients receiving NRT relapse during the first week after hospital discharge (45% relapsing on the first day).

Data suggest that 50% of smokers stop smoking without assistance immediately after a cardiovascular event that results in hospitalization. However, the smoking relapse rate after hospitalization for a cardiovascular event is 50%. The occurrence of withdrawal symptoms immediately after discharge and of depressive symptoms 3-6 months later are the main factors related to smoking relapse after hospitalization.

Many types of resources are used for outpatient smoking cessation treatment, including self-help materials, counseling, cognitive behavioral therapy, and pharmacological treatment.[9] Nevertheless, there are few data available about intra-hospital smoking cessation therapy. According to a recent meta-analysis,[10] smoking cessation intervention during hospitalization must be intensive to be effective. The objective of this study was to compare two cognitive behavioral therapy-based interventions for smoking cessation in hospitalized patients, in terms of their effectiveness, and to evaluate the factors associated with relapse after discharge. A secondary objective was to evaluate the effectiveness of a video

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counseling intervention, which was tested because it is feasible, requiring fewer resources, and if effective would be a useful tool at every kind of hospital, even when specialists are not available.

METHODS

This was a randomized prospective study involving smokers hospitalized between January and December of 2016 on the medical or surgical ward of Antônio Pedro University Hospital, a 232-bed teaching community hospital located in the city of Niterói, Brazil. For the purposes of this study, we excluded a total of 108 of those beds in the departments of obstetrics, neonatal care, and pediatrics, as well as in the nursery, adult ICU, and emergency room.

To be eligible for the study, subjects had to be current cigarette smokers; between 18 and 80 years of age; and motivated to remain abstinent from smoking after hospital discharge. Individuals who had smoked regularly (at least one cigarette per day) for at least 30 days before hospitalization, were classified as current smokers.[11] Prospective subjects were excluded if they were receiving end-of-life care, were clinically unstable, had cognitive or memory deficits, had a psychiatric disorder, or were pregnant.

Patients were enrolled within the first 48 h after hospital admission, at which time an interviewer collected data related to sociodemographic characteristics, medical history, smoking history, intention to stop smoking during hospitalization/after discharge, and nicotine withdrawal symptoms. The level of nicotine dependence was assessed with the Fagerström Test for Nicotine Dependence (FTND).[12] To assess the level of nicotine craving, we used the Brief Questionnaire of Smoking Urges (QSU-brief),[13] whereas we assessed the use/abuse of alcohol with the Cut down, Annoyed, Guilty, and Eye-opener questionnaire.[14] Patient records were further evaluated in order to confirm and complement the data.

Interventions

We calculated that a sample of 90 subjects would be required in order to achieve sufficient statistical power to identify differences between two groups. Therefore, 90 inpatients were randomly assigned to one of two treatment groups: the brief intervention (BrInter) group (n = 45) and the intensive intervention with an educational video (InInterV) group (n = 45).

BrInter group

Patients in the BrInter group received counseling on the dangers of smoking and the benefits of quitting in an ordinary session lasting 10 min. No audiovisual resources were used, nor was any pharmacological intervention proposed.

InInterV group

The intensive cognitive behavioral therapy-based intervention was performed by a researcher who had previously been trained in smoking cessation treatment at the Brazilian National Cancer Institute. Patients assigned to the InInterV group were counseled in a session that lasted approximately 40 min, comprising a 10-min oral intervention and a 30-min educational video presentation. In that session, the counselor reviewed the dangers of smoking and the benefits of quitting; assessed the knowledge and beliefs of the participant, as well as the potential barriers to smoking cessation; explained the mechanisms of nicotine dependence and the symptoms of withdrawal; presented counter-arguments to belief barriers; and discussed behavioral self-management strategies to counter relapse triggers. No pharmacological intervention was proposed. A team of researchers, composed of a cardiologist, a pulmonologist, and a psychiatrist created the intellectual content and produced the video. The video presentation was performed with a notebook computer installed at the bedside. This video will be made available upon request.

Follow up

All participants were contacted by telephone at 1, 3, and 6 months after discharge from the hospital. During hospitalization and at 6 months after discharge, smoking status was assessed and self-reported abstinence was biochemically validated by measuring exhaled carbon monoxide (eCO) with a portable breath analyzer (Micro CO; Micro Medical Ltd, Rochester, UK). Values of eCO over 6 ppm were considered indicative of recent smoking.[15]

In the telephone interviews conducted at 6 months after discharge, additional data were obtained. Patients were asked about possible improvements in their lives after smoking cessation, such as those related to respiratory symptoms, family relationships, physical activities, and financial well-being. They were also invited to schedule an appointment at our hospital within the next seven days, in order to submit to eCO evaluation.

For patients who were unable to come to the hospital, the eCO measurement was performed in the home. Patients who could not be contacted after at least two telephone calls were considered lost to follow-up. Participants who had relapsed were encouraged to undergo outpatient treatment at our institution.

Statistical analysis

The sample size (n = 90) was calculated according to the expected prevalence of smoking among hospitalized patients. That calculation was based on data collected in a previous study conducted by our group, in which that prevalence was found to be 13%.[16]

Continuous variables are expressed as mean and standard deviation or as median where appropriate. Categorical variables are expressed as absolute and relative frequencies. To compare the two groups, the Mann-Whitney U test was used for continuous variables, whereas the chi-square test and Fisher's exact test were used for categorical variables. Logistic

regression analysis was used in order to identify independent predictors of relapse. The Kaplan-Meier method and log-rank tests were used in order to identify event-free patients. An event was defined as any relapse after the initial intervention. The strength of the associations between continuous variables was determined with Spearman's correlation coefficient. To evaluate the distribution of the data collected, we used the Kolmogorov-Smirnov test. For variables that did not present a normal distribution, due to dispersion, we used nonparametric methods of analysis. A level of significance of 5% was adopted. All statistical analyses were performed with the Statistical Analysis System, version 6.11 (SAS Institute Inc., Cary, NC, USA) and the IBM SPSS Statistics software package, version 18.0 (IBM Corporation, Armonk, NY, USA).

The study was approved by the Research Ethics Committee of Fluminense Federal University School of Medicine (Reference no. 0008.0.258.000-10). All participating patients gave written informed consent.

RESULTS

Of the 90 hospitalized smokers evaluated, 55 (61.1%) were male; 47 (52.2%) were unmarried; only 30 (32.3%) had graduated high school; 65 (72.2%) earned less than minimum wage; 47 (52.2%) were hospitalized on medical wards; and 43 (47.8%) were hospitalized on surgical wards. The mean age of the patients was 51 ± 12.2 years (range, 20-72 years). The reasons for admission were as follows: cancer (in 23.3%); cardiovascular diseases (in 21.1%), primarily coronary artery disease; respiratory diseases (in 14.4%); and osteoarticular diseases (in 13.4%). There were no significant differences between the groups in terms of the reasons for admission.

The most prevalent smoking-related diseases prior to the hospitalization were hypertension (in 51.1%), gastritis (in 33.3%), COPD (in 28.8%), and diabetes mellitus (in 26.6%). Of the 35 female smokers, 14 (40%) reported having had at least one miscarriage. Of the 90 patients evaluated, 16 (17.8%) reported dependence on alcohol and 19 (21.1%) reported dependence on one or more other drugs. Seventy-eight (86.7%) reported having a sedentary lifestyle.

Among the patients evaluated, the mean number of cigarettes smoked daily was 20.7 ± 13.1, the mean time since taking up the smoking habit was 34.8 ± 13.5 years, the mean smoking history was 38.8 ± 31.4 pack-years, and the mean age at smoking initiation was 15.9 ± 5.4 years. In addition, the degree of nicotine dependence was classified as high or very high in 40 (43.4%) of the patients and 58 (64.5%) had already attempted to quit smoking at least once. Patients gave the following reasons for remaining abstinent after hospital discharge: health concerns (in 85 patients); family related concerns (in 13); financial problems (in 8); aesthetic concerns (in 3); improvement in their quality of life (in 2); social acceptance (in 2); improved personal hygiene (in 2); and religious concerns (in 1). All patients reported needing help to remain abstinent. During hospitalization, 53 (58.9%) of the 90 patients reported at least one nicotine-withdrawal symptom and presented at least a minimum or a light degree of craving according to the QSU-brief. The mean eCO in the initial evaluation was 4.8 ± 4.5 ppm, which correlated positively with the FTND score ($r = 0.244$; $p = 0.020$) and negatively with smoke-free days at enrollment ($r = -0.284$; $p = 0.006$).

Of the 90 patients evaluated, 9 were excluded from the 6-month assessment: due to death, in 5 (3 BrInter group patients and 2 InInterV group patients); and due to loss to follow-up, in 4 (2 BrInter group patients and 2 InInterV group patients). Therefore, a total of 81 patients were evaluated at 6 months after discharge. No significant difference was observed between the two groups in terms of demographic characteristics, socioeconomic variables, or smoking history (Tables 1 and 2).

At 6 months of follow-up, the estimated overall abstinence rate was 40.7%, 9 and 24 patients in the BrInter and InInterV groups, respectively, having remained abstinent from smoking, whereas the estimated overall relapse rate was 59.3%, 31 and 17 patients in the BrInter and InInterV groups, respectively, having relapsed. The mean eCO at 6 months was 0.7 ± 0.6 ppm (range, 0-2 ppm). As can be seen in Figure 1, there were fewer cases of relapse in the InInterV group than in the BrInter group.

Of the 48 patients who relapsed, 38 (79.1%) had resumed smoking within the first month after discharge—27 within the first week (15 on the first day); 8 (16.6%) had resumed smoking between the first and third month; and 2 (4.1%) had resumed smoking between the fourth and sixth month. As shown in Figure 2, there was a significant difference between the BrInter and InInterV groups in terms of the event-free curve ($p = 0.002$), the InInterV group presenting a higher event-free rate. The mean time to relapse was approximately 24 days. The main reason for relapse, reported by 37 patients (77.0%), was craving.

In the comparison between the patients who had relapsed by 6 months after discharge and those who had not (Figure 3), the former presented significantly higher QSU-brief scores ($p = 0.001$). The differences between the relapsing and abstinent patients were not significant for any of the other variables evaluated: the condition that prompted admission ($p = 0.75$); alcohol dependence ($p = 0.31$); drug dependence ($p = 0.47$); and a sedentary lifestyle ($p = 0.59$).

There was a significant positive correlation between the FTND score and the QSU-brief score ($r = 0.209$; $p = 0.048$), whereas there was a significant negative correlation between the number of smoke-free days and the QSU-brief score ($r = -0.353$; $p = 0.001$). Figure 4 shows the ROC curve for the QSU-brief scores vis-à-vis relapse. The best QSU-brief cut-off score for identifying relapse was 20, which had a sensitivity of 66.7% and a specificity of 72.7%. According to the

Table 1. Demographic and socioeconomic characteristics of the patients evaluated, by treatment group.

Variables		Group		p*
		BrInter (n = 45) n (%)	InInterV (n = 45) n (%)	
Gender	Male	28 (62.2)	27 (60.0)	0.83
	Female	17 (37.8)	18 (40.0)	
Age (years)	Median	54	54	0.47
Marital status	Married	22 (48.9)	21 (46.7)	0.83
	Unmarried	23 (51.1)	24 (53.3)	
Religion	Catholic	31 (68.9)	28 (62.2)	0.51
	Other	14 (31.1)	17 (37.8)	
Schooling	< 9 years	20 (44.4)	20 (44.4)	0.13
	9-11 years	14 (31.1)	7 (15.6)	
	≥ 12 years	11 (24.4)	18 (40.0)	
Income	(US$/year)	4,300	4,300	0.16

BrInter: brief intervention; and InInterV: intensive intervention with an educational video. *Mann-Whitney test.

Table 2. Smoking variables among the patients evaluated, by treatment group.[a]

Variables	Group		p*
	BrInter (n = 45)	InInterV (n = 45)	
Age at smoking initiation (years)	16.0 ± 5.5	15.8 ± 5.4	0.73
Time since smoking initiation (years)	33.7 ± 13.8	35.9 ± 13.3	0.48
Cigarettes smoked/day	21.2 ± 12.1	20.2 ± 14.2	0.61
Smoking history (pack-years)	30	34	0.99
Smoking cessation attempts	1	1	0.98
FTND score	5.2 ± 2.0	5.1 ± 2.6	0.91
Initial eCO (ppm)	5.4 ± 5.4	4.3 ± 3.4	0.65

BrInter: brief intervention; InInterV: intensive intervention with an educational video; FTND: Fagerström Test for Nicotine Dependence; and eCO: exhaled carbon monoxide. [a]Values expressed as mean ± SD or median. *Mann-Whitney test.

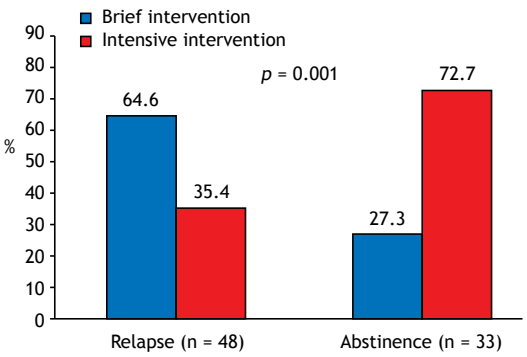

Figure 1. Comparison between the groups studied, in terms of the rates of relapse and abstinence, at 6 months after discharge from the hospital.

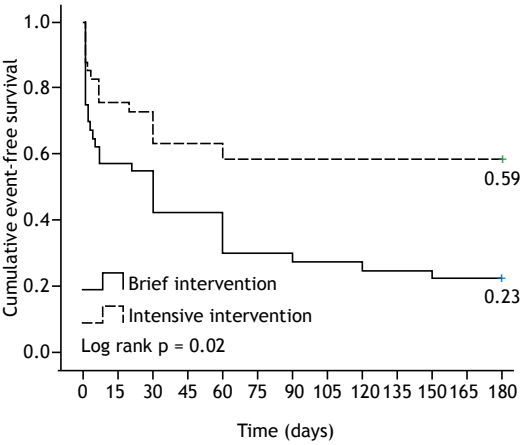

Figure 2. ROC curves for event-free follow-up, by group.

logistic regression, the factors that were independent predictors of relapse were being in the BrInter group (p = 0.008) and having moderate or intense cravings (p = 0.034), with relative risks of 3.9 and 3.0, respectively.

Of the 33 patients who had remained abstinent throughout the 6-month follow-up period, 18 (54.5%) reported improvement in their respiratory symptoms; 15 (45.4%) reported improvement in their financial situation; 13 (39.3%) reported improvement in their sense of smell; and 10 (30.3%) reported improvement in their sense of taste. Only one patient reported having observed no improvement whatsoever.

DISCUSSION

Every year, millions of smokers are hospitalized for smoking-related diseases. Those admissions constitute a window of opportunity for implementing smoking

cessation programs.[7] Smokers who are hospitalized are more susceptible to anti-smoking messages for a number of reasons[17]: their frailty; their fear of complications or death from the disease that prompted their admission; and the fact that they are forced to refrain from smoking because of the smoking ban in hospitals. Few hospitals identify smokers during hospitalization, and even fewer offer smoking cessation treatment and follow-up after discharge.[5] In this study, all hospitalized smokers reported being motivated to quit smoking for good, although they stated that they needed help to remain abstinent, supporting the concept that hospitalization is an opportune time to initiate smoking cessation treatment.

There have been few epidemiological studies on in-hospital smoking cessation treatment and its management. In a previous study conducted by our group and involving 136 hospitalized patients,[16] 18 (13.2%) of the patients were smokers. Of those 18 patients, 16 (88.9%) experienced withdrawal symptoms during hospitalization. In the present study, the prevalence of smoking was lower (8.1%) and only 53 (58.9%) of the 90 patients experienced withdrawal symptoms, minimum or mild craving being the predominant symptom. Warner et al.[18] did not observe intense withdrawal symptoms in smokers hospitalized for elective surgery. The authors suggest that psychological stress caused by the surgical procedure reduced withdrawal symptoms. A study conducted in a hospital in the United States evaluated 650 hospitalized smokers and found a prevalence of 25% of current smoking among inpatients, 55% of the smokers reporting withdrawal symptoms during their hospital stay.[19] In smoke-free psychiatric hospitals, nearly 50% of hospitalized patients are smokers.[20] Emmons & Goldstein[5] found the prevalence of smoking to be 16% among 304 patients admitted to a cardiovascular disease ward. The reported prevalence of smoking at various hospitals ranges from 12.1% to 34.0%.[21-23]

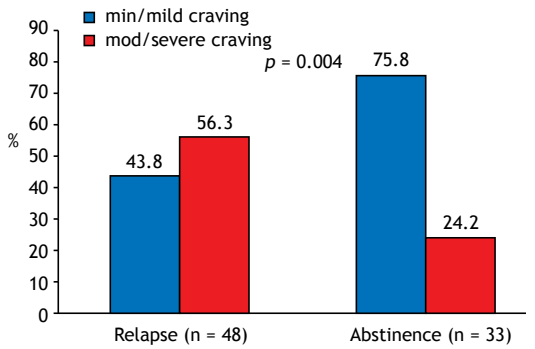

Figure 3. Scores on the Brief Questionnaire of Smoking Urges, by outcome.

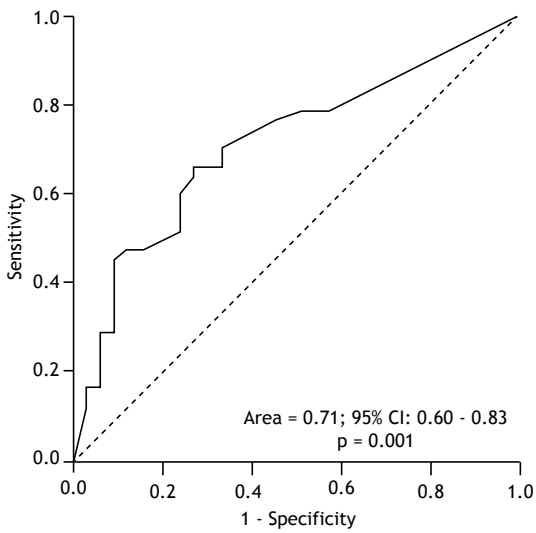

Figure 4. ROC curve for the Brief Questionnaire of Smoking Urges score, in relation to relapse.

Smoking cessation treatment programs for hospitalized patients have been implemented worldwide,[24,25] with significant variation in the rates of success. Studies of different intervention techniques for smoking cessation among hospitalized patients have produced inconsistent, unreliable results.[25,26] In a review of several interventional studies of smoking among hospitalized patients,[17] patient follow-up at 30 days after hospital discharge was found to significantly reduce the relapse rate over the subsequent 6 months. This indicates the strategic need to monitor patients after hospital discharge. Hajek et al.[27] evaluated 540 smokers hospitalized after myocardial infarction or for coronary artery bypass surgery and concluded that a brief intervention during hospitalization was insufficient to prevent relapse. Simon et al.[7] demonstrated that intensive medical advice during hospitalization, together with use of NRT for 2 months and telephone support after hospital discharge, increased smoking cessation in comparison with minimum in-hospital counseling. Wolfenden et al.[28] showed that hospital intervention longer than 20 min, followed by at least five telephone calls after discharge, for a minimum of 3 months, is effective to increase smoking cessation rates. In two systematic reviews of studies of smoking cessation interventions in hospitalized patients—published in 2003 and 2007, involving 17 and 33 trials, respectively[29,30]—the authors concluded that intensive behavioral interventions that begin during a hospital stay and extend for at least 30 days after discharge increase smoking cessation rates. Such interventions are effective regardless of the diagnosis at admission. Brief interventions have not been shown to provide significant benefits from a statistical point of view. Similar results were obtained in smokers admitted to the hospital because of cardiovascular disease. In that subgroup, intensive intervention with support after discharge increased the smoking cessation rate, no such increase being observed after a brief intervention.[19] An updated review, involving 50 trials and published in 2012,[10] confirmed those findings and showed that smoking cessation rates were significantly higher after intensive counseling plus NRT than after

counseling alone, although there is insufficient evidence to conclude that adding bupropion or varenicline to intensive counseling results in cessation rates that are higher than those achieved with counseling alone. In the present study, the use of an intensive approach with an educational video presentation followed by telephone contact was found to be superior to the brief intervention regarding the relapse rate at 6 months of follow-up.

Relapse is a common event among former smokers. Seventy-five percent of abstinent individuals relapse within the first 12 months, most relapsing within the first 6 months, regardless of the nature of the initial intervention.[31,32] In our study, 48 (59.3%) of the 81 smokers evaluated at 6 months after discharge had relapsed. Of those 48 patients, 38 (79.1%) resumed smoking within the first month after hospital discharge, the relapse rate progressively decreasing over time, similar to what has been reported in other trials.[32,33] Hawkins et al.[33] showed that the relapse rate decreases in direct proportion to the duration of abstinence, as was also shown by Hughes et al.[34] in a meta-analysis of smoking relapse after 12 months of abstinence. These data demonstrate the need for greater support during the first months of smoking abstinence. Goodman et al.[35] reviewed the history of smoking cessation during hospitalization in a smoke-free hospital and showed that only 7% of patients remained abstinent from smoking at 6 months after discharge. Among the patients who relapsed in that study, 45% did so on the first day after discharge.

The potential predictors of smoking relapse vary among treatment centers. In the present study, only the degree of craving was found to be an independent predictor of relapse, which differs from the findings of previous studies.[33,36-38]

Knowledge of long-term abstinence rates after hospital discharge is extremely important for evaluating the effectiveness of inpatient treatments. In the present study, the abstinence rate among the patients evaluated at 6 months after discharge was 40.7%, higher than that reported in the literature.[31-33]

Here, we have presented a cognitive behavioral therapy-based technique that is easily accessible and inexpensive. This intervention, which can be applied by doctors and other health professionals, proved to be effective in reducing long-term relapse rates. Because craving at admission was the main predictor of relapse, the technique could be complemented with medication (NRT, bupropion, or varenicline) or treatment for the comorbid psychiatric disorders emerging with abstinence, on an individual and selective basis.

REFERENCES

1. Ockene IS, Miller NH. Cigarette smoking, cardiovascular disease, and stroke: a statement for healthcare professionals from the American Heart Association. American Heart Association Task Force on Risk Reduction. Circulation. 1997;96(9):3243-7. https://doi.org/10.1161/01.CIR.96.9.3243
2. Juster HR, Loomis BR, Hinman TM, Farrelly MC, Hyland A, Bauer UE, et al. Declines in hospital admissions for acute myocardial infarction in New York state after implementation of a comprehensive smoking ban. Am J Public Health. 2007;97(11):2035-9. https://doi.org/10.2105/AJPH.2006.099994
3. Mohiuddin SM, Moos AN, Hunter CB, Grollmes TL, Cloutier DA, Hilleman DE. Intensive smoking cessation intervention reduces mortality in high-risk smokers with cardiovascular disease. Chest. 2007;131(2):446-52. https://doi.org/10.1378/chest.06-1587
4. Reichert J, Araújo AJ, Gonçalves CM, Godoy I, Chatkin JM, Sales MP, et al. Smoking cessation guidelines–2008. J Bras Pneumol. 2008;34(10):845-80. https://doi.org/10.1590/S1806-37132008001000014
5. Emmons KM, Goldstein MG. Smokers who are hospitalized: a window of opportunity for cessation interventions. Prev Med. 1992;21(2):262-9. https://doi.org/10.1016/0091-7435(92)90024-C
6. Molyneux A, Lewis S, Leivers U, Anderton A, Antoniak M, Brackenridge A, et al. Clinical trial comparing nicotine replacement therapy (NRT) plus brief counselling, brief counselling alone, and minimal intervention on smoking cessation in hospital inpatients. Thorax. 2003;58(6):484-8. https://doi.org/10.1136/thorax.58.6.484
7. Simon JA, Carmody TP, Hudes ES, Snyder E, Murray J. Intensive smoking cessation counseling versus minimal counseling among hospitalized smokers treated with transdermal nicotine replacement: a randomized trial. Am J Med. 2003;114(7):555-62. https://doi.org/10.1016/S0002-9343(03)00081-0
8. Rigotti NA, Arnsten JH, McKool KM, Wood-Reid KM, Singer DE, Pasternak RC. The use of nicotine-replacement therapy by hospitalized smokers. Am J Prev Med. 1999;17(4):255-9. https://doi.org/10.1016/S0749-3797(99)00095-1
9. Le Foll B, George TP. Treatment of tobacco dependence: integrating recent progress into practice. CMAJ. 2007;177(11):1373-80. https://doi.org/10.1503/cmaj.070627
10. Rigotti NA, Clair C, Munafò MR, Stead LF. Interventions for smoking cessation in hospitalized patients. Cochrane Database Syst Rev. 2012;(5):CD001837. https://doi.org/ 10.1002/14651858.CD001837.pub2
11. Stramari LM, Kurtz M, Silva LC. Prevalence of and variables related to smoking among medical students at a university in the city of Passo Fundo, Brazil. J Bras Pneumol. 2009;35(5):442-8. https://doi.org/10.1590/S1806-37132009000500009
12. Fagerstrom KO, Schneider NG. Measuring nicotine dependence: a review of the Fagerstrom Tolerance Questionnaire. J Behav Med. 1989;12(2):159-82. https://doi.org/10.1007/BF00846549
13. Araujo RB, Oliveira MS, Moraes JF, Pedroso RS, Port F, De Castro MG. Validation of the Brazilian version of Questionnaire of Smoking Urges-Brief. Rev Psiq Clin. 2007;34(4):166-75. https://doi.org/10.1590/S0101-60832007000400002
14. Mayfield D, McLeod G, Hall P. The CAGE questionnaire: validation of a new alcoholism screening instrument. Am J Psychiatry. 1974;131(10):1121-3.
15. 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;(2):124-32. https://doi.org/10.1590/S1806-37132015000004526
16. Ferreira ÂS, Campos AC, dos Santos IP, Beserra MR, Silva EN, Fonseca VA. Smoking among inpatients at a university hospital. J Bras Pneumol. 2011;37(4):488-94. https://doi.org/10.1590/S1806-37132011000400011
17. Munafò M, Rigotti N, Lancaster T, Stead L, Murphy M. Interventions for smoking cessation in hospitalized patients: a systematic review. Thorax. 2001;56(8):656-63. https://doi.org/10.1136/thorax.56.8.656
18. Warner DO, Patten CA, Ames SC, Offord K, Schroeder D. Smoking behavior and perceived stress in cigarette smokers undergoing elective surgery. Anesthesiology. 2004;100(5):1125-37. https://doi.org/10.1097/00000542-200405000-00014
19. Rigotti NA, Arnsten JH, McKool KM, Wood-Reid KM, Pasternak RC, Singer DE. Smoking by patients in a smoke-free hospital: prevalence, predictors, and implications. Prev Med. 2000;31(2 Pt 1):159-66. https://doi.org/10.1006/pmed.2000.0695

20. Prochaska JJ, Gill P, Hall SM. Treatment of tobacco use in an inpatient psychiatric setting. Psychiatr Serv. 2004;55(11):1265-70. https://doi.org/10.1176/appi.ps.55.11.1265
21. Oliveira MV, Oliveira TR, Pereira CA, Bonfim AV, Leitão Filho FS, Voss LR. Smoking among hospitalized patients in a general hospital. J Bras Pneumol. 2008;34(11):936-41. https://doi.org/10.1590/S1806-37132008001100008
22. Tanni SE, Iritsu NI, Tani M, Camargo PA, Sampaio MG, Godoy I, et al. Evaluation of hospitalized patients in terms of their knowledge related to smoking. J Bras Pneumol. 2010;36(2):218-23. https://doi.org/10.1590/S1806-37132010000200010
23. Bösch D. Smoking habits and teachable moment among hospitalized patients admitted to the internal medicine department. Chest Dis Rep. 2012;2(1):e6. https://doi.org/10.4081/cdr.2012.e6
24. Bolliger CT, van Biljon X, Humair JP, El Fehri V, Cornuz J. Promoting hospital-based smoking cessation services at major Swiss hospitals: a before and after study. Swiss Med Wkly. 2008;138(29-30):427-31.
25. Borglykke A, Pisinger C, Jørgensen T, Ibsen H. The effectiveness of smoking cessation groups offered to hospitalised patients with symptoms of exacerbations of chronic obstructive pulmonary disease (COPD). Clin Respir J. 2008;2(3):158-65. https://doi.org/10.1111/j.1752-699X.2008.00055.x
26. Hjalmarson A, Boëthius G. The effectiveness of brief advice and extended smoking cessation counseling programs when implemented routinely in hospitals. Prev Med. 2007;45(2-3):202-7. https://doi.org/10.1016/j.ypmed.2007.06.014
27. Hajek P, Taylor TZ, Mills P. Brief intervention during hospital admission to help patients to give up smoking after myocardial infarction and bypass surgery: randomized controlled trial. BMJ. 2002;324(7329):87-9. https://doi.org/10.1136/bmj.324.7329.87
28. Wolfenden L, Campbell E, Walsh R, Wiggers J. Smoking cessation interventions for in-patients: a selective review with recommendations for hospital-based health professionals. Drug Alcohol Rev. 2003;22(4):437-52. https://doi.org/10.1080/09595230310001613967
29. Rigotti NA, Munafo MR, Murphy MF, Stead LF. Interventions for smoking cessation in hospitalized patients. Cochrane Database Syst Rev. 2003;(1):CD001837.
30. Rigotti NA, Munafo MR, Stead LF. Interventions for smoking cessation in hospitalized patients. Cochrane Database Syst Rev. 2007;(3):CD001837. https://doi.org/10.1002/14651858.CD001837.pub2
31. Agboola S, McNeill A, Coleman T, Leonardi Bee J. A systematic review of the effectiveness of smoking relapse prevention interventions for abstinent smokers. Addiction. 2010;105(8):1362-80. https://doi.org/10.1111/j.1360-0443.2010.02996.x
32. Ferguson J, Bauld L, Chesterman J, Judge K. The English smoking treatment services: one-year outcomes. Addiction. 2005;100Suppl 2:59-69. https://doi.org/10.1111/j.1360-0443.2005.01028.x
33. Hawkins J, Hollingworth W, Campbell R. Long-term smoking relapse: a study using the British house hold panel survey. Nicotine Tob Res. 2010;12(12):1228-35. https://doi.org/10.1093/ntr/ntq175
34. Hughes JR, Peters EN, Naud S. Relapse to smoking after 1 year of abstinence: a meta-analysis. Addict Behav. 2008;33(12):1516-20. https://doi.org/10.1016/j.addbeh.2008.05.012
35. Goodman MJ, Nadkarni M, Schorling JB. The Natural History of Smoking Cessation Among Medical Patients in a Smoke-Free Hospital. Subst Abus. 1998;19(2):71-79. https://doi.org/10.1080/08897079809511376
36. Wetter DW, Cofta-Gun L, Fouladi RT, Cinciprini PM, Sui D, Gritz ER. Late relapse/sustained abstinence among former smokers: a longitudinal study. Prev Med. 2004;39(6):1156-63. https://doi.org/10.1016/j.ypmed.2004.04.028
37. Gilpin EA, Pierce JP, Farkas AJ. Duration of smoking abstinence and success in quitting. J Natl Cancer Inst. 1997;89(8):572-6. https://doi.org/10.1093/jnci/89.8.572
38. Fernández E, Schiaffino A, Borrell C, Benach J, Ariza C, Ramon JM, et al. Social class, education, and smoking cessation: Long-term follow-up of patients treated at a smoking cessation unit. Nicotine Tob Res. 2006;8(1):29-36. https://doi.org/10.1080/14622200500264432

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ORIGINAL ARTICLE

The triad of obstructive sleep apnea syndrome, COPD, and obesity: sensitivity of sleep scales and respiratory questionnaires

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Study carried out at the Ambulatório de Pneumologia, Hospital Regional de Presidente Prudente; Faculdade de Fisioterapia e Faculdade de Medicina, Universidade do Oeste Paulista – Unoeste – Presidente Prudente (SP) Brasil; and at the Hospital das Clínicas, Faculdade de Medicina de Botucatu, Universidade Estadual Paulista, Botucatu (SP) Brasil.

ABSTRACT

Objective: To investigate whether the presence of obstructive sleep apnea syndrome (OSAS) alters the perception of respiratory symptoms and quality of life in COPD patients, by using specific questionnaires, as well as to determine whether scales for assessing daytime sleepiness and for screening for OSAS can be used in the triad of OSAS, COPD, and obesity. **Methods:** We included 66 patients diagnosed with mild-to-moderate or severe COPD and presenting with a body mass index > 27 kg/m^2. After polysomnography, patients completed the Epworth sleepiness scale (ESS), the Berlin questionnaire (BQ), the modified Medical Research Council (mMRC) scale, the Baseline Dyspnea Index (BDI), and the Saint George's Respiratory Questionnaire (SGRQ). **Results:** Patients were first divided into two groups: COPD + OSAS (n = 46); and COPD-only (n = 20). The COPD + OSAS group was subdivided into a COPD + mild-to-moderate OSAS group (n = 32) and a COPD + severe OSAS group (n = 14), all of which were compared with the COPD-only group. There was a significant difference in mean FEV_1 (L) between the COPD + OSAS groups and the COPD-only group (p = 0.073). The presence of the triad did not lead to significantly higher ESS scores, and scores > 10 had a specificity of 0.58. The BQ did not identify high risk for OSAS in the presence of the triad (specificity of 0.31). There were no significant differences in domain or total scores of the SGRQ between the COPD + OSAS groups and the COPD-only group. **Conclusions:** The confounding factors present in the triad of OSAS, COPD, and obesity prevented the perception of increased daytime sleepiness and high risk for OSAS. We observed no worsening of dyspnea perception or quality of life.

Keywords: Sleep apnea, obstructive; Pulmonary disease, chronic obstructive; Obesity; Surveys and questionnaires.

INTRODUCTION

Obstructive sleep apnea (OSA) is characterized by intermittent partial or complete obstruction of the airways during sleep, being called OSA syndrome (OSAS) when it is associated with daytime/nighttime symptoms and/or comorbidities, such as systemic arterial hypertension or diabetes mellitus.[1] The prevalence of OSAS is as high as 32%[2] in the general population, ranges from 1% to 20% in subjects with COPD (overlap syndrome),[1,3] and is reported to be greater than 60% in subjects with COPD and obesity (triad of COPD, OSAS, and obesity).[4,5] The major daytime symptom of OSAS is sleepiness,[1] which can be assessed by the Epworth sleepiness scale (ESS).[6] The likelihood of having OSAS can be determined by the Berlin Questionnaire,[7] which has been used as a screening instrument; however, the gold standard for diagnosis is overnight polysomnography (PSG).[1,2]

COPD is characterized by lower airway airflow limitation that is not fully reversible,[1] and its prevalence ranges from 8% to 10% in subjects over 40 years of age in developed countries, although it can be as high as 15%.[8,9] The progressive impairment of pulmonary function can proportionally increase exertional dyspnea, which causes changes in and limits activities of daily living (ADL) and leads to functional disability; this has been assessed by the modified Medical Research Council (mMRC) scale[10] and the Baseline Dyspnea Index (BDI).[11] Quality of life in COPD patients has been assessed by the Saint George's Respiratory Questionnaire (SGRQ),[12] and there have been reports of worsening in (increased scores on) all domains of assessment.[13,14]

A combination of diseases can limit the use of sleep scales and respiratory questionnaires. COPD and obesity can contribute to the presence of dyspnea and the sensation of fatigue or tiredness in patients suspected of having OSA.[15] They act as confounding factors that could affect the accuracy of those scales and questionnaires.

In this context, it is necessary to clarify the use of respiratory questionnaires (quality of life and dyspnea) and sleep scales (sleepiness and risk for OSAS) in the triad of COPD, OSAS, and obesity. The combination of COPD, obesity, and OSAS makes it difficult to use the

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Berlin Questionnaire as a screening tool for OSAS, as well as making the ESS lose its specificity. Assessment of functional capacity by the mMRC scale and the BDI, as well as assessment of quality of life by the SGRQ, will be compromised by the presence of OSAS and obesity in combination with COPD.

The objective of the present study was to investigate whether the presence of OSAS alters the perception of respiratory symptoms and quality of life in COPD patients, by using specific questionnaires, as well as to determine whether scales for assessing daytime sleepiness and for screening for OSAS can be used in the triad of OSAS, COPD, and obesity.

METHODS

This study was approved by the Research Ethics Committee of the *Universidade do Oeste Paulista* (Unoeste, Western São Paulo State University), located in the city of Presidente Prudente, Brazil, and by the Research Ethics Committee of the São Paulo State University Botucatu School of Medicine, located in the city of Botucatu, Brazil (*Plataforma Brasil*; Registration no. 0905.1212.7.0000.551). All patients gave written informed consent.

We included 66 COPD patients presenting with a body mass index (BMI) > 27 kg/m^2 and treated at the pulmonology outpatient clinics of either the Regional Hospital of Presidente Prudente or the Unoeste Schools of Medicine and Physiotherapy, or at the Botucatu School of Medicine *Hospital das Clínicas*. COPD severity was classified (as moderate or severe) on the basis of spirometry results, in accordance with the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2016 criteria,[16] with moderate COPD (GOLD II) being defined as 50% ≤ FEV_1 < 80% and severe COPD (GOLD III) being defined as 30% ≤ FEV_1 < 50%.

Patients completed the ESS and the Berlin Questionnaire, which assess sleepiness and risk for the presence of OSAS, respectively. The ESS determines the likelihood of dozing off in eight situations involving ADL, and scores > 10 points correspond to daytime sleepiness.[6] The Berlin Questionnaire comprises questions that investigate snoring, tiredness/fatigue, and the presence of systemic arterial hypertension or obesity, and that are grouped into categories. High risk for OSAS is defined as a positive score on two or more categories.[7] In addition, patients completed the mMRC scale[10] and the BDI[11] to assess the sensation of dyspnea, as well as the SGRQ[12] to measure quality of life.

The first component of the BDI assesses the magnitude of the task triggering dyspnea. The second and third components assess the magnitude of the effort leading to dyspnea and the functional impairment caused by dyspnea, respectively. The total score is obtained by summing the scores for each of the three domains and ranges from 0 to 12. Lower scores indicate greater severity of dyspnea.[11] The mMRC scale, which ranges from 1 to 4, measures the level of dyspnea in four everyday situations. Higher scores indicate greater severity of dyspnea.[10] The SGRQ comprises three domains: symptoms (problems caused by respiratory symptoms); activities (activity restrictions caused by dyspnea); and psychosocial impact (impact of the disease on daily life). The score ranges from 0 (no reduction in quality of life) to 100 (maximum reduction in quality of life).[12]

All patients underwent overnight PSG to confirm the diagnosis of OSAS. On the basis of the PSG results, patients were first divided into two groups: COPD + OSAS (overlap syndrome); and COPD-only; in addition, the overlap syndrome group was subdivided on the basis of the severity of OSAS into COPD + mild-to-moderate OSAS—defined as an apnea-hypopnea index (AHI) between 5 and 30 events/h—and COPD + severe OSAS—defined as an AHI > 30 events/h.[17]

Statistical method

Descriptive statistics were calculated using frequencies and proportions for qualitative variables and using means and standard deviations or medians and interquartile ranges for quantitative variables.

The chi-square test or Fisher's exact test, as appropriate, was used to test the association between the outcome variable and the explanatory variables of interest.

Quantitative variables were tested for normality of distribution, and, for variables that had a normal distribution, ANOVA with Tukey's post hoc test was used for multiple comparison among the groups (COPD + OSAS vs. COPD + mild-to-moderate OSAS vs. COPD + severe OSAS vs. COPD-only). For variables that had a non-normal distribution, a generalized linear model adjusted to gamma distribution was used.

Values of $p < 0.05$ were considered significant. We used the Statistical Analysis System, version 9.3 (SAS Institute Inc., Cary, NC, USA).

RESULTS

We included 66 COPD patients, 46 (69.70%) of whom were diagnosed with overlap syndrome (COPD + OSAS) by PSG. The patients with overlap syndrome were subdivided on the basis of the severity of OSAS into a COPD + mild-to-moderate OSAS group (n = 42; 48.48%) and a COPD + severe OSAS group (n = 14; 21.21%). The groups were homogeneous regarding gender and BMI (Table 1).

All of the selected patients had obstructive lung disease on spirometry. The mean FVC, FEV_1, and FEV_1/FVC ratio, and their respective standard deviations, can be seen in Table 2. Although the mean FVC in L was lowest in the COPD-only group, the mean FVC in % of predicted showed statistical similarity among the groups. The mean FEV_1 in L and the mean FEV_1 in % of predicted were similar among the groups (Table 2).

A diagnosis of overlap syndrome did not lead to statistically significantly higher ESS scores (11.77 ± 4.89 vs. 9.68 ± 5.58), and scores > 10 had an accuracy of 0.57, with a sensitivity and specificity of 0.61 and 0.58, respectively. The Berlin Questionnaire did not identify patients diagnosed with overlap syndrome, although it had a sensitivity of 0.83 for recognition of OSAS and of 100% for recognition of severe OSAS, with a very low specificity and accuracy, 0.31 and 0.63, respectively (Tables 3 and 4). These data suggest that the ESS and the Berlin Questionnaire have no or low accuracy for identification of the overlap syndrome.

ADL-limiting dyspnea was assessed by the mMRC scale, and the values obtained were similar between COPD patients with and without OSAS, regardless of severity. Distribution by BMI category also did not indicate significant differences among the groups.

All domains of the SGRQ had high scores in the different groups evaluated. However, the presence or greater severity of OSAS did not affect the quality of life scores determined by the questionnaire (Table 5).

DISCUSSION

The present study investigated the presence of OSAS in COPD patients, as well as whether a diagnosis of overlap syndrome would worsen the perception of dyspnea, quality of life, and daytime sleepiness, making a research questionnaire a potential tool in the identification of the overlap syndrome. In the present study sample, the ESS was unable to identify increased sleepiness, and the Berlin Questionnaire did not identify increased risk for OSAS, considering the triad of COPD, obesity, and OSAS. The combination of OSAS and obesity in COPD patients did not increase the severity of dyspnea as assessed by the mMRC scale, nor did it increase functional disability as assessed by the BDI. The scores on the domains of the SGRQ were similar between patients with and without OSAS.

The present study found similar ESS scores between patients with and without OSAS, with little likelihood of identifying increased daytime sleepiness. There are controversial data in the literature. In a study by Marin et al.,[18] the mean ESS score was 12 ± 4 and 6 ± 3, respectively, in the presence of overlap

Table 1. Characteristics of the study sample by group.[a]

Variable	Group				p
	COPD + OSAS	COPD + mild-to-moderate OSAS	COPD + severe OSAS	COPD-only	
	(n = 46)	(n = 32)	(n = 14)	(n = 20)	
Prevalence, %	69.70	48.48	21.21	30.30	
Male gender, n (%)	26 (56.52)	16 (50.0)	10 (71.43)	4 (20.0)*	0.006
Age, years	61.56 ± 11.30	63.78 ± 10.82	56.50 ±11.13	59.75 ±9.68	0.163
BMI, kg/m^2	34.00 ± 5.67	32.95 ± 5.34	36.41 ± 5.84	33.89 ±6.75	0.157
AHI, events/h	18.35 (11.05-39.62)	12.95 (9.75-19.97)*	68.55 (41.25-61.22)	1.70 (0.65-2.40)*	0.006

OSAS: obstructive sleep apnea syndrome; BMI: body mass index; and AHI: apnea-hypopnea index. [a]Values expressed as mean ± SD or as median (interquartile range), except where otherwise indicated. *p < 0.05.

Table 2. Spirometric parameters for the study participants by group.[a]

Variable	Group				p
	COPD + OSAS	COPD + mild-to-moderate OSAS	COPD + severe OSAS	COPD-only	
	(n = 46)	(n = 32)	(n = 14)	(n = 20)	
FVC, L	2.54 ± 0.76	2.37 ± 0.68	2.92 ± 0.82[a]	2.16 ± 0.77*	0.002
FVC, % predicted	70.16 ± 17.47	70.38 ± 18.46	69.59 ± 15.23	67.30 ± 21.65	0.522
FEV_1, L	1.63 ± 0.54	1.54 ± 0.48	1.84 ± 0.63	1.39 ± 0.52	0.073
FEV_1, % predicted	56.00 (48.75-65.25)	56.50 (51.25-64.75)	53.50 (37.25-71.75)	51.50 (41.25-64.50)	0.824
FEV_1/FVC, %	65.00 (48.75-65.25)	65.00 (60.00-73.00)	63.50 (58.00-67.25)	63.50 (55.75-73.50)	0.476

OSAS: obstructive sleep apnea syndrome. [a]Values expressed as mean ± SD or as median (interquartile range). *p < 0.05.

Table 3. Results of the Berlin Questionnaire and the Epworth sleepiness scale for the study participants by group.[a]

Variable	Group				p
	COPD + OSAS	COPD + mild-to-moderate OSAS	COPD + severe OSAS	COPD-only	
	(n = 46)	(n = 32)	(n = 14)	(n = 20)	
Berlin Questionnaire, %					
Positive	89	84	100	68	
Negative	11	16	0	31	
ESS, score	11.77 ± 4.89	11.08 ± 4.81	13.50 ± 4.90	9.68 ± 5.58	0.217

OSAS: obstructive sleep apnea syndrome; and ESS: Epworth sleepiness scale. [a]Values expressed as mean ± SD, except where otherwise indicated.

syndrome and in COPD patients with no OSAS. The mean AHI, which was higher in the study by Marin et al.[18] (34 events/h) than it was in our study, may have influenced the observed level of sleepiness. In our study, the COPD + severe OSAS group also had higher scores, but the difference did not reach significance, probably because of the small number of patients in this group (n = 14). In a study by Venkateswaran & Tee,[19] ESS scores were compared in patients diagnosed with OSAS, those diagnosed with overlap syndrome, and those diagnosed with COPD (11.39 vs. 13.89 vs. 4.84) and were found to be highest in the overlap syndrome group. Shiina et al.[20] reported no such finding. In their study, including 524 individuals with OSAS, 64 patients (12%) were diagnosed with overlap syndrome, with a mean ESS of 9.0 (range, 6.0-13.0) in the OSAS group and a mean ESS of 7.0 (range, 4.5-11.0) in the overlap syndrome group ($p < 0.05$). The mean BMI of the patients in the overlap syndrome group was 24.8 kg/m^2, which is different from that found in our study, and may have contributed to the finding of lower scores. Steveling et al.[21] found only 20% of patients with ESS scores > 10 in the population diagnosed with overlap syndrome, although it included only obese patients with an AHI > 10 events/h. In a study by Faria et al.,[22] 40% of the patients had that characteristic, but the mean BMI in the overlap syndrome group was considered normal. In our sample, daytime sleepiness was found not only in patients with overlap syndrome, with 60% of our population having ESS scores > 10, but also in patients with no OSAS (in 40%). We believe that our study included patients with more severe COPD, with overlap of limitation of daytime activities and the subjective perception of sleepiness.

Subjective assessment of sleepiness with the ESS as a predictor of OSAS has been questioned in the literature. Ulasli et al.[23] found a sensitivity of 45% and a specificity of 60% in populations with OSAS, which were both even lower than those found in our study (62.8% and 57.8%, respectively), and questioned the applicability of the ESS as a screening tool. Similarly, in our study, the Berlin Questionnaire was found to be ineffective as a screening instrument for OSAS in COPD patients. Although the Berlin Questionnaire identified the presence of severe OSAS in COPD patients, it was unable to recognize patients without a diagnosis of overlap syndrome or those with mild-to-moderate OSAS. We believe that the questions regarding "fatigue" and "tiredness" (category 2) may be a confounding factor for COPD patients, who frequently have these complaints because of the limitation in performing ADL. Similar data were observed by Mahamoud et al.,[24] who identified high risk for OSAS in 70% of their sample of COPD patients. However, in the study by Faria et al.,[22] high risk for OSAS was identified in fewer patients (in 32.5% of the sample), which may be explained by the fact that all patients with overlap syndrome who were evaluated had normal BMI, which directly influences category 3 of the Berlin Questionnaire.

The presence or absence of OSAS did not influence the sensation of dyspnea or health status of COPD patients, as assessed by the mMRC scale. The mMRC scale is strongly related to dyspnea-induced limitations in ADL, and dyspnea is not a typical symptom in patients with OSAS.

The impact of dyspnea was similar as assessed by the BDI and the mMRC scale. A diagnosis of overlap syndrome did not lead to an increased sensation of dyspnea. Once again, it is clear that dyspnea is not a symptom commonly reported by individuals with OSAS.

In the three domains of assessment (symptoms, activities, and impact), as well as in the total score, quality of life as measured by the SGRQ was similar, regardless of the presence or severity of OSAS in the COPD patients. Scores > 25 were found, which is common among COPD patients,[13,14] and were also present in those with overlap syndrome. Therefore, the SGRQ was not sensitive enough to assess the presence of OSAS and obesity in combination with COPD.

Mermigkis et al.[25] observed that quality of life as assessed by the SGRQ was worse in patients with overlap syndrome than in COPD patients. However, the

Table 4. Accuracy, sensitivity, and specificity for the use of the Epworth sleepiness scale and the Berlin Questionnaire in the study sample of COPD patients with and without obstructive sleep apnea syndrome (n = 66).

Variable	Epworth sleepiness scale	Berlin Questionnaire
Accuracy	0.57	0.63
Sensitivity	0.61	0.83
Specificity	0.58	0.31

Table 5. Domain and total scores on the Saint George's Respiratory Questionnaire, by group.[a]

Variable	Group				p
	COPS + OSAS (n = 46)	COPD + mild-to-moderate OSAS (n = 32)	COPD + severe OSAS (n = 14)	COPD-only (n = 20)	
Symptoms domain	52.93 ± 24.43	49.36 ± 26.73	63.64 ± 11.51	48.96 ± 25.50	0.606
Activities domain	70.14 ±17.89	72.46 ±19.02	63.18 ± 12.84	73.56 ± 15.71	0.605
Impact domain	39.38 ± 16.03	40.20 ± 15.96	36.91 ± 17.49	45.74 ± 24.08	0.719
Total score	50.97 ± 15.99	51.47 ±17.10	54.72 ± 13.36	54.92 ±18.40	0.889

OSAS: obstructive sleep apnea syndrome. [a]Values expressed as mean ± SD.

mean FEV_1 in % of predicted was lower in the COPD group than in the overlap syndrome group (48.2% vs. 49.1%), which may have contributed to the worsened perception of quality of life.

The present study has various limitations. The study population is small in number, which may be a limitation for statistical analysis. We also believe that, because of the open invitation for participation in the study and the lack of randomization of outpatients, patients with more frequent symptoms and greater concern about having OSAS may have accepted the invitation, which would explain the high prevalence of overlap syndrome in our sample. However, data collection was blinded to the PSG results, which maintained the impartiality of the researchers.

In conclusion, the ESS and the Berlin Questionnaire as screening tools were unable to identify the presence of OSAS in patients with the triad of COPD, obesity, and OSAS in our sample. The mMRC scale and the BDI did not indicate poorer perception of dyspnea in ADL, nor was the SGRQ able to identify worsening of quality of life. Current instruments for clinical assessment of daytime sleepiness, risk for OSAS, effects of dyspnea on ADL, and quality of life do not allow recognition of the presence of OSAS in COPD patients, and its diagnosis depends on PSG.

REFERENCES

1. McNicholas WT. Chronic obstructive pulmonary disease and obstructive sleep apnoea-the overlap syndrome. J Thoracic Dis. 2016;8(2):236-42.
2. 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. https://doi.org/10.1016/j.sleep.2009.10.005
3. Chaouat A, Weitzenblum E, Kessler R, Charpentier C, Enhart M, Schott R. A randomized trial of nocturnal oxygen therapy in chronic obstructive pulmonary disease patients. Eur Respir J. 1999;14(5):1002-8. https://doi.org/10.1183/09031936.99.14510029
4. Povitz M, James MT, Pendharkar SR, Raneri J, Hanly PJ, Tsai WH. Prevalence of Sleep-disordered Breathing in Obese Patients with Chronic Hypoxemia. A Cross-Sectional Study. Ann Am Thorac Soc. 2015:12(6):921-7. https://doi.org/10.1513/AnnalsATS.201412-551OC
5. Soler X, Gaio E, Powell LF, Ramsdell JW, Loredo JS, Malhotra A, et al. High Prevalence of Obstructive Sleep Apnea in Patients with Moderate to Severe Chronic Obstructive Pulmonary Disease. Ann Am Thorac Soc. 2015;12(8):1219-25.
6. Bertolazi AN, Fagondes SC, Hoff LS, Pedro VD, Menna Barreto SS, Johns MW. Portuguese-language version of the Epworth sleepiness scale: validation for use in Brazil. J Bras Pneumol. 2009;35(9):877-83. https://doi.org/10.1590/S1806-37132009000900009
7. Netzer NC, Stoohs RA, Netzer CM, Clark K, Strohl KP. Using the Berlin questionnaire to identify patients at risk for the sleep apnea syndrome. Ann Intern Med. 1999;131(7):485-91. https://doi.org/10.7326/0003-4819-131-7-199910050-00002
8. Bednarek M, Plywaczewsk R, Jonczak L, Zielinsk J. There is no relationship between chronic obstructive pulmonary disease and obstructive sleep apnea syndrome: a population study. Respiration. 2005;72(2):142-9. https://doi.org/10.1159/000084044
9. Menezes AM, Perez-Padilla R, Jardim JR, Muiño A, Lopez MV, Valdivia G, et al. Chronic obstructive pulmonary disease in five Latin American cities (the PLATINO study): a prevalence study. Lancet. 2005;366(9500):1875-81. https://doi.org/10.1016/S0140-6736(05)67632-5
10. Kovelis D, Segretti NO, Probst VS, Lareau SC, Brunetto AF, Pitta F. Validation of the Modified Pulmonary Functional Status and Dyspnea Questionnaire and the Medical Research Council scale for use in Brazilian patients with chronic obstructive pulmonary disease. J Bras Pneumol. 2008;34(12):1008-18. https://doi.org/10.1590/S1806-37132008001200005
11. Mahler DA, Weinberg DH, Wells CK, Feinstein AR. The measurement of dyspnea. Contents, interobserver agreement, and physiologic correlates of two new clinical indexes. Chest. 1984;85(6):751-8. https://doi.org/10.1378/chest.85.6.751
12. Camelier A, Rosa FW, Salmi C, Nascimento OA, Cardoso F, Jardim JR. Using the Saint George's Respiratory Questionnaire to evaluate quality of life in patients with chronic obstructive pulmonary disease: validating a new version for use in Brazil. J Bras Pneumol. 2006;32(2):114-22. https://doi.org/10.1590/S1806-37132006000200006
13. Agusti A, Calverley PM, Celli B, Coxson HO, Edwards LD, Lomas DA, et al. Characterisation of COPD heterogeneity in the ECLIPSE cohort. Respir Res. 2010;11:122. https://doi.org/10.1186/1465-9921-11-122
14. Miravitlles M, Soriano JB, García-Rio F, Mu-oz L, Duran-Tauleria E, Sanchez G, et al. Prevalence of COPD in Spain: impact of undiagnosed COPD on quality of life and daily life activities. Thorax. 2009;64(10):863-8. https://doi.org/10.1136/thx.2009.115725
15. Koutsourelakis I, Perraki E, Bonakis A, Vagiakis E, Roussos C, Zakynthinos S. Determinants of subjective sleepiness in suspected obstructive sleep apnoea. J Sleep Res. 2008;17(4):437-43. https://doi.org/10.1111/j.1365-2869.2008.00663.x
16. Global Initiative for Chronic Obstructive Lung Disease - GOLD [homepage on the Internet]. Bethesda: Global Initiative for Chronic Obstructive Lung Disease [cited 2016 Jun 24]. Global Strategy for the Diagnosis, Management, and Prevention of COPD 2016. Available from: http://goldcopd.org/global-strategy-diagnosis-management-prevention-copd-2016/
17. American Academy of Sleep Medicine. The International Classification of Sleep Disorders. Diagnostic and Coding Manual. Westchester (IL): American Academy of Sleep Medicine; 2005.
18. Marin JM, Soriano JB, Carrizo SJ, Boldova A, Celli B. Outcomes in patients with chronic obstructive pulmonary disease and obstructive sleep apnea: the overlap syndrome. Am J Respir Crit Care Med. 2010;182(3):325-31. https://doi.org/10.1164/rccm.200912-1869OC
19. Venkateswaran S, Tee A. Overlap syndrome between chronic obstructive pulmonary disease and obstructive sleep apnoea in a Southeast Asian teaching hospital. Singapore Med J. 2014;55(9):488-92. https://doi.org/10.11622/smedj.2014117
20. Shiina K, Tomiyama H, Takata Y, Yoshida M, Kato K, Nishihata Y, et al. Overlap syndrome: additive effects of COPD on the cardiovascular damages in patients with OSA. Respir Med. 2012;106(9):1335-41. https://doi.org/10.1016/j.rmed.2012.05.006
21. Steveling EH, Clarenbach CF, Miedinger D, Enz C, Dürr S, Maier S, et al. Predictors of the overlap syndrome and its association with comorbidities in patients with chronic obstructive pulmonary disease. Respiration. 2014;88(6):451-7. https://doi.org/10.1159/000368615
22. Faria AC, da Costa CH, Rufino R. Sleep Apnea Clinical Score, Berlin Questionnaire, or Epworth Sleepiness Scale: which is the best obstructive sleep apnea predictor in patients with COPD? Int J Gen Med. 2015;8:275-81.
23. Ulasli SS, Gunay E, Koyuncu T, Akar O, Halici B, Ulu S, et al. Predictive value of Berlin Questionnaire and Epworth Sleepiness Scale for obstructive sleep apnea in a sleep clinic population. Clin Respir J. 2014;8(3):292-6. https://doi.org/10.1111/crj.12070
24. Mahamoud HA, Sallama SS, Ahmad AM. Validation of the Epworth sleepiness scale, Berlin, STOPBANG questionnaires and American Society of Anesthesiologists checklist as screening tools for obstructive sleep apnea in patients with chronic obstructive pulmonary disease, asthma and cardiovascular disease. Eur Respir J. 2013;42:P2032.
25. Mermigkis C, Kopanakis A, Foldvary-Schaefer N, Golish J, Polychronopoulos V, Schiza S, et al. Health-related quality of life in patients with obstructive sleep apnoea and chronic obstructive pulmonary disease (overlap syndrome). Int J Clin Pract. 2007;61(2):207-11. https://doi.org/10.1111/j.1742-1241.2006.01213.x

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ORIGINAL ARTICLE

Obesity and asthma: clinical and laboratory characterization of a common combination

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ABSTRACT

Objective: To evaluate the relationship between obesity and asthma. **Methods:** This was a preliminary cross-sectional analysis involving 925 subjects with mild-to-moderate or severe asthma evaluated between 2013 and 2015. Obesity was defined on the basis of body mass index (BMI) and abdominal circumference. We collected clinical, laboratory, and anthropometric parameters, as well as pulmonary function test results and data regarding comorbidities. The subjects also completed asthma control and quality of life questionnaires. **Results:** Obese individuals had a significantly higher number of neutrophils in peripheral blood than did nonobese individuals (p = 0.01). Among the obese individuals, 163 (61%) had positive skin-prick test results, as did 69% and 71% of the individuals classified as being overweight or normal weight, respectively. Obese individuals showed lower spirometric values than did nonobese individuals, and 32% of the obese individuals had uncontrolled asthma, a significantly higher proportion than that found in the other groups (p = 0.02). **Conclusions:** Obese individuals with asthma seem to present with poorer asthma control and lower pulmonary function values than do nonobese individuals. The proportion of subjects with nonatopic asthma was higher in the obese group. Our results suggest that obese individuals with asthma show a distinct inflammatory pattern and are more likely to present with difficult-to-control asthma than are nonobese individuals.

Keywords: Asthma; Obesity; Overweight; Eosinophilia.

INTRODUCTION

Asthma and obesity are very prevalent diseases and are considered public health problems. Evidence from cross-sectional studies suggests that obese individuals are at increased risk of asthma and that obese individuals with asthma have more severe asthma, experience a greater number of hospitalizations, and make a greater number of emergency room visits.[1,2] However, the causal association of obesity with asthma prevalence and severity remains an object of study.

Studies aimed at clarifying the relationship between obesity and asthma have suggested that obesity has effects on respiratory mechanics, alters immune response, and has metabolic implications.[1,3-5] There is evidence that obesity increases the inflammatory process in the lungs of subjects with asthma. Pro-inflammatory mediators are directly correlated with abdominal visceral fat and can lead to increased bronchial hyperresponsiveness and bronchospasm.[6,7] Cross-sectional studies have also suggested that obese individuals with asthma have airway inflammation that is more neutrophilic than eosinophilic.[7,8]

Studies evaluating the relationship between obesity and asthma control have reported controversial findings.[9,10] In addition, there have been few studies evaluating the effects of obesity on the immunopathology of asthma. Therefore, the objective of the present study was to

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evaluate the relationship between obesity and asthma, regarding peripheral eosinophilia and neutrophilia, atopy, asthma severity, asthma control, and late-onset asthma.

METHODS

Study design

This was a cross-sectional study evaluating subjects with mild-to-moderate or severe asthma. A total of 925 subjects treated by the Brazilian Unified Health Care System in the city of Salvador, Brazil, participated in the study. Participants were selected between January 2013 and July 2015 and were evaluated at the Federal University of Bahia Center of Excellence in Asthma, located in that same city. This study is part of a more comprehensive project, called "*Fatores de risco, biomarcadores e endofenótipos da asma grave*" (Risk factors and biomarkers for and endophenotypes of severe asthma) that was approved by the Brazilian National Research Ethics Committee (Ruling/Resolution no. 450/2010) and the Research Ethics Committee of the Federal University of Bahia Climério de Oliveira Maternity Hospital (Additional Resolution no. 095/2012).

Study population

Posters were placed in areas heavily used by pedestrians and in public transport vehicles, in order to recruit subjects with mild-to-moderate asthma throughout the city of Salvador. In addition, the research team advertised the study among patients and physicians at the primary care clinics affiliated with the public health care system in the city of Salvador, and interviews were conducted in the waiting rooms of those clinics. Subjects with severe asthma were selected from the cohort of subjects enrolled in the *Programa para o Controle da Asma na Bahia* (ProAR, Bahia State Program for the Control of Asthma), which is a major referral program providing specialized care in the treatment of severe asthma in the city of Salvador.[11]

The inclusion criteria were having physician-diagnosed asthma and being ≥ 18 years of age. All participants gave written informed consent. The exclusion criteria were being pregnant, having any disease severe enough to make it difficult to assess asthma symptoms or any other disease that causes dyspnea.

The subjects with mild-to-moderate asthma recruited from the community and primary care clinics were referred to a specialist at the *Núcleo de Excelência em Asma*-ProAR (NEA, Center of Excellence in Asthma-ProAR) at the Federal University of Bahia for confirmation of the diagnosis of asthma. For the subjects with severe asthma recruited from the cohort of subjects enrolled in the ProAR, the diagnosis of asthma was validated by two specialists at the NEA-ProAR. The specialists evaluated the subjects and reviewed their medical charts in order to confirm the diagnosis of asthma. The criteria for diagnosing asthma were typical symptoms, symptomatic improvement with a bronchodilator or an inhaled corticosteroid, and a 12% and 200 mL increase in FEV_1 after bronchodilator use.

The subjects were classified as having mild-to-moderate asthma in accordance with the 2006 Global Initiative for Asthma guidelines[12] in order to use similar criteria to those used among the subjects with severe asthma, whose asthma severity was evaluated in accordance with the 2002 Global Initiative for Asthma guidelines,[13] which were in effect at the time the ProAR was established, and who fit the category of having untreated severe asthma as per the classification proposed to the World Health Organization in 2010.[14]

Study procedures

All subjects underwent blood collection, spirometry,[15,16] immediate skin-prick testing,[17] clinical evaluation by a specialist, and collection of fasting anthropometric measurements.

All subjects also completed the following questionnaires: the six-item Asthma Control Questionnaire[18]; the Asthma Quality of Life Questionnaire[19]; the Symptom Questionnaire for Gastroesophageal Reflux Disease[20]; and the Beck Depression Inventory.[21]

Definitions

Subjects with difficult-to-control asthma are those whose lack of asthma control is due to factors such as low adherence to medication, poor inhaler technique, environmental exposure, psychosocial problems, or comorbidities.[14]

Uncontrolled asthma was defined as a score ≥ 1.5 on the six-item Asthma Control Questionnaire.[18]

A high dose of inhaled corticosteroid was defined as use of more than 800 µg of budesonide daily.[22]

The criteria for the presence of airway obstruction were an FEV_1 < 80% of predicted and an FEV_1/FVC ratio below the lower limit of normal.[23] This limit is adjusted for age, being obtained on the basis of the fifth percentile of healthy nonsmokers.

The criterion for the presence of atopy was a positive, immediate skin-prick test result. A test result was considered positive if the wheal to any allergen tested was ≥ 3 mm. The antigens tested were *Dermatophagoides pteronyssinus*, *Aspergillus flavus, Dermatophagoides farinae, Aspergillus fumigatus, Blomia tropicalis, Aspergillus niger*, cat dander, *Alternaria alternata*, dog dander, *Blatella germanica*, *Cladosporium herbarum*, *Periplaneta americana*, *Paspalum notatum*, and *Cynodon dactylon*.[17]

Late-onset asthma was defined as asthma diagnosed at age 18 years or older.[24] Eosinophilic asthma was defined as a peripheral blood eosinophil count greater than 260 cells/µL. Zhang et al.,[25] demonstrated that this cut-off point of peripheral blood eosinophil count has good ability to detect induced sputum eosinophilia.

The diagnostic criterion for comorbidities (hypertension, dyslipidemia, and/or diabetes) was a positive report of use of specific medications for each of those diseases.

Body weight was measured with a digital scale (Tanita, Arlington Heights, IL, USA), and height was measured with a wall-mounted wooden stadiometer graduated in cm from 40 to 220. Body mass index was calculated as body weight in kilograms divided by height in meters squared.[26] Obesity was defined on the basis of BMI (kg/m^2) in accordance with the World Health Organization criteria—underweight: BMI < 18.5; normal weight: 18.5 ≤ BMI ≤ 24.9; overweight: 25 ≤ BMI ≤ 29.9; and obesity: BMI ≥ 30.[26] Abdominal obesity was classified using abdominal circumference (AC), which was measured at the midpoint between the lowest rib and the iliac crest. Abdominal obesity was defined as an AC ≥ 80 cm in women and ≥ 90 cm in men.[27]

Statistical analysis

We used the Statistical Package for the Social Sciences for Windows, version 17.0 (SPSS Inc., Chicago, IL, USA). Associations were analyzed by BMI group and by abdominal obesity group. The chi-square test was used to detect associations between dichotomous variables, and the nonparametric Kruskal-Wallis test was used to compare three or more independent groups on continuous or ordinal variables. The Mann-Whitney test was used to compare two groups on continuous and ordinal variables with non-normal distribution. Continuous and ordinal variables are presented as mean and standard deviation and as median and interquartile range, respectively. Categorical variables are presented as absolute numbers and percentages.

RESULTS

We included 925 subjects with asthma, and, of those, 299 were obese according to their BMI. Table 1 presents the characteristics of participants by BMI group. As can be seen in this table, BMI was associated with gender, age, level of education, comorbidities, atopy, dose of inhaled corticosteroid, eosinophilic phenotype, and peripheral blood neutrophils ($p < 0.05$).

Table 2 also presents data on participants by BMI group. Although BMI was associated with various pulmonary function parameters ($p < 0.05$), there was no significant difference in the frequency of airway obstruction among the groups. BMI was associated with asthma symptoms, asthma-related quality of life, asthma exacerbations, and difficult-to-treat asthma ($p < 0.05$).

Tables 3 and 4 present data on participants by abdominal obesity group. The groups differed in gender, age, level of education, late-onset asthma, comorbidities, atopy, dose of inhaled corticosteroid, eosinophilic phenotype, pulmonary function, asthma symptoms, asthma-related quality of life, and frequency of exacerbations ($p < 0.05$).

DISCUSSION

Our findings indicated that obese subjects with asthma had a higher number of neutrophils and a lower number of eosinophils in peripheral blood compared with nonobese subjects with asthma. These observations suggest that asthma in obese individuals more commonly has a noneosinophilic immunopathological mechanism. This helps understand why obese subjects have more severe asthma, given that eosinophilic airway inflammation has better response to inhaled corticosteroid therapy.[7,8,10,28]

In our study, we analyzed immediate skin-prick test results because a positive result on this test is a

Table 1. Sociodemographic, clinical, and laboratory characteristics of the subjects included in the study, by body mass index group.[a]

Variable	BMI group				p*
	Underweight (n = 20)	Normal weight (n = 286)	Overweight (n = 319)	Obese (n = 299)	
Female gender	17 (85)	203 (71)	245 (77)	266 (89)	< 0.01
Age, years	34 ± 19	40 ± 16	47 ± 14	47 ± 13	< 0.01
Low level of education[b]	3 (15)	26 (9)	47 (15)	54 (18)	0.02
Late-onset asthma (≥ 18 years)	4 (20)	90 (31)	120 (38)	92 (31)	0.14
Comorbidities[c]	2 (10)	61 (21)	130 (41)	171 (57)	< 0.01
Diagnosis of rhinitis	18 (90)	258 (91)	300 (94)	277 (93)	0.42
Positive skin-prick test result	10 (50)	191 (67)	199 (62)	163 (55)	0.03
Diagnosis of GERD	8 (40)	101 (35)	141 (44)	149 (66)	0.38
Severe depression[d]	0 (0)	10 (4)	21 (7)	26 (9)	< 0.01
High dose of asthma medication[e]	4 (20)	102 (36)	158 (50)	173 (58)	< 0.01
Total serum IgE, IU/mL	237 (39-642)	291 (115-542)	261 (100-451)	269 (105-530)	0.64
Eosinophils ≥ 260 cells/μL	15 (75)	141 (49)	141 (44)	134 (45)	0.02
Eosinophils, cells/μL	433 (251-579)	258 (137-401)	232 (130-378)	240 (139-383)	0.01
Neutrophils, cells/μL	2,641 (1,922-4,938)	3,399 (2,470-4,338)	3,431 (2,394-4,533)	3,711 (2,765-4,942)	0.01

BMI: body mass index; and GERD: gastroesophageal reflux disease. [a]Values expressed as n (%), as mean ± SD, or as median (interquartile range). [b]Low level of education: being illiterate or having had fewer than 5 years of schooling. [c]Comorbidities: hypertension, diabetes, and/or dyslipidemia. [d]Severe depression: severe level of depression as assessed by the Beck Depression Inventory. [e]High dose of medication: based on use of inhaled corticosteroids. *Chi-square test for categorical variables and Kruskal-Wallis test for continuous variables.

Table 2. Spirometric values and asthma severity parameters in the subjects included in the study, by body mass index group.[a]

Variable	BMI group				p*
	Underweight (n = 20)	Normal weight (n = 286)	Overweight (n = 319)	Obese (n = 299)	
Post-BD FVC, % of predicted	82 (70-93)	87 (79-95)	86 (78-95)	83 (75-92)	< 0.01
Post-BD FEV_1, % of predicted	75 (62-95)	82 (70-92)	79 (67-90)	75 (63-88)	< 0.01
Post-BD $FEF_{25-75\%}$, % of predicted	70 (46-90)	73 (44-98)	67 (35-94)	62 (36-91)	0.02
Post-BD FEV_1/FVC, % of predicted	0.9 (0.7-0.9)	0.8 (0.7-0.9)	0.8 (0.6-0.8)	0.8 (0.7-0.8)	< 0.01
Airway obstruction[b]	3 (15)	35 (12)	53(17)	34 (11)	0.26
ACQ-6 score ≥ 1.5	4 (20)	63 (22)	75 (24)	97 (32)	0.02
AQLQ score	5.0 (3.7-5.9)	5 (4-6)	4.8 (3.7-5.8)	4.5 (3.3-5.4)	< 0.01
Oral corticosteroid use for asthma in the past year	9 (45)	100 (35)	126 (40)	151 (51)	< 0.01
Severe difficult-to-treat asthma	6 (30)	97 (34)	147 (46)	179 (60)	0.03

BMI: body mass index; BD: bronchodilator; ACQ-6: 6-item Asthma Control Questionnaire; AQLQ: Asthma Quality of Life Questionnaire; and GERD: gastroesophageal reflux disease. [a]Values expressed as n (%) or as median (interquartile range). [b]FEV_1 < 80% and FEV_1/FVC < the lower limit of normal.[23] *Kruskal-Wallis test for continuous variables and chi-square test for categorical variables.

Table 3. Sociodemographic, clinical, and laboratory characteristics of the subjects included in the study, by abdominal obesity group.[a]

Variable	Without abdominal obesity (n = 258)	With abdominal obesity (n = 667)	p*
Female gender	167 (65)	564 (85)	< 0.01
Age, years	36 ± 15	48 ± 14	< 0.01
Low level of education[b]	16 (6)	114 (17)	< 0.01
Late-onset asthma (≥ 18 years)	67 (26)	239 (36)	< 0.01
Comorbidities[c]	37 (14)	327 (49)	< 0.01
Diagnosis of rhinitis	234 (91)	620 (93)	0.13
Positive skin-prick test result	174 (67)	389 (58)	0.01
Diagnosis of GERD	96 (37)	303 (45)	0.31
Severe depression[d]	4 (2)	53 (8)	< 0.01
High dose of asthma medication[e]	75 (29)	362 (54)	< 0.01
Total serum IgE, IU/mL	300 (114-566)	262 (103-498)	0.20
Eosinophils ≥ 260 cells/μL	138 (54)	294 (45)	0.01
Eosinophils, cells/μL	282 (143-464)	236 (132-379)	0.05
Neutrophils, cells/μL	3,326 (2,404-4,387)	3,581 (2,529-4,663)	0.09

GERD: gastroesophageal reflux disease. [a]Values expressed as n (%), as mean ± SD, or as median (interquartile range). [b]Low level of education: being illiterate or having had fewer than 5 years of schooling. [c]Comorbidities: hypertension, diabetes, and/or dyslipidemia. [d]Severe depression: severe level of depression as assessed by the Beck Depression Inventory. [e]High dose of medication: based on use of inhaled corticosteroids. *Chi-square test for categorical variables and Kruskal-Wallis test for continuous variables.

marker of atopy; however, obesity was associated with negative skin-prick test results. Similar findings have been observed previously, with obesity defined either by BMI or AC; however, the mechanisms involving this association remain unknown.[29-31] Interestingly, we found no association between obesity and total peripheral blood IgE, which is also a marker of atopy. Further studies are needed to investigate whether obese individuals with asthma have lower levels of systemic Th2 immune activity or whether the association between asthma and negative skin-prick test results is due to specificities related to excess of subcutaneous adipose tissue.

Our findings also indicated an association between obesity and severe difficult-to-treat asthma. The obese individuals in our sample also had higher scores on the symptom questionnaire, poorer quality of life, and more frequent asthma exacerbations requiring oral corticosteroids than did the nonobese individuals. Although other authors have also observed these associations,[8,32] the present study contributes to the medical literature because it included a large sample of individuals with a broad spectrum of asthma severity, recruited from a referral center and the community. In addition, the subjects in the present study were followed by specialists and were provided free-of-charge treatment to control their asthma symptoms, which was not ensured in previous studies.

The obese individuals with asthma in the present study, when considering either BMI or AC, used higher doses of inhaled corticosteroids to control their asthma. This increased dependence on inhaled corticosteroids might

Table 4. Spirometric values and asthma severity parameters in the subjects included in the study, by abdominal obesity group.[a]

Variable	Without abdominal obesity (n = 258)	With abdominal obesity (n = 667)	p*
Post-BD FVC, % of predicted	87 (80-95)	85 (76-93)	< 0.01
Post-BD FEV_1, % of predicted	84 (72-94)	77 (64-89)	< 0.01
Post-BD $FEF_{25-75\%}$, % of predicted	78 (54-101)	62 (35-91)	< 0.01
Post-BD FEV_1/FVC, % of predicted	0.8 (0.7-0.9)	0.8 (0.6-0.8)	< 0.01
Airway obstruction[b]	29 (11)	96 (14)	0.11
ACQ-6 score ≥ 1.5	47 (18)	192 (29)	< 0.01
AQLQ score	5.1 (4.2-6.0)	4.6 (3.4-5.6)	< 0.01
Oral corticosteroid use for asthma in the past year	90 (35)	296 (44)	< 0.01
Severe difficult-to-treat asthma	77 (29)	352 (53)	0.63

BD: bronchodilator; ACQ-6: 6-item Asthma Control Questionnaire; and AQLQ: Asthma Quality of Life Questionnaire. [a]Values expressed as n (%) or as median (interquartile range). [b]FEV_1 < 80% and FEV_1/FVC < lower limit of normal.[23] *Kruskal-Wallis for continuous variables and chi-square test for categorical variables.

be related to the lower frequency of noneosinophilic asthma in our sample of obese individuals, given that individuals with noneosinophilic asthma tend to have poorer response to corticosteroid therapy and, therefore, require higher doses of medication to control inflammation.[10,33]

Previous studies have demonstrated a relationship between age at asthma onset and the severity of respiratory symptoms in obese individuals.[30,34] We found no association between obesity and late-onset asthma in our sample. This is an important observation because it indicates that age at symptom onset did not bias the relationship between obesity and asthma severity in our study.

Data in the literature show that, in terms of pulmonary function, obese individuals have restrictive lung disease, probably because of changes in body structure.[35,36] Although we did not measure lung volumes to confirm the presence of restrictive lung disease, decreased FVC values in obese individuals indicate a higher frequency of restrictive lung disease than that found in nonobese individuals. We also observed that, when obesity was defined on the basis of AC, lung volumes were lower. The literature reports that increased abdominal adiposity may reflect poorer pulmonary function.[31] The pathophysiological mechanism of more severe asthma in obese individuals might be in part related to structural changes in the rib cage rather than exclusively to a lower airway pathology. This hypothesis is supported by the lack of association between obesity and obstructive lung disease in our sample.

Obese individuals with asthma had a higher frequency of comorbidities. Obesity is associated with an increased frequency of comorbidities in individuals without asthma; therefore, our findings were expected.[37,38] Comorbidities might contribute to a change in asthma severity in obese individuals, which may be clarified in future studies.

One strength of the present study is that we evaluated subjects recruited from the community and from primary and secondary care clinics, which increases the external validity of the findings. Another strength is that the diagnosis of asthma was validated by a specialist. In the case of severe asthma, it is important to make the differential diagnosis with COPD and other respiratory diseases, and that diagnosis was validated by two specialists to avoid the inclusion of patients without asthma. However, as in all cross-sectional studies, it was not possible to explore the causal relationship between obesity and the study variables. A question arises as to whether neutrophilic inflammation is a different phenotype of obese individuals with asthma or is also a characteristic of obese individuals without asthma. This question still represents a gap in current knowledge and may be answered by analyzing data on individuals without asthma.

In conclusion, we found that obese subjects with asthma have poorer asthma control and poorer quality of life, require higher doses of inhaled corticosteroid, and experience a reduction in some pulmonary function parameters, such as FVC. In addition, we found a smaller proportion of subjects with eosinophilic asthma and a lower frequency of atopy among obese individuals with asthma. Therefore, our study can satisfactorily validate data on a common combination in a Brazilian population and may help improve knowledge about the influence of obesity on asthma. However, the clinical relevance of these observations should be interpreted with caution and should be examined in future studies with analyses specific to that end.

REFERENCES

1. Baffi CW, Winnica DA, Holguin F. Asthma and obesity: mechanisms and clinical implications. Asthma Res Pract. 2015;1:1. https://doi.org/10.1186/s40733-015-0001-7
2. Barros LL, Souza-Machado A, Corrêa LC, Santos JS, Cruz C, Leite M, et al. Obesity and poor asthma control in patients with severe asthma. J Asthma. 2011;48(2):171-6. https://doi.org/10.3109/02770903.2011.554940
3. Capelo AV, Fonseca VM, Peixoto VM, Carvalho SR, Guerino LG.

Central obesity and other factors associated with uncontrolled asthma in women. Allergy Asthma Clin Immunol. 2015;11(1):12. https://doi.org/10.1186/s13223-015-0076-y

4. Dias-Júnior SA, Reis M, de Carvalho-Pinto RM, Stelmach R, Halpern A, Cukier A. Effects of weight loss on asthma control in obese patients with severe asthma. Eur Respir J. 2014;43(5):1368-77. https://doi.org/10.1183/09031936.00053413
5. Lavoie KL, Bacon SL, Labrecque M, Cartier A, Ditto B. Higher BMI is associated with worse asthma control and quality of life but not asthma severity. Respir Med. 2006;100(4):648-57. https://doi.org/10.1016/j.rmed.2005.08.001
6. Arteaga-Solis E, Zee T, Emala CW, Vinson C, Wess J, Karsenty G. Inhibition of leptin regulation of parasympathetic signaling as a cause of extreme body weight-associated asthma. Cell Metab. 2013;17(1):35-48. https://doi.org/10.1016/j.cmet.2012.12.004
7. Scott HA, Gibson PG, Garg ML, Wood LG. Airway inflammation is augmented by obesity and fatty acids in asthma. Eur Respir J. 2011;38(3):594-602. https://doi.org/10.1183/09031936.00139810
8. van Veen IH, Ten Brinke A, Sterk PJ, Rabe KF, Bel EH. Airway inflammation in obese and nonobese patients with difficult-to-treat asthma. Allergy. 2008;63(5):570-4. https://doi.org/10.1111/j.1398-9995.2007.01597.x
9. Clerisme-Beaty EM, Karam S, Rand C, Patino CM, Bilderback A, Riekert KA, et al. Does higher body mass index contribute to worse asthma control in an urban population? J Allergy Clin Immunol. 2009;124(2):207-12. https://doi.org/10.1016/j.jaci.2009.05.034
10. Telenga ED, Tideman SW, Kerstjens HA, Hacken NH, Timens W, Postma DS, et al. Obesity in asthma: more neutrophilic inflammation as a possible explanation for a reduced treatment response. Allergy. 2012;67(8):1060-8. https://doi.org/10.1111/j.1398-9995.2012.02855.x
11. Cruz AA, Souza-Machado A, Franco R, Souza-Machado C, Ponte EV, Moura Santos P, et al. The impact of a program for control of asthma in a low-income setting. World Allergy Organ J. 2010;3(4):167-74. https://doi.org/10.1097/WOX.0b013e3181dc3383
12. Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention 2006; Bethesda: GINA; 2006.
13. Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention. Bethesda: GINA; 2002.
14. Bousquet J, Mantzouranis E, Cruz AA, Aït-Khaled N, Baena-Cagnani CE, Bleecker ER, et al. Uniform definition of asthma severity, control, and exacerbations: document presented for the World Health Organization Consultation on Severe Asthma. J Allergy Clin Immunol. 2010;126(5):926-38. https://doi.org/10.1016/j.jaci.2010.07.019
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. https://doi.org/10.1590/S1806-37132007000400008
16. Standardization of Spirometry, 1994 Update. American Thoracic Society. Am J Respir Crit Care Med. 1995;152(3):1107-36. https://doi.org/10.1164/ajrccm.152.3.7663792
17. Bousquet J, Heinzerling L, Bachert C, Papadopoulos NG, Bousquet PJ, Burney PG, et al. Practical guide to skin prick tests in allergy to aeroallergens. Allergy. 2012;67(1):18-24. https://doi.org/10.1111/j.1398-9995.2011.02728.x
18. Leite M, Ponte E, 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. https://doi.org/10.1590/S1806-37132008001000002
19. Juniper EF, Buist AS, Cox FM, Ferrie PJ, King DR. Validation of a standardized version of the Asthma Quality of Life Questionnaire. Chest, 1999;115(5):1265-70. https://doi.org/10.1378/chest.115.5.1265
20. Fornari F, Gruber AC, Lopes Ade B, Cecchetti D, de Barros SG. Symptom's questionnaire for gastroesophageal reflux disease [Article in Portuguese]. Arq Gastroenterol. 2004;41(4):263-7. https://doi.org/10.1590/S0004-28032004000400012
21. Cunha JA. Manual da versão em português das Escalas Beck. São Paulo: Casa do Psicólogo; 2001.
22. Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention. Bethesda: GINA; 2015.
23. Pereira CA, Duarte AA, Gimenez A, Soares MR. Comparison between reference values for FVC, FEV1, and FEV1/FVC ratio in White adults in Brazil and those suggested by the Global Lung Function Initiative 2012. J Bras Pneumol. 2014;40(4):397-402. https://doi.org/10.1590/S1806-37132014000400007
24. de Groot JC, Storm H, Amelink M, de Nijs SB, Eichhorn E, Reitsma BH, et al. Clinical profile of patients with adult-onset eosinophilic asthma. ERJ Open Res. 2016;2(2). pii: 00100-2015. https://doi.org/10.1183/23120541.00100-2015
25. Zhang XY, Simpson JL, Powell H, Yang IA, Upham JW, Reynolds PN, et al. Full blood count parameters for the detection of asthma inflammatory Phenotypes. Clin Exp Allergy. 2014;44(9):1137-45. https://doi.org/10.1111/cea.12345
26. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. World Health Organ Tech Rep Ser. 2000;894:i-xii, 1-253.
27. The IDF consensus worldwide definition of the metabolic syndrome. Brussels: International Diabetes Federation; 2005.
28. Lintomen L, Calixto MC, Schenka A, Antunes E. Allergen-induced bone marrow eosinophilopoiesis and airways eosinophilic inflammation in leptin-deficient ob/ob mice. Obesity (Silver Spring). 2012;20(10):1959-65. https://doi.org/10.1038/oby.2012.93
29. Ma J, Xiao L. Association of general and central obesity and atopic and nonatopic asthma in US adults. J Asthma. 2013;50(4):395-402. https://doi.org/10.3109/02770903.2013.770014
30. Chen Y, Rennie D, Cormier Y, Dosman J. Atopy, obesity, and asthma in adults: the Humboldt study. J Agromedicine. 2009;14(2):222-7. https://doi.org/10.1080/10599240902724051
31. Fenger RV, Gonzalez-Quintela A, Vidal C, Gude F, Husemoen LL, Aadahl M, et al. Exploring the obesity-asthma link: do all types of adiposity increase the risk of asthma? Clin Exp Allergy. 2012;42(8):1237-45. https://doi.org/10.1111/j.1365-2222.2012.03972.x
32. Flegal KM, Kruszon-Moran D, Carroll MD, Fryar CD, Ogden CL. Trends in obesity among adults in the United States, 2005 to 2014. JAMA. 2016;315(21):2284-91. https://doi.org/10.1001/jama.2016.6458
33. Anderson WJ, Lipworth BJ. Does body mass index influence responsiveness to inhaled corticosteroids in persistent asthma? Ann Allergy Asthma Immunol. 2012;108(4):237-42. https://doi.org/10.1016/j.anai.2011.12.006
34. Mosen DM, Schatz M, Magid DJ, Camargo CA Jr. The relationship between obesity and asthma severity and control in adults. J Allergy Clin Immunol. 2008;122(3):507-11.e6. https://doi.org/10.1016/j.jaci.2008.06.024
35. Sin DD, Jones RL, Man SF. Obesity is a risk factor for dyspnea but not for airflow obstruction. Arch Intern Med. 2002;162(13):1477-81. https://doi.org/10.1001/archinte.162.13.1477
36. Farah CS, Kermode JA, Downie SR, Brown NJ, Hardaker KM, Berend N, et al. Obesity is a determinant of asthma control, independent of inflammation and lung mechanics. Chest. 2011;140(3):659-666. https://doi.org/10.1378/chest.11-0027
37. Brumpton B, Langhammer A, Romundstad P, Chen Y, Mai XM. General and abdominal obesity and incident asthma in adults: the HUNT study. Eur Respir J. 2013;41(2):323-9. https://doi.org/10.1183/09031936.00012112
38. Guh DP, Zhang W, Bansback N, Amarsi Z, Birmingham CL, Anis AH. The incidence of co-morbidities related to obesity and overweight: a systematic review and meta-analysis. BMC Public Health. 2009;9:88. https://doi.org/10.1186/1471-2458-9-88

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ORIGINAL ARTICLE

Is the COPD Assessment Test sensitive for differentiating COPD patients from active smokers and nonsmokers without lung function impairment? A population-based study

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ABSTRACT

Objective: To assess COPD Assessment Test (CAT) scores in adults with and without COPD, as well as to compare the CAT scores for nonsmokers, former smokers, and smokers without COPD with those for patients with COPD. **Methods:** This was a cross-sectional population-based study (the *Respira Floripa* study). The study included adults ≥ 40 years of age residing in the city of Florianópolis, Brazil. A total of 846 households were surveyed. In addition to completing the *Respira Floripa* questionnaire and the CAT, participants underwent pulmonary function testing. **Results:** We analyzed data on 1,057 participants (88.1% of the predicted sample size). A functional diagnosis of COPD was made in 92 participants (8.7%). Of those, 72% were unaware that they had COPD. The mean CAT score was higher in the group of COPD patients than in that of individuals without COPD (10.6 [95% CI: 8.8-12.4] vs. 6.6 [95% CI: 6.1-7.0]; $p < 0.01$). Individual item scores were significantly higher in the patients with COPD than in the individuals without COPD ($p < 0.001$), the exception being the scores for the items related to sleep ($p = 0.13$) and energy ($p = 0.08$). The mean CAT score was higher in the group of COPD patients than in nonsmokers (5.8 [95% CI: 5.3-6.4]) and former smokers (6.4 [95% CI: 5.6-7.2]; $p < 0.05$). However, there were no significant differences in the mean CAT score between the group of COPD patients and smokers without COPD (9.5 [95% CI: 8.2-10.8]; $p > 0.05$), the exception being the mean scores for confidence leaving home ($p = 0.02$). **Conclusions:** CAT scores were higher in the group of patients with COPD than in nonsmokers and former smokers without COPD. However, there were no significant differences in CAT scores between COPD patients and smokers without COPD. Smokers with an FEV_1/FVC ratio > 0.70 have impaired health status and respiratory symptoms similar to those observed in COPD patients.

Keywords: Respiratory function tests; Pulmonary disease, chronic obstructive; Smoking.

INTRODUCTION

COPD is an inflammatory lung disease characterized by chronic, progressive and not fully reversible airflow limitation.[1] Although COPD is primarily a lung disease, it also produces significant systemic effects that might result in impaired functional capacity, exercise capacity, quality of life, and health status.[1,2]

According to the 2011 update of the Global Initiative for Chronic Obstructive Lung Disease (GOLD)[3] strategy document, COPD management and treatment should consider disease impact (as determined by symptom burden) and the risk of exacerbation (as determined on the basis of airflow limitation and exacerbation history) rather than functional findings alone.[3] Since the publication of the 2011 GOLD guidelines, the COPD Assessment Test (CAT) has been increasingly used in clinical and research settings. The CAT has proved to be a reliable, valid, and responsive tool for health status assessment in patients with COPD.[4] Nonresponse rates, as well as floor and ceiling effects, together with the minimum clinically important difference for the CAT, are currently known.[5] In addition to studies examining the psychometric properties of the CAT, studies exploring other characteristics of the CAT in different scenarios and for different purposes are on the rise.[6] A recent systematic review showed that the CAT can be used as a complementary tool to predict COPD exacerbations, depression, acute deterioration of health status, and mortality.[6]

Although there is a growing body of evidence on the CAT and its features, the cross-sectional validity of the CAT

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in specific population subgroups and its discriminatory properties in such groups (e.g., smokers and former smokers) have yet to be adequately studied.[7] Another gap in the literature regarding the CAT is related to its use in the general population. The parameters thus obtained are important because they allow comparisons between specific populations and the normative data obtained from population-based studies.

To our knowledge, there have been only two studies reporting the use of the CAT in the general population.[8,9] In Brazil, there have been no population-based studies examining the CAT, despite the fact that the CAT is considered to be valid and reliable for patients with COPD.[10]

The objective of the present study was to assess CAT scores in a sample of adults ≥ 40 years of age with and without COPD. A secondary objective was to compare the CAT scores for nonsmokers, former smokers, and smokers without COPD with those for patients with COPD.

METHODS

Study design and sample selection

This was a cross-sectional population-based study. The study was part of the *Respira Floripa* study, in which the methodology employed in the Latin American Project for the Investigation of Obstructive Lung Disease (PLATINO) study was used,[11] albeit with modifications.

A representative sample of individuals ≥ 40 years of age residing in the greater metropolitan area of Florianópolis, Brazil, was randomly obtained by cluster sampling of census tracts and households. The study sample was stratified by socioeconomic class and location in the metropolitan area. Given that the population of Florianópolis residents ≥ 40 years of age was estimated at 157,450 inhabitants and that the number of ≥ 40-year-old residents per household was estimated at 1.42, 68 of the 419 census tracts in the area were randomly assigned to the study, a total of 846 households being included.

The study consisted of one or more household visits in which the participants answered the *Respira Floripa* questionnaire. The questionnaire contains questions regarding demographic characteristics and respiratory symptoms, among others. Participants underwent anthropometric and vital sign measurements, as well as pulmonary function testing. The inclusion criteria were as follows: being 40 years of age or older, residing in the greater metropolitan area of Florianópolis, and agreeing to participate in the study. The exclusion criteria were as follows: being institutionalized; being nonautonomous; having undergone thoracic, abdominal, or ophthalmologic surgery in the last three months; having had angina, acute myocardial infarction, or both in the last three months; having tuberculosis; having an HR > 120 bpm or < 60 bpm; having a systemic blood pressure > 180/90 mmHg; being pregnant; having had a respiratory infection in the three weeks preceding the assessment; being unable to perform spirometry; and failing to complete the CAT. The study was approved by the Research Ethics Committee of the Federal University of Santa Catarina (Protocol no. 766/2010), located in the city of Florianópolis, and all participants gave written informed consent. All household interviews were conducted between April of 2012 and July of 2013.

Study procedures

The Respira Floripa questionnaire

Participants answered the *Respira Floripa* questionnaire, a standardized questionnaire based on the PLATINO study questionnaire[11] with minor modifications, which were based on the following: the American Thoracic Society (ATS) Division of Lung Diseases questionnaire,[12] the European Community Respiratory Health Survey II,[13] the Lung Health Study questionnaire,[14] and the 12-Item Short-Form Health Survey.[15] Demographic and socioeconomic data were collected, as were data on respiratory symptoms, respiratory diseases, medication use, medical diagnosis of respiratory diseases and other comorbidities, smoking history, and quality of life, among others. Questions regarding reasons for continued smoking,[16] sinonasal symptoms,[17] symptoms of depression and anxiety,[18] quality of sleep,[19] and health status[20] were added to the interview.

CAT

The CAT[20] assesses the health status of patients with COPD by quantifying the impact of common COPD symptoms (including cough, phlegm, chest tightness, breathlessness going up hills/stairs, activity limitations at home, confidence leaving home, sleep, and energy) on the lives of patients.[21] Individual question scores range from 0 to 5, total CAT scores therefore ranging from 0 to 40; a higher CAT score translates to a poorer health status.[20] A cut-off point ≥ 10 indicates impaired health status. The impact of COPD symptoms on the lives of patients can be divided into four categories, on the basis of the CAT score: low (i.e., CAT scores of 1-10), medium (i.e., CAT scores of 11-20), high (i.e., CAT scores of 21-30), and very high (i.e., CAT scores of 31-40).[22] The Portuguese version of the CAT has been validated for use in Brazil, and its reproducibility has been established.[10]

Pulmonary function testing and anthropometry

Spirometry was performed in accordance with ATS/European Respiratory Society standards,[23] with the use of an ATS-certified, portable, ultrasound-based spirometer (EasyOne®; ndd Medical Technologies, Inc., Andover, MA, USA). The following spirometric parameters were assessed: FEV_1, FVC, and FEV_1/FVC. The diagnosis of COPD was based on a post-bronchodilator FEV_1/FVC ratio of < 0.70. The reference values were those from the third National Health and

Nutrition Examination Survey.[24] Height was measured with a portable stadiometer (Seca®; Hamburg, Germany), and weight was measured with an electronic scale (Tanita Corporation of America, Inc., Arlington Heights, IL, USA). Height and weight were measured with participants barefoot and wearing light clothing.

Statistical analysis

Descriptive statistics were used in order to summarize the demographic characteristics of the study participants. Continuous variables were summarized as mean and 95% confidence interval. Categorical variables were expressed as absolute and relative frequencies. The Kolmogorov-Smirnov test was used. Between-group differences were determined by the Student's t-test for independent samples and by analysis of variance (one-way ANOVA or the Kruskal-Wallis test) with post hoc Bonferroni correction. Within-group differences were determined by the Student's t-test for paired samples. The significance level was set at 95%. All statistical analyses were performed with the IBM SPSS Statistics software package, version 20.0 (IBM Corporation, Armonk, NY, USA).

Sample size

The sample size calculation was based on the primary objective of the *Respira Floripa* study, which was to determine the prevalence of COPD in Florianópolis. The sample size was calculated by using parameters that were similar to those of the PLATINO study.[11] The required sample size was initially calculated to be 432. However, on the basis of the assumption that the prevalence of COPD might be lower than hypothesized and of the need for a higher number of COPD patients to allow between-group comparisons, the required sample size was calculated to be 1,200.

RESULTS

Of a total of 1,184 eligible adults residing in Florianópolis, 102 declined to participate. The response rate was 91.3%. A total of 23 interviews were subsequently excluded because the interviewees were unable to perform reproducible flow-volume loops during spirometry, and another 2 were excluded because the interviewees did not complete the CAT (Figure 1).

We analyzed data on 1,057 participants, which accounted for 88.1% of the predicted sample size. The mean age was 58 years (95% CI: 57-59), the mean body mass index was 28.0 kg/m^2 (95% CI: 27.7-28.3), the mean FEV_1/FVC ratio was 79.6 (95% CI: 79.1-80.0), the mean percent predicted FEV_1 was 92.2% (95% CI: 91.0-93.5), and the mean percent predicted FVC was 89.0% (95% CI: 87.9-90.0). A functional diagnosis of COPD was made in 92 participants (8.7%). Of those, 72% were unaware that they had COPD. Patients with a diagnosis of COPD had a mean smoking history of 29.6 pack-years (95% CI: 23.7-35.6). Approximately half of the sample (52.9%) had never smoked, 18.0% were smokers, and 29.1% were former smokers (Table 1).

The mean CAT score was higher in the group of patients with COPD than in that of individuals without COPD (10.6 [95% CI: 8.8-12.4] vs. 6.6 [95% CI: 6.1-7.0]; $p < 0.01$). Individual item scores were significantly higher in the patients with COPD than in the individuals without COPD ($p < 0.001$), the exception being the scores for the items related to sleep ($p = 0.13$) and energy ($p = 0.08$).

The mean CAT score was higher in the group of COPD patients than in nonsmokers (5.8 [95% CI: 5.3-6.4]) and former smokers (6.4 [95% CI: 5.6-7.2]; $p < 0.05$; Figure 2). However, there were no significant differences in the mean CAT score between the group of COPD patients and smokers without COPD (9.5 [95% CI: 8.2-10.8]; $p > 0.05$). In addition, there were no significant differences between those two groups regarding individual item scores, the exception being the scores for the question regarding confidence leaving home ($p = 0.02$; Figure 3).

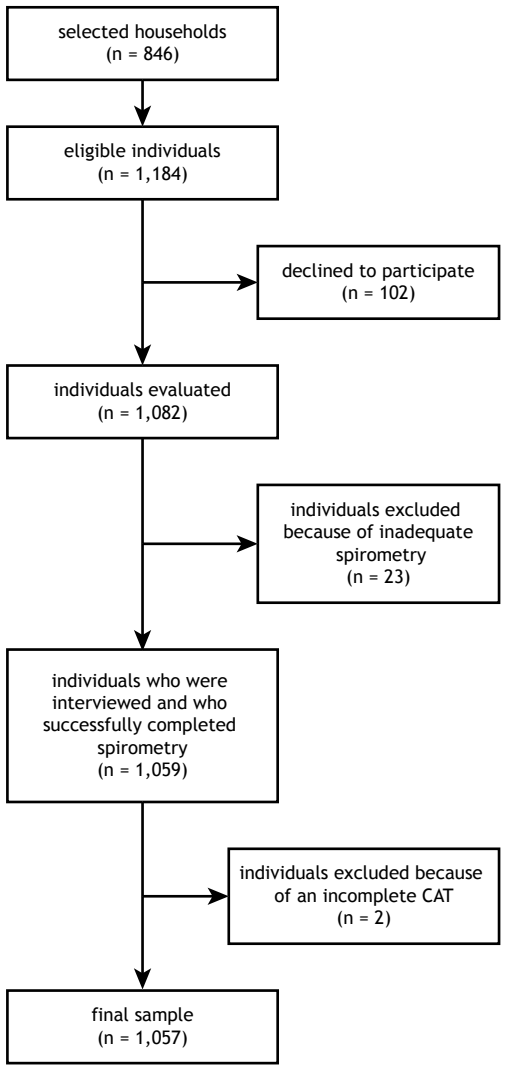

Figure 1. Flow chart of the sample selection process. CAT: COPD Assessment Test.

Table 1. Characteristics of the sample of individuals with and without COPD, the latter being stratified by smoking status.[a]

Characteristic	Individuals without COPD			Individuals with COPD	p
	Nonsmokers	Former smokers	Smokers		
	n = 539	n = 274	n = 152	n = 92	
Age, years	57.8 (56.8-58.9)	58.8 (57.5-60.1)	53.4 (52.0-54.8)*,†	65.0 (62.8-67.3)*,†,‡	< 0.01
Smoking history, pack-years	-	23.4 (20.7-26.2)	30.9 (37.4-24.5)	29.6 (23.7-35.6)*,†	< 0.01
Sex, n (%)					< 0.01
Female	362 (67.2)	136 (49.6)	95 (62.5)	40 (43.5)	
Male	177 (32.8)	138 (50.4)	57 (37.5)	52 (56.5)	
Self-reported race[b]					< 0.01
White	465 (86.3)	245 (89.4)	117 (77.0)	73 (79.3)	
Other	74 (13.7)	29 (10.6)	35 (23.0)	19 (20.7)	
Level of education, no. of years of schooling[b]					< 0.01
0-4	129 (23.9)	56 (20.5)	35 (23.0)	37 (40.2)	
5-8	85 (15.8)	51 (18.6)	39 (25.7)	15 (16.3)	
≥ 9	325 (60.3)	167 (60.9)	78 (51.3)	40 (43.5)	
Socioeconomic class[b]					0.03
A and B	81 (15.0)	42 (15.3)	19 (12.5)	12 (13.0)	
C	409 (75.9)	208 (75.9)	105 (69.1)	66 (71.7)	
D and E	49 (9.1)	24 (8.8)	28 (18.4)	14 (15.3)	
BMI, kg/m^2[b]					0.02
< 25	139 (25.8)	73 (26.7)	58 (38.2)	36 (39.1)	
25-29	228 (42.3)	116 (42.3)	56 (36.8)	36 (39.1)	
≥ 30	172 (31.9)	85 (31.0)	38 (25.0)	20 (21.8)	
Lung function					
FEV_1, % predicted	96.6 (94.9-98.3)	95.1 (93.1-97.2)	88.8 (86.0-91.5)*,†	63.7 (59.5-68.0)*,†,‡	< 0.01
FVC, % predicted	91.0 (89.6-92.4)	90.1 (88.2-91.9)	87.6 (85.3-90.0)	76.1 (72.0-80.1)*,†,‡	< 0.01
FEV_1/FVC	82.0 (81.6-82.4)	80.7 (80.0-81.3)*	79.8 (79.0-80.6)*	61.8 (60.3-63.4)*,†,‡	< 0.01

BMI: body mass index. [a]Data expressed as mean (95% CI), except where otherwise indicated. [b]Data expressed as n (%). *vs. nonsmokers. †vs. former smokers. ‡vs. smokers.

DISCUSSION

The results of the present study confirm that the CAT is sensitive for differentiating the health status of patients with COPD from that of individuals without the disease, even when it is administered to a sample of individuals without a previous diagnosis of COPD. In addition, the present study shows that the degree of health status impairment is similar between smokers without COPD and COPD patients.

This is the first population-based study in which the CAT score obtained during household interviews was followed by functional assessment to confirm the presence of COPD. Although the CAT was originally developed for patients with COPD, the data obtained by administering it to the general population (i.e., individuals without COPD) contribute to improving the interpretation of the CAT, especially regarding the magnitude, severity, and relevance of the symptoms on the rating scale,[9] as well as contributing to a deeper understanding of the impact of diseases such as COPD on patient health status.

Jones et al.[8] assessed the CAT in a large, random population-based survey conducted in 11 countries in the Middle East and northern Africa. Mean CAT scores were 6.99 ± 6.91 for the participants who answered the Arabic version and 9.88 ± 9.04 for those who answered the Turkish version.[8] Limitations of the study included data obtained by telephone interview and the fact that no functional evaluation was performed.[8]

In a cohort study designated the Canadian Cohort Obstructive Lung Disease (CanCOLD) study and investigating 1,500 individuals residing in nine urban/suburban areas in Canada,[9] the CAT was administered to a sample of 500 individuals without COPD, and the mean score was 6.00 ± 5.09. As in the present study, all CanCOLD study participants underwent pulmonary function testing by spirometry.[9] In another study,[25] which was part of the CanCOLD study, 481 individuals without COPD were evaluated, and the mean CAT score was similar to that observed in the present study (6.9 ± 6.2).

Several studies have shown that the CAT is sensitive to changes in health status in various groups of individuals. In agreement with other studies,[8,25-28] the present study showed that the mean CAT score for the general population of individuals without COPD was nearly half that for patients with COPD. This finding confirms the known-group validity of the CAT, mean CAT scores being significantly higher in patients with COPD than in individuals without the disease.

The magnitude of differences between individuals with and without COPD regarding the CAT score varies widely across studies. Among the Arabic-speaking participants of the BREATHE study,[8] mean CAT scores

were 16.6 (95% CI: 15.5-16.8) for those with COPD and 5.4 (95% CI: 5.2-5.6) for those without COPD; among Turkish-speaking respondents, mean scores were 20.9 (95% CI: 19.6-22.2) for those with COPD and 8.1 (95% CI: 7.6-8.6) for those without COPD. In a study by Nishimura et al.,[27] mean CAT scores were 7.3 ± 5.2 for the COPD group and 5.8 ± 4.4 for the non-COPD group. Raghavan et al.[25] reported mean scores of 9.2 ± 6.6 for the COPD group and 6.9 ± 6.2 for the non-COPD group. The three aforementioned studies evaluated individuals from the general population. In contrast, Miyazaki et al.[28] and Gao et al.[26] investigated individuals selected from among those treated at tertiary care centers. Miyazaki et al.[28] and Gao et al.[26] reported mean scores of 12.4 ± 8.3 and 10.3 ± 5.3 in the COPD groups and 9.4 ± 6.6 and 4.0 ± 2.1 in the non-COPD groups, respectively. This variability among studies involving different populations suggests the need for local scoring systems and emphasizes the relevance of our study.

We found significant differences between individuals with and without COPD regarding total CAT scores and individual item scores, the latter being higher in the COPD group than in the non-COPD group (the exception being the scores for sleep and energy). Although analysis of individual item scores is not recommended,[29] we decided to include it in the present study in order to provide a more detailed understanding of the behavior of the questionnaire and a qualitative analysis of the data. Of the eight items that constitute the CAT, sleep and energy are the only items that do not refer specifically to signs, symptoms, or limitations that are characteristic of patients with COPD. The item related to energy reads "I have lots of energy"/"I have no energy at all"; there is no mention of lung disease. However, the item related to sleep quality reads "I sleep soundly"/"I don't sleep soundly because of my lung condition". Nevertheless, although the item states that the reason for not sleeping soundly is the presence of a lung disease, increased scores are common among individuals without COPD because they perceive the sentence "I don't sleep soundly" as applying to them. Rating scales, such as CAT, can be interpreted in different ways depending on the content of the anchors (e.g., "I sleep soundly"/"I don't sleep soundly because of my lung condition"). It has been argued that the aforementioned items might require refinement depending on the population being evaluated.[25] In addition, because they are the most comprehensive items on the questionnaire, they might be unable to differentiate between patients with COPD and individuals without the disease, given that sleep and energy changes are important findings in other diseases.[28,30]

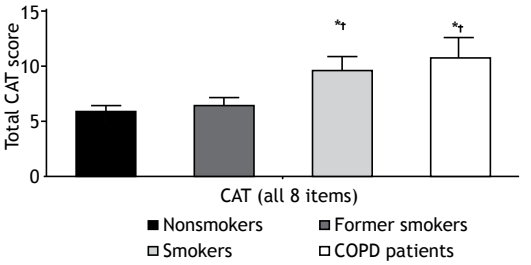

Figure 2. Total COPD Assessment Test (CAT) scores for each group of individuals in the study sample. *p < 0.05 vs. nonsmokers. †p < 0.05 vs. former smokers. ‡p < 0.05 vs. smokers.

In the individuals without COPD, CAT scores were found to be significantly higher in smokers than in nonsmokers and former smokers. The same was true for the items cough, phlegm, chest tightness, and breathlessness going up hills/stairs. These findings are important because they show that smokers have impaired health status and respiratory symptoms characteristic of chronic respiratory diseases despite the absence of changes in the fixed FEV_1/FVC ratio as assessed by spirometry, their CAT scores being similar to those observed in COPD patients.

The results of the present study are consistent with those of a recent nonpopulation-based study[31] showing that the presence of respiratory symptoms, as determined by the CAT, is common in approximately 50% of current and former smokers, despite their having preserved lung function (as assessed by spirometry).

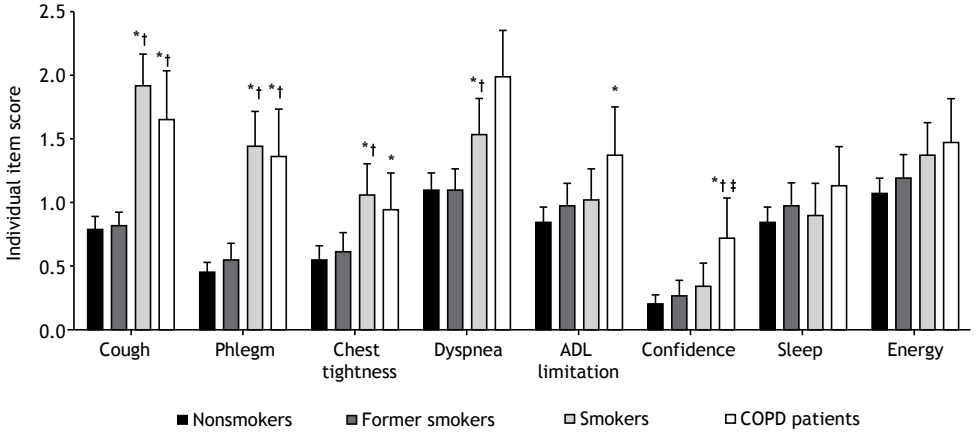

Figure 3. Individual COPD Assessment Test (CAT) item scores for each group of individuals in the study sample. ADL: activities of daily living. *p < 0.05 vs. nonsmokers. †p < 0.05 vs. former smokers. ‡p < 0.05 vs. smokers.

Although the prevalence of respiratory symptoms is slightly lower in current and former smokers than in patients with GOLD stage I or II COPD (65%), it is much higher in ever smokers (current or former) than in never smokers (16%).[31] In addition, ever smokers with preserved lung function and a CAT score ≥ 10 are more likely to have respiratory exacerbations, worse performance on the six-minute walk test, and radiological evidence of bronchiolitis than are individuals with a CAT score of < 10.[31] Other studies have reported similar findings for the CAT[8,26] and the Saint George's Respiratory Questionnaire.[32]

In a recent study,[33] 54.1% of all smokers or former smokers with post-bronchodilator FEV_1/FVC > 0.70 and FEV_1 ≥ 80% of the predicted value reported one or more limitations related to respiratory disease. According to Fabbri,[34] the results of the aforementioned studies[31,33] indicate that individuals with respiratory symptoms without changes in lung function suffer the same consequences as do patients with spirometric changes consistent with mild to moderate airflow obstruction. In addition, he suggests that FEV_1 might not be a sensitive marker for COPD diagnosis in most individuals who smoke. According to Woodruff et al.,[31] the use of spirometry to establish a diagnosis of COPD might not adequately cover the breadth of symptomatic smoking-related lung disease. Therefore, it could be argued that a fixed FEV_1/FVC ratio should be used as a screening tool rather than a diagnostic tool for COPD, given that it is unable to detect early changes in lung function.

Although the CAT is a disease-specific tool developed to complement the evaluation of patients with COPD, its score seems to be influenced by the presence of comorbidities. Although the CAT has a "COPD-centric" origin, three of its items (cough, phlegm, and breathlessness going up hills/stairs) address symptoms that are very common in, but not exclusive to, patients with COPD. The remaining five items (chest tightness, activity limitations at home, confidence leaving home, sleep, and energy) are even less exclusive to COPD. Therefore, it is possible that the attempt to create a multidimensional instrument capable of reflecting the complexity of COPD resulted in a nonspecific tool.

One potential limitation of the present study is the use of a fixed post-bronchodilator FEV_1/FVC ratio of < 70% for the diagnosis of COPD; a post-bronchodilator FEV_1/FVC ratio of < 70% tends to underestimate the presence of COPD in younger individuals and overestimate it in older individuals.[35,36] In addition, a post-bronchodilator FEV_1/FVC ratio of < 70% is not exclusive to patients with COPD. It can be found in asthma patients with airway remodeling,[35] in the asthma-COPD overlap syndrome, and in other chronic respiratory diseases characterized by airflow obstruction.[23,36] Furthermore, in patients with severe COPD and decreased FVC due to lung hyperinflation, the FEV_1/FVC ratio could be falsely increased,[37] contributing to underdiagnosis. However, the use of the FEV_1/FVC ratio for the diagnosis of COPD is a simple method that does not depend on reference equations and has been widely used in numerous studies worldwide, some of which have provided the basis for COPD guidelines.

Another potential limitation is the sample size calculation. It was based on the primary objective of the *Respira Floripa* study, which was to determine the prevalence of COPD in Florianópolis. However, in order to support the results obtained by comparing the groups, the statistical power of the study was calculated and was found to be > 85% for the main comparisons.

In summary, CAT scores were higher in the group of patients with COPD than in nonsmokers and former smokers without COPD. However, there were no significant differences in CAT scores between COPD patients and smokers without COPD. Despite the apparent absence of changes in lung function on spirometry, smokers have impaired health status and respiratory symptoms similar to those observed in COPD patients. Symptomatic smokers with CAT scores above the cut-off point should undergo further pulmonary function tests for a better evaluation of their lung function.

REFERENCES

1. Global Initiative for Chronic Obstructive Lung Disease - GOLD [homepage on the Internet]. Bethesda: Global Initiative for Chronic Obstructive Lung Disease [cited 2018 Mar 24]. Global Strategy for the Diagnosis, Management, and Prevention of COPD 2016. Available from: http://goldcopd.org/global-strategy-diagnosis-management-prevention-copd-2016/
2. Reardon JZ, Lareau SC, ZuWallack R. Functional status and quality of life in chronic obstructive pulmonary disease. Am J Med. 2006;119(10 Suppl 1):32-7. https://doi.org/10.1016/j.amjmed.2006.08.005
3. Global Initiative for Chronic Obstructive Lung Disease - GOLD [homepage on the Internet]. Bethesda: Global Initiative for Chronic Obstructive Lung Disease [cited 2018 Mar 24]. Global Strategy for the Diagnosis, Management, and Prevention of COPD - Revised 2011. [Adobe Acrobat document, 90p.]. Available from: http://www.goldcopd.org/uploads/users/files/GOLD_Report_2011_Feb21.pdf
4. Gupta N, Pinto LM, Morogan A, Bourbeau J. The COPD assessment test: a systematic review. Eur Respir J. 2014;44(4):873-84. https://doi.org/10.1183/09031936.00025214
5. Kon SS, Canavan JL, Jones SE, Nolan CM, Clark AL, Dickson MJ, et al. Minimum clinically important difference for the COPD Assessment Test: a prospective analysis. Lancet Respir Med. 2014;2(3):195-203. https://doi.org/10.1016/S2213-2600(14)70001-3
6. Karloh M, Fleig Mayer A, Maurici R, Pizzichini MMM, Jones PW, Pizzichini E. The COPD Assessment Test: What Do We Know So Far?: A Systematic Review and Meta-Analysis About Clinical Outcomes Prediction and Classification of Patients Into GOLD Stages. Chest. 2016;149(2):413-425. https://doi.org/10.1378/chest.15-1752
7. Gupta N, Pinto L, Benedetti A, Li PZ, Tan W, Aaron S, et al. The COPD Assessment Test: can it discriminate across COPD subpopulations? Chest. 2016;150(5):1069-1079. https://doi.org/10.1016/j.chest.2016.06.016.
8. Jones PW, Shahrour N, Nejjari C, Lahlou A, Doble A, Rashid N, et al. Psychometric evaluation of the COPD assessment test: data from the BREATHE study in the Middle East and North Africa region. Respir Med. 2012;106 Suppl 2:S86-99. https://doi.org/10.1016/S0954-6111(12)70017-3
9. Pinto LM, Gupta N, Tan W, Li PZ, Benedetti A, Jones PW, et al. Derivation of normative data for the COPD assessment test (CAT).

Respir Res. 2014;15:68. https://doi.org/10.1186/1465-9921-15-68

10. Silva GP, Morano MT, Viana CM, Magalhães CB, Pereira ED. Portuguese-language version of the COPD Assessment Test: validation for use in Brazil. J Bras Pneumol. 2013;39(4):402-8. https://doi.org/10.1590/S1806-37132013000400002
11. Menezes AM, Victora CG, Perez-Padilla R; PLATINO Team. The Platino project: methodology of a multicenter prevalence survey of chronic obstructive pulmonary disease in major Latin American cities. BMC Med Res Methodol. 2004;4:15. https://doi.org/10.1186/1471-2288-4-15
12. Ferris BG. Epidemiology Standardization Project (American Thoracic Society). Am Rev Respir Dis. 1978;118(6 Pt 2):1-120.
13. European Community Respiratory Health Survey II Steering Committee. The European Community Respiratory Health Survey II. Eur Respir J. 2002;20(5):1071-9. https://doi.org/10.1183/09031936.02.00046802
14. Connett JE, Kusek JW, Bailey WC, O'Hara P, Wu M. Design of the Lung Health Study: a randomized clinical trial of early intervention for chronic obstructive pulmonary disease. Control Clin Trials. 1993;14(2 Suppl):3S-19S. https://doi.org/10.1016/0197-2456(93)90021-5
15. Ware J Jr, Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. Med Care. 1996;34(3):220-33. https://doi.org/10.1097/00005650-199603000-00003
16. Souza ES, Crippa JA, Pasian SR, Martinez JA. University of São Paulo Reasons for Smoking Scale: a new tool for the evaluation of smoking motivation. J Bras Pneumol. 2010;36(6):768-78. https://doi.org/10.1590/S1806-37132010000600015
17. Caminha GP, Melo Junior JT, Hopkins C, Pizzichini E, Pizzichini MM. SNOT-22: psychometric properties and cross-cultural adaptation into the Portuguese language spoken in Brazil. Braz J Otorhinolaryngol. 2012;78(6):34-9. https://doi.org/10.5935/1808-8694.20120030
18. Botega NJ, Bio MR, Zomignani MA, Garcia C Jr, Pereira WA. Mood disorders among inpatients in ambulatory and validation of the anxiety and depression scale HAD [Article in Portuguese]. Rev Saude Publica. 1995;29(5):355-63.
19. Bertolazi AN, Fagondes SC, Hoff LS, Dartora EG, Miozzo IC, de Barba ME, et al. Validation of the Brazilian Portuguese version of the Pittsburgh Sleep Quality Index. Sleep Med. 2011;12(1):70-5. https://doi.org/10.1016/j.sleep.2010.04.020
20. Jones PW, Harding G, Berry P, Wiklund I, Chen WH, Kline Leidy N. Development and first validation of the COPD Assessment Test. Eur Respir J. 2009;34(3):648-54. https://doi.org/10.1183/09031936.00102509
21. Jones PW, Brusselle G, Dal Negro RW, Ferrer M, Kardos P, Levy ML, et al. Properties of the COPD assessment test in a cross-sectional European study. Eur Respir J. 2011;38(1):29-35. https://doi.org/10.1183/09031936.00177210
22. Jones PW, Tabberer M, Chen WH. Creating scenarios of the impact of COPD and their relationship to COPD assessment test (CATTM) scores. BMC Pulm Med. 2011;11:42. https://doi.org/10.1186/1471-2466-11-42
23. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J. 2005;26(2):319-38. https://doi.org/10.1183/09031936.05.00034805
24. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. Am J Respir Crit Care Med. 1999;159(1):179-87. https://doi.org/10.1164/ajrccm.159.1.9712108
25. Raghavan N, Lam YM, Webb KA, Guenette JA, Amornputtisathaporn N, Raghavan R, et al. Components of the COPD Assessment Test (CAT) associated with a diagnosis of COPD in a random population sample. COPD. 2012;9(2):175-83. https://doi.org/10.3109/15412555.2011.650802
26. Gao Y, Hou Q, Wang H. Assessment of health status in patients with newly diagnosed chronic obstructive pulmonary disease. PloS One. 2013;8(12):e82782. https://doi.org/10.1371/journal.pone.0082782
27. Nishimura K, Mitsuma S, Kobayashi A, Yanagida M, Nakayasu K, Hasegawa Y, et al. COPD and disease-specific health status in a working population. Respir Res. 2013;14:61. https://doi.org/10.1186/1465-9921-14-61
28. Miyazaki M, Nakamura H, Chubachi S, Sasaki M, Haraguchi M, Yoshida S, et al. Analysis of comorbid factors that increase the COPD assessment test scores. Respir Res. 2014;15:13. https://doi.org/10.1186/1465-9921-15-13
29. COPD Assessment Test (CAT) [homepage on the Internet]. Brentford (UK): GlaxoSmithKline Services Unlimited; c2009-2016 [updated 2012 Feb; cited 2015 Oct 15]. The COPD Assessment test: Healthcare Professional User Guide 2012. [Adobe Acrobat document, 9p.]. Available from: http://www.catestonline.org/images/UserGuides/CATHCPUser%20guideEn.pdf
30. Lee YS, Park S, Oh YM, Lee SD, Park SW, Kim YS, et al. Chronic obstructive pulmonary disease assessment test can predict depression: a prospective multi-center study. J Korean Med Sci. 2013;28(7):1048-54. https://doi.org/10.3346/jkms.2013.28.7.1048
31. Woodruff PG, Barr RG, Bleecker E, Christenson SA, Couper D, Curtis JL, et al. Clinical Significance of Symptoms in Smokers with Preserved Pulmonary Function. N Engl J Med. 2016;374(19):1811-21. https://doi.org/ 10.1056/NEJMoa1505971
32. Spencer S, Calverley PM, Sherwood Burge P, Jones PW; ISOLDE Study Group. Inhaled Steroids in Obstructive Lung Disease. Health status deterioration in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2001;163(1):122-8. https://doi.org/10.1164/ajrccm.163.1.2005009
33. Regan EA, Lynch DA, Curran-Everett D, Curtis JL, Austin JH, Grnier PA, et al. Clinical and radiologic disease in smokers with normal spirometry. JAMA Intern Med. 2015;175(9):1539-49. https://doi.org/10.1001/jamainternmed.2015.2735
34. Fabbri LM. Smoking, Not COPD, as the Disease. N Engl J Med. 2016;374(19):1885-6. https://doi.org/10.1056/NEJMe1515508
35. Celli BR, MacNee W; ATS/ERS Task Force. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. Eur Respir J. 2004;23(6):932-46. https://doi.org/10.1183/09031936.04.00014304
36. Miller MR, Crapo R, Hankinson J, Brusasco V, Burgos F, Casaburi R, et al. General considerations for lung function testing. Eur Respir J. 2005;26(1):153-61. https://doi.org/10.1183/09031936.05.00034505
37. Fletcher C, Peto R. The natural history of chronic airflow obstruction. Br Med J. 1977;1(6077):1645-8. https://doi.org/10.1136/bmj.1.6077.1645

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ORIGINAL ARTICLE

Validity and reliability of assessing diaphragmatic mobility by area on X-rays of healthy subjects

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ABSTRACT

Objective: To investigate the concurrent validity, as well as the intra- and inter-rater reliability, of assessing diaphragmatic mobility by area (DM_{area}) on chest X-rays of healthy adults. **Methods:** We evaluated anthropometric parameters, pulmonary function, and diaphragmatic mobility in 43 participants. Two observers (rater A and rater B) determined diaphragmatic mobility at two time points. We used Pearson's correlation coefficient to evaluate the correlation between DM_{area} and the assessment of diaphragmatic mobility by distance (DM_{dist}). To evaluate intra- and inter-rater reliability, we used the intraclass correlation coefficient (ICC [2,1]), 95% CI, and Bland-Altman analysis. **Results:** A significant correlation was found between the DM_{area} and DM_{dist} methods ($r = 0.743$; $p < 0.0001$). For DM_{area}, the intra-rater reliability was found to be quite high for the right hemidiaphragm (RHD)—ICC (2,1) = 0.92 (95% CI: 0.86-0.95) for rater A and ICC (2,1) = 0.90 (95% CI: 0.84-0.94) for rater B—and the left hemidiaphragm (LHD)—ICC (2,1) = 0.96 (95% CI: 0.93-0.97) for rater A and ICC (2,1) = 0.91 (95% CI: 0.81-0.95) for rater B—($p < 0.0001$ for all). Also for DM_{area}, the inter-rater reliability was found to be quite high for the first and second evaluations of the RHD—ICC (2,1) = 0.99 (95% CI: 0.98-0.99) and ICC (2,1) = 0.95 (95% CI: 0.86-0.97), respectively—and the LHD—ICC (2,1) = 0.99 (95% CI: 0.98-0.99) and ICC (2,1) = 0.94 (95% CI: 0.87-0.97)—($p < 0.0001$ for both). The Bland-Altman analysis showed good agreement between the mobility of the RHD and that of the LHD. **Conclusions:** The DM_{area} method proved to be a valid, reliable measure of diaphragmatic mobility.

Keywords: Diaphragm/physiology; Validation studies; Reproducibility of results; Radiography.

INTRODUCTION

The diaphragm is the main respiratory muscle and is responsible for 70-80% of ventilation.[1] Therefore, in clinical practice, the evaluation of its mobility is essential to assess the degree of muscle involvement in respiratory and neuromuscular diseases.[2] When a reduction in diaphragmatic motion is identified, it is possible to establish therapeutic strategies to increase muscle movement, as well as to monitor the effectiveness of interventions aimed at improving the functional capacity and quality of life of patients with diaphragmatic dysfunction.

In various clinical settings, it is necessary to evaluate diaphragmatic function in order to diagnose possible malfunctions. Such malfunctions can occur in many situations, including muscular dystrophies, phrenic nerve injury, thoracic surgery, abdominal surgery, and COPD.[3-6] When a reduction in diaphragmatic mobility is identified and objectively measured, it is possible to establish therapeutic strategies to increase muscle movement and to monitor its progression and response to interventions, with the goal of improving functional capacity and quality of life in patients with impaired diaphragmatic mobility.[7]

Among the various imaging methods used in evaluating the mobility of the diaphragm, fluoroscopy is considered the most reliable because it provides dynamic images of the diaphragm and direct visualization of diaphragmatic movements in real time.[8] Ultrasound is also considered a valid tool and is widely used in evaluating the mobility of the diaphragm.[9] However, chest X-ray is a noninvasive method that is easily applied and is typically more accessible at hospitals and clinics. Chest X-ray allows direct evaluation of the two hemidiaphragms because it provides static images of the diaphragm.[10]

To date, two different methods have been described as means of measuring diaphragmatic mobility on chest X-rays.[11,12] In both methods, two X-ray images are obtained, one at maximum inspiration and the other at maximum expiration, the images then being superimposed and placed on a light box. Although both methods utilize the same images, the measurements are made in different ways. In one of those methods, as

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described by Toledo et al.,[11] the highest point of one hemidiaphragm at maximum expiration is identified, and a longitudinal line is drawn from that point to the highest point of the same hemidiaphragm at maximum inspiration. The mobility of each hemidiaphragm is then determined by using a caliper to measure the distance between the two points. Hereafter, we refer to that process as the assessment of diaphragmatic mobility by distance (DM_{dist}) method. In the other method, as described by Fernandes et al.,[12] after the two images have been superimposed on a light box, tracing paper is placed over the radiographs. The areas represented by the diaphragm in each of the two images are drawn onto the paper and transferred to software that calculates the corresponding area of diaphragmatic mobility. Hereafter, we refer to that process as the assessment of diaphragmatic mobility by area (DM_{area}) method. Although both methods are valid for assessing diaphragmatic mobility, the reliability has been tested only for the DM_{dist}, as in the study conducted by Toledo et al.[11] and in a previous study conducted by our group.[10] In that study, we evaluated the intra- and inter-rater reliability of the method and found a very high intraclass correlation coefficient (ICC) for all measurements, thus demonstrating that the DM_{dist} is a reliable method for the evaluation of diaphragmatic motion. When comparing the two methods, it is important to note that the DM_{area} depends on the use of materials that are simpler and more readily available than are those used in the DM_{dist}. Despite the advantages of the DM_{area} method, there have as yet been no studies investigating its validity and reliability. Given the importance of and need for every measurement method or instrument to be valid and reliable, together with the lack of studies on the validity and reliability of the DM_{area},[12] the objective of the present investigation was to assess the concurrent validity of the DM_{area} method to measure diaphragmatic mobility, as well as to assess the intra- and inter-rater reliability of the method in healthy adults.

METHODS

The present study was approved by the Ethics Committee for Research Involving Human Subjects of Santa Catarina State University (protocol no. 74/2011). All participants gave written informed consent. The study sample consisted of 43 healthy adults between 20 and 59 years of age, who were sampled by convenience, because they lived near or in the catchment area of the hospital where the testing was performed.

To be included in the study, participants needed to have pulmonary function within normal limits. Prospective participants were excluded if they were smokers; were pregnant or suspected of being pregnant; had any cardiorespiratory or neurological disease; had a history of cancer; or were unable to perform any of the study procedures (because of a lack of understanding or cooperation). We also excluded participants for whom the X-ray images obtained did not provide sufficient visibility.

The study was conducted in a physical therapy laboratory and in the radiology department of a public hospital. In the laboratory, participants underwent physical examination, in which anthropometric measurements were recorded, and spirometry was performed on the same day and conducted by a single evaluator. After the initial evaluation, participants were given appointments at the hospital radiology department for the evaluation of diaphragmatic mobility, which was performed by a radiology technician with at least one year of experience.

Participants underwent ventilometry before and during the radiographic examination, to ensure that they performed the respiratory maneuver at the same slow vital capacity (SVC) previously measured. For the DMarea and the DMdist, the mobility of the right hemidiaphragm (RHD) and left hemidiaphragm (LHD) was determined by two observers (rater A and rater B), working independently, at two time points (first and second evaluations, respectively), one-week apart. The same images were analyzed at the first and second evaluations. Both raters were blinded to the identity of the study participants and to the contents of the report provided by the other rater. A third researcher, who was blinded to rater A and B analyses, as well as to which rater was which, made the drawings and used software to perform a random analysis of the area marked by each rater. The X-ray images were analyzed after the completion of all assessments. The RHD was always assessed first.

Anthropometry

For the measurement of body weight and height, we used a previously calibrated scale (W200/5; Welmy, São Paulo, Brazil) and a stadiometer (Welmy), respectively. The body mass index (BMI) was calculated, from the anthropometric values obtained, as weight in kilograms divided by height in meters squared (kg/m^2).

Spirometry

Spirometry was performed with a portable digital spirometer (EasyOne; ndd Medical Technologies, Zurich, Switzerland), calibrated in accordance with the methods and criteria recommended by the American Thoracic Society.[13] The criteria for normal pulmonary function were an FVC ≥ 80% of the predicted value, an FEV_1 ≥ 80% of the predicted value, and an FEV_1/FVC ratio ≥ 0.7.

Ventilometry

Before and during the radiographic examination, SVC maneuvers were measured with a Wright respirometer (Mark 8; nSpire Health Inc., Hertford, England), with the participants in the supine position. Three SVC maneuvers were performed before the radiographic examination, and the highest value was recorded for later comparison with those obtained during the examination. During the radiographic examination, two SVC maneuvers were performed: from TLC to RV (at the time of the recording of the first X-ray image); and from

RV to TLC (at the time of the recording of the second X-ray image). The values of the SVC maneuvers were recorded, and the data recorded before and during the radiographic examination were compared in order to determine whether the participants produced the same respiratory effort before and during the evaluation of diaphragmatic mobility.

Diaphragmatic mobility

In the DM_{dist} and DM_{area}, diaphragmatic mobility was evaluated on the basis of chest X-rays obtained in anteroposterior views. To obtain the X-rays, an experienced, well-qualified radiology technician positioned each participant on an X-ray table in the supine position. Participants were instructed to remain in the same position on the table, moving only their right upper limb to perform the ventilometry maneuver. The radiology technician used a standard distance between the film and the X-ray tube (1.15 m) for all participants, increasing or decreasing the amount of radiation as required.

Images were recorded on two different films, one obtained at maximum inspiration and one obtained at maximum expiration. Prior to exposure, each film was placed into the tray of the X-ray machine, remaining immobile and always in the same position during the exposure. The same researchers accompanied all of the radiographic examinations to their completion, guiding participants in a standardized manner regarding the posture adopted during exposure, providing verbal cues and performing the ventilometry while the images were being obtained. To ensure their safety during the examination, the researchers stood behind a concrete wall with radiological protection barite while guiding the participants through the respiratory maneuvers.

We measured diaphragmatic mobility using the DM_{dist} [11] and DM_{area} [12] methods. For the DM_{dist}, after superimposing the images, the rater identified the highest point of one hemidiaphragm (i.e., at maximum expiration) and drew a longitudinal line to the lowest point of the same hemidiaphragm (i.e., at maximum inspiration). The mobility of the hemidiaphragm, as illustrated in Figure 1, was then determined by measuring the distance between the two points with a caliper.[10] The same procedure was followed to measure the mobility of the other hemidiaphragm. To correct for the magnification of the images caused by divergence of the X-rays, the distance between the two points on the radiopaque X-ray ruler (in mm) was multiplied by 10 and divided by the graduation of the ruler, with the following formula:

$$CM\ (mm) = \frac{MM\ (mm) \times 10\ (mm)}{RG\ (mm)}$$

where CM is the corrected mobility, MM is the mobility measurement, and RG is the ruler graduation.

Figure 2 shows the DM_{area} methodology. After the two images had been superimposed, tracing paper was placed over the X-rays. For each hemidiaphragm, the outlines of the upper, lower, and lateral borders, as well as the right cardiac border in the medial area, were then traced. A 5-cm line was drawn to calibrate the measurement, and the final value was expressed in cm^2. The paper images were scanned, and the area corresponding to the displacement of the diaphragm was calculated with the ImageTool for Windows, version 1.28, developed by the University of Texas Health Science Center at San Antonio.[14]

Table 1. Anthropometric characteristics and pulmonary function variables of the study participants.[a]

Variable	(n = 43)
Age (years)	34 ± 10
Weight (kg)	68.77 ± 15.13
Height (cm)	161.45 ± 36.94
BMI (kg/m^2)	24.20 ± 3.86
FVC	
Measured (L)	5.91 ± 12.23
Estimated (% of predicted)	94.70 ± 9.21
FEV_1	
Measured (L)	3.36 ± 0.68
Estimated (% of predicted)	93.93 ± 8.06
FEV_1/FVC ratio	
Measured	0.83 ± 0.07
Estimated (% of predicted)	100.02 ± 8.15

BMI: body mass index. [a]Values are expressed as mean ± standard deviation.

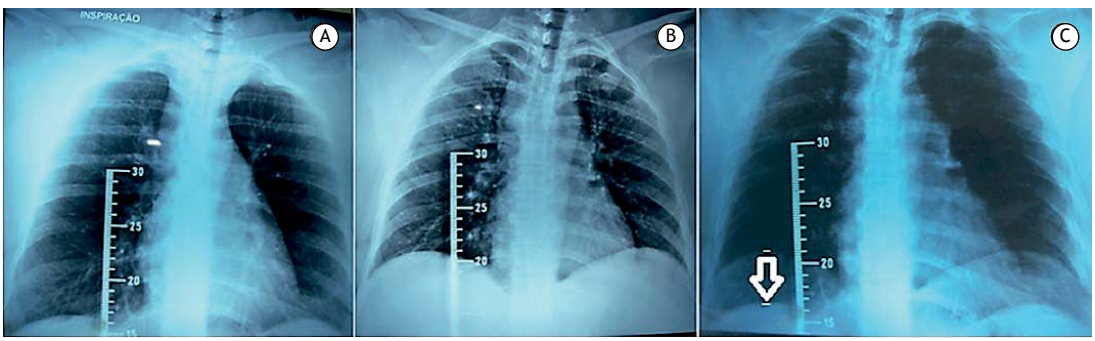

Figure 1. Chest X-rays, in anteroposterior views, used in order to determine the mobility of the right and left hemidiaphragms: A) image obtained at maximum inspiration; B) image obtained at maximum expiration; C) superimposition of images (the image obtained at maximum expiration laid over the image obtained at maximum inspiration), using the radiolopaque ruler as a reference. Source: Saltiel et al.[10]

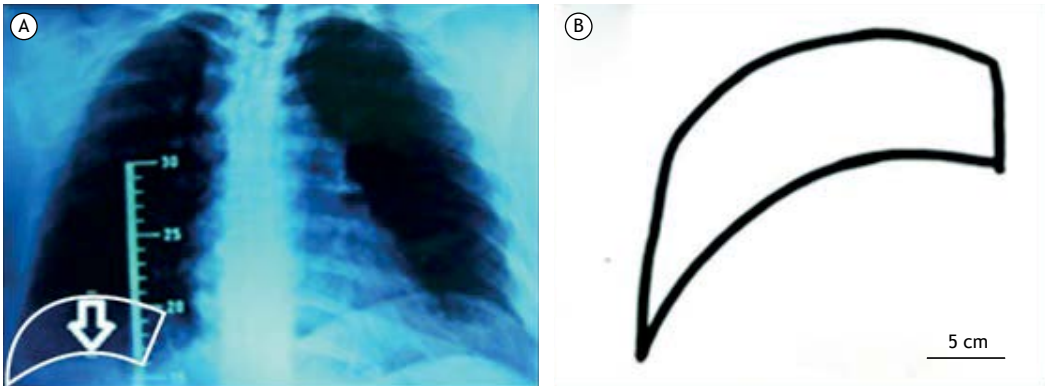

Figure 2. Method of assessing diaphragmatic mobility by area: A) superimposition of images (the image obtained at maximum expiration laid over the image obtained at maximum inspiration); B) Drawing obtained by tracing the left hemidiaphragm at maximum inspiration and at maximum expiration.

Statistical analysis

The data were analyzed with SPSS Statistics software package for Windows, version 20.0 (IBM Corporation, Armonk, NY, USA). To determine the ideal sample size for this study, a preliminary analysis was carried out, based on the criteria established by Toledo et al.[6]—r = 0.65; a statistical power of 90%; and p = 0.001—which indicated that the appropriate minimum sample size would be 38 subjects. The study included 43 individuals, we are confident that the study had sufficient power to detect statistical significance.

Data were checked for normality with the Shapiro-Wilk test, and the homogeneity of variance was checked with Levene's test. Pearson's correlation coefficient was used in order to quantify the strength of the association between the DM_{area} and DM_{dist}. Paired t-tests were conducted in order to compare the SVC values obtained before and during the radiographic examination. The Wilcoxon test was used in order to compare the mobility of the RHD with that of the LHD. The level of significance was set at 5% ($p < 0.05$).

For the radiographic measurements, the intra- and inter-rater reliability, based on consistency, was analyzed by determining the two-way 231 mixed-effects ICC (ICC [2,1]) values and 95% confidence intervals (CIs). The ICC (2,1) was interpreted according to the classification system devised by Carter et al.[15]: 0-0.25 indicating "little or no reliability"; 0.26-0.49 indicating "low reliability"; 0.50-0.69 indicating "moderate reliability"; 0.70-0.89 indicating "high reliability"; and 0.90-1.00 indicating "very high reliability". Bland-Altman analysis[16] was also conducted to allow better visualization of the agreement between measures.

RESULTS

A total of 43 participants were evaluated, including 25 females and 18 males. The mean age was 34 ± 10 years. Table 1 shows the anthropometric characteristics of the participants and the lung function values obtained.

As can be seen in Figure 3, there was a positive correlation between diaphragmatic mobility determined with the DM_{area} method and that determined with the DM_{dist} method ($r = 0.743$; $p < 0.0001$). No statistically significant difference was found between the mean of the SVC maneuvers performed before the radiographic examination and that of those performed during the examination (4.36 ± 0.98 vs. 4.41 ± 1.08; $p = 0.17$).

In the DM_{area} method, no statistically significant differences were found between the mobility of the RHD and that of the LHD. For rater A, the DM_{area} measures of the mobility of the RHD and LHD were 66.12 ± 17.47 cm^2 and 67.31 ± 19.30 cm^2, respectively, in the first evaluation ($p = 0.36$), whereas they were 64.22 ± 15.58 cm^2 and 66.66 ± 18.86 cm^2, respectively, in the second evaluation ($p = 0.15$). For rater B, the $DM_{area,}$ measures of the mobility of the RHD and LHD were 66.36 ± 17.44 cm^2 and 67.54 ± 19.34 cm^2, respectively, in the first evaluation ($p = 0.37$), whereas they were 66.93 ± 16.45 cm^2 and 63.88 ± 17.62 cm^2, respectively, in the second evaluation ($p = 0.054$).

The intra-rater analysis indicated that rater A showed "very high reliability" for the evaluation of the mobility of the RHD and LHD—ICC (2,1) = 0.92 (95% CI: 0.86-0.90) and ICC (2,1) = 0.96 (95% CI: 0.93-0.97), respectively ($p < 0.001$ for both)—as did rater B—ICC (2,1) = 0.90 (95% CI: 0.84-0.94) and ICC (2,1) = 0.91 (95% CI: 0.81-0.95), respectively ($p < 0.001$ for both). The inter-rater analysis indicated "very high reliability" between the first and second evaluations of the RHD—ICC (2,1) = 0.99 (95% CI: 0.98-0.99) and ICC (2,1) = 0.95 (95% CI: 0.86-0.97), respectively ($p < 0.001$ for both)—as well as between the first and second evaluations of the LHD—ICC (2,1) = 0.99 (95% CI: 0.98-0.99) and ICC [2,1] = 0.94 (95% CI: 0.87-0.97), respectively ($p < 0.001$ for both).

Regarding intra-rater agreement, Figure 4 shows Bland-Altman plots indicating good agreement between the measurements of RHD and LHD mobility obtained by each rater, at the two different time points. These are clinically acceptable values. For the inter-rater agreement, the Bland-Altman plots (Figure 5) indicate good agreement between the measures of RHD and LHD mobility obtained by rater A in the first and second

radiographic assessments. The measures obtained by rater B showed good agreement only for the mobility of the RHD.

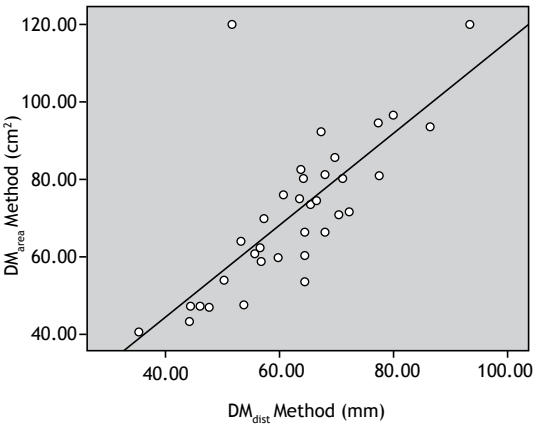

Figure 3. Correlation between diaphragmatic mobility assessed by area (DM_{area} method) and by distance (DM_{dist} method).

DISCUSSION

In the present study, the DM_{area} calculations proved to be valid and reliable, potentially representing an alternative means of assessing diaphragmatic mobility. The DM_{area} method allows the two hemidiaphragms to be assessed directly, using static chest X-ray images. It is a simple method that is readily available at hospitals and clinics, which makes it feasible and applicable in research and clinical practice.[10]

Although the DM_{area} method was not compared with the fluoroscopy method, which is considered the most reliable method, comparisons with the well-established DM_{dist} method revealed its concurrent validity in assessing diaphragmatic mobility.[17] We demonstrated a significant correlation between the range of diaphragmatic mobility values obtained with the DM_{area} method and that of those obtained with the DM_{dist} method. We also found the reliability to be very high (ICC [2,1] > 0.90) for all measurements obtained by both raters. A measure is considered reliable if the ICC is greater than 0.70.[18] Results shown with the

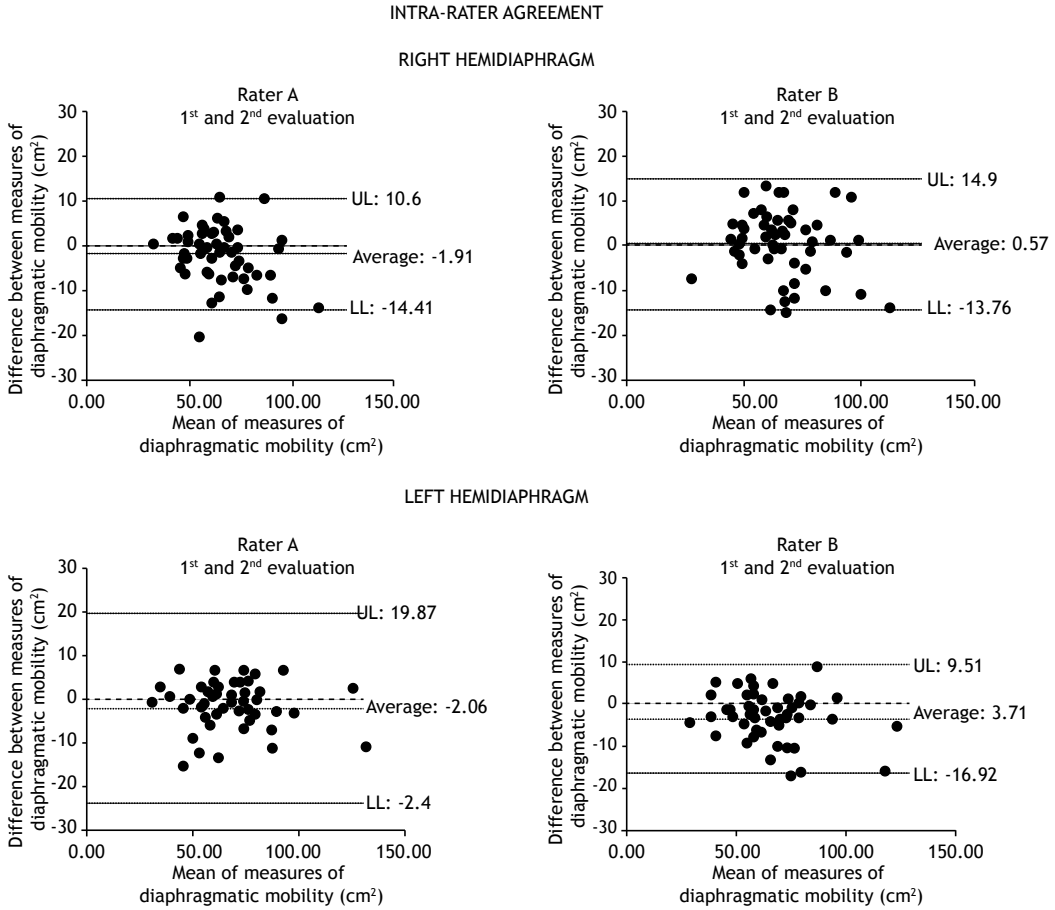

Figure 4. Bland-Altman plots for the analysis of agreement between measures of the mobility of the right and left hemidiaphragms, obtained by rater A and rater B, in the 1st and 2nd evaluations (intra-rater agreement). The x-axes show the means of the measures of diaphragmatic mobility (the measure obtained in the 1st evaluation plus the measure obtained in the 2nd evaluation, divided by 2). The y-axes show the differences between the measures of diaphragmatic mobility (the measure obtained in the second evaluation minus the measure obtained in the first evaluation). UL: upper limit; and LL: lower limit.

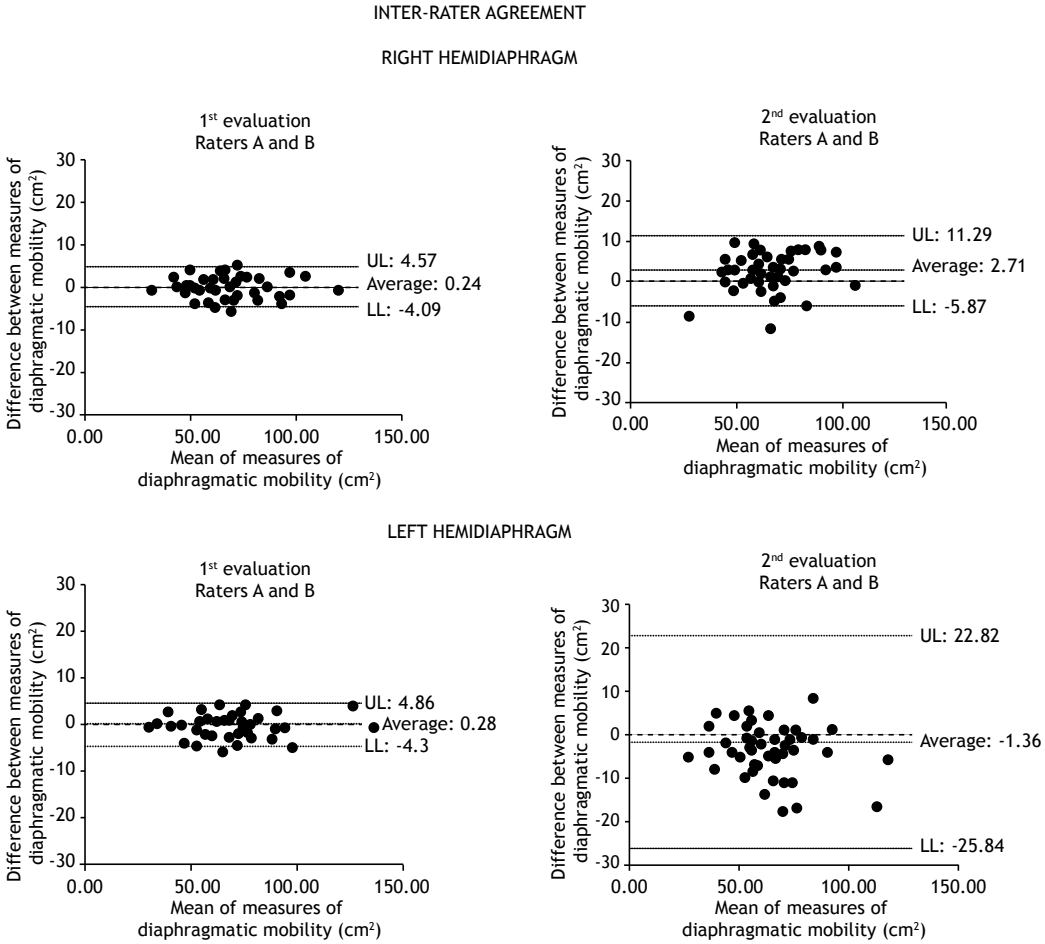

Figure 5. Bland-Altman plots for the analysis of agreement between measures of the mobility of the right and left hemidiaphragms, obtained by raters A and B (inter-rater agreement) in the 1st and 2nd evaluations. The x-axes show the means of measures of diaphragmatic mobility, obtained by raters A and B, for each participant (the measure obtained by rater A plus the measure obtained by rater B, divided by 2). The y-axes show the differences between the measures of diaphragmatic mobility, obtained by raters A and B, for each participant (the measure obtained by rater B minus the measure obtained by rater A). UL: upper limit; and LL: lower limit.

Bland-Altman plots support the idea that there was good agreement between the measurements.

An important factor in achieving the high reliability found in our investigation of the DM_{area} method is very likely the methodological rigor adopted by our two evaluators, given that they had been extensively trained in the use of the method, both following the same exact procedures. In addition, the X-ray technician had ample experience conducting radiographic examinations and standardized the technique to be used, always adopting the same distance between the film and the X-ray tube when conducting the examinations.

For inter-rater agreement, the Bland-Altman analysis showed good agreement between the measures of RHD and LHD mobility obtained by rater A in the first and second evaluations. In the analysis of rater B, there was good agreement for RHD mobility only. The ICC showed that the inter-rater reliability was very high for the first and second evaluations, confirming the overall good reliability of the DM_{area} method.

In the present study, there were no significant differences between the mobility of the RHD and that of the LHD. Our results are similar to those reported in other studies.[19,20] In addition, our own research group recently evaluated diaphragmatic mobility by chest X-ray in 42 patients admitted for cholecystectomy and also found no difference in mobility between the two hemidiaphragms of those patients.[10]

There was considerable variability between the minimum and maximum values of diaphragmatic mobility obtained in our study (from 40.47 cm^2 to 119.94 cm^2). Other studies have also reported high variability in diaphragmatic mobility, the values ranging from 0 mm to 97 mm.[9,19] The possible causes of such variability include the type of sample studied. In the present study, we evaluated not only normal-weight individuals but also those who were obese or overweight, which could have contributed to the wide variability. Obesity is known to hinder respiratory mechanics because a decrease in functional residual capacity due to chest compression results in an elevated diaphragm. [21]

Therefore, increased mechanical work is required for breathing and the diaphragm acts against the pressure of the distended abdomen,[22] which can limit its mobility. However, it is worth noting that this variability does not affect the applicability of the evaluation method.

The main limitations of this study were the position adopted by the participants for the evaluation of diaphragmatic mobility and the radiographic incidence used. In the study conducted by Fernandes et al.,[12] who employed the groundbreaking DM_{area} method, participants were assessed in the orthostatic position and in a posteroanterior view. In our study, we chose to use the supine position and an anteroposterior view, given that the method most consistently reported in the literature (DM_{dist}) evaluates diaphragmatic mobility in that position and view. In addition, more patients are able to assume the supine position than are able to assume the orthostatic position, the use of the former allowing the evaluation of patients in the postoperative period and wheelchair-bound individuals. Although it was not the goal of the study, the results would have been more robust if the method presented had been compared with the gold-standard method (fluoroscopy).

The DM_{area} method proved to be a valid, reliable tool for assessing the extent of the mobility of the LHD and RHD when compared with the more well-established DM_{dist} method. This DM_{area} method is therefore an easy-to-use alternative for evaluating diaphragmatic mobility.

REFERENCES

1. Reid WD, Dechman G. Considerations when testing and training the respiratory muscles. Phys Ther. 1995;75(11):971-82. https://doi.org/10.1093/ptj/75.11.971
2. Yi LC, Nascimento OA, Jardim JR. Reliability of an analysis method for measuring diaphragm excursion by means of direct visualization with videofluoroscopy. Arch Bronconeumol. 2011;47(6):310-4. https://doi.org/10.1016/j.arbr.2010.12.002
3. Maish MS. The diaphragm. Surg Clin N Am. 2010; 90(5):955-68. https://doi.org/10.1016/j.suc.2010.07.005
4. Houston JG, Morris AD, Howie CA, Reid JL, McMillan N. Technical report: quantitative assessment of diaphragmatic movement--a reproducible method using ultrasound. Clin Radiol. 1992;46(6):405-7. https://doi.org/10.1016/S0009-9260(05)80688-9
5. Ayoub J, Cohendy R, Prioux J, Ahmaidi S, Bourgeois JM, Dauzat M, et al. Diaphragm movement before and after cholecystectomy: a sonographic study. Anesth Analg. 2001;92(3):755-61. https://doi.org/10.1213/00000539-200103000-00038
6. Paulin E, Yamaguti WP, Chammas MC, Shibao S, Stelmach R, Cukier A, et al. Influence of diaphragmatic mobility on exercise tolerance and dyspnea in patients with COPD. Respir Med. 2007;101(10):2113-8. https://doi.org/10.1016/j.rmed.2007.05.024
7. Yamaguti WP, Claudino RC, Neto AP, Chammas MC, Gomes AC, Salge JM, et al. Diaphragmatic breathing training program improves abdominal motion during natural breathing in patients with chronic obstructive pulmonary disease: a randomized controlled trial. Arch Phys Med Rehabil. 2012;93(4):571-7. https://doi.org/10.1016/j.apmr.2011.11.026
8. Gierada DS, Slone RM, Fleishman MJ. Imaging evaluation of the diaphragm. Chest Surg Clin N Am. 1998;8(2):237-80.
9. Grams ST, Von Saltiél R, Mayer AF, Schivinski CI, de S Nobre LF, Nóbrega IS, et al. Assessment of the reproducibility of the indirect ultrasound method of measuring diaphragm mobility. Clin Physiol Funct Imaging. 2014;34(1):18-25. https://doi.org/10.1111/cpf.12058
10. Saltiel RV, Grams ST, Pedrini A, Paulin E. High reliability of measure of diaphragmatic mobility by radiographic method in healthy individuals. Braz J Phys Ther. 2013;17(2):128-36. https://doi.org/10.1590/S1413-35552012005000076
11. Toledo NS, Kodaira SK, Massarollo PC, Pereira OI, Mies S. Right hemidiaphragmatic mobility: assessment with US measurement of craniocaudal displacement of left branches of portal vein. Radiology. 2003; 228(2):389-94. https://doi.org/10.1148/radiol.2282011554
12. Fernandes M, Cukier A, Ambrosino N, Leite JJ, Feltrim MI. Respiratory pattern, thoracoabdominal motion and ventilation in chronic airway obstruction. Monaldi Arch Chest Dis. 2007;67(4):209-16.
13. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J. 2005;26(2):319-38. https://doi.org/10.1183/09031936.05.00034805
14. UTHSCSA ImageTool for Windows, Version 1.28. San Antonio (TX) University of Texas Health Science Center at San Antonio, Image Processing and Analysis Program; 1997.
15. Carter R, Lubinsky J, Domholdt E, editors. Rehabilitation Research: Principles and Applications. 4th ed. Philadelphia: WB Saunders Company; 2013.
16. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet. 1986;1(8476):307-10. https://doi.org/10.1016/S0140-6736(86)90837-8
17. Maher CG, Latimer J, Costa LO. The relevance of cross-cultural adaptation and clinimetrics for physical therapy instruments. Rev Bras Fisioter. 2007;11(4):245-52. https://doi.org/10.1590/S1413-35552007000400002
18. Freedman D, Pisani R, Purves R. Statistics. 4th ed. New York (NY): WW Norton & Company; 2008.
19. Boussuges A, Gole Y, Blanc P. Diaphragmatic motion studied by m-mode ultrasonography: methods, reproducibility, and normal values. Chest. 2009;135(2):391-400. https://doi.org/10.1378/chest.08-1541
20. Kantarci F, Mihmanli I, DemireL MK, Harmanci K, Akman C, Aydogan F, et al. Normal diaphragmatic motion and the effects of body composition: determination with M-mode sonography. J Ultrasound Med. 2004;23(2):255-60. https://doi.org/10.7863/jum.2004.23.2.255
21. Enzi G, Baggio B, Vianello A. Respiratory disturbances in visceral obesity. Int J Obesity. 1990;14(26).
22. Zerah F, Harf A, Perlemuter L, Lorino H, Lorino AM, Atlan G. Effects the obesity on respiratory resistance. Chest. 1993;103(5):1470-6. https://doi.org/10.1378/chest.103.5.1470

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Mini-thoracostomy with vacuum-assisted closure: a minimally invasive alternative to open-window thoracostomy

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ABSTRACT

Thoracostomy is a common treatment option for patients with stage III pleural empyema who do not tolerate pulmonary decortication. However, thoracostomy is considered mutilating because it involves a thoracic stoma, the closure of which can take years or require further surgery. A new, minimally invasive technique that uses the vacuum-assisted closure has been proposed as an alternative to thoracostomy. This study aims to analyze the safety and effectiveness of mini-thoracostomy with vacuum-assisted closure in an initial sample of patients.

Keywords: Infection; Empyema, pleural; Negative-pressure wound therapy; Thoracostomy.

Pleural empyema is a source of major morbidity and mortality worldwide. Recent studies have demonstrated that the incidence of pleural empyema remains high even in developed countries.[1] The recommended treatment for stage III pleural empyema, which is characterized by trapped lung,[2] is pulmonary decortication,[3] a major surgical procedure that produces significant surgical trauma and considerable morbidity/mortality, principally in patients with chronic comorbidities or who are elderly.[4] A less invasive alternative for treating phase lll pleural empyema is thoracostomy as classically described by Eloesser.[5] Thoracostomy has the advantage of being a minor surgical procedure that is quite effective in resolving infection. However, the procedure is considered mutilating because it depends on the creation of a large stoma, usually involving a 12 cm × 12 cm area and resection of at least two ribs (three ribs in most cases). Stoma closure can take years or require further surgery. In addition, even with thoracostomy closure, the anatomy of the rib cage is profoundly altered.

Vacuum-assisted closure was first investigated by Morykwas et al. in 1997.[6] Their original work follows on from studies of negative pressure that suggested that it improved healing.[7] The first data showed that negative pressure increased blood flow and local hyperemia.[8]

Currently, vacuum-assisted closure is a widely accepted technique for treatment of various types of infected wounds.[9] A recent systematic review[10] concluded that quality of life is initially impacted, especially in the first week, probably because of the anxiety caused by the constant presence of the device; however, at the end of therapy, the results regarding quality of life are superior to those of the control group.

Among the intracavitary indications for vacuum-assisted closure are treatment of perforated diverticulitis, peritonitis, and abdominal sepsis, with studies demonstrating not only the safety of using the vacuum-assisted closure in contact with the viscera but also the efficacy of the technique.[11,12]

In the chest, the most well-established indication for vacuum-assisted closure is treatment of mediastinitis following cardiac surgery.[13] A review published in 2013[14] concluded that, for patients with mediastinitis following cardiac surgery, the vacuum-assisted closure is better tolerated by the patient because it precludes the need for daily dressing changes, resulting in granulation and healing more rapidly and in reduced length of hospital stay.

The use of the intrapleural device was first targeted at accelerating thoracostomy closure. A retrospective study published in 2009[15] compared 11 patients who underwent thoracostomy with vacuum-assisted closure for treatment of pleural empyema with 8 patients who underwent thoracostomy with standard care. All of the patients in the group submitted to vacuum-assisted closure responded well, and the thoracostomy closed

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spontaneously or was closed with a muscle flap. In contrast, in the control group, stoma closure occurred in only 2 patients over a one-year follow-up period. In addition, there were 4 deaths in the control group.

Another possible, intrathoracic application of the vacuum-assisted closure technique is as an adjuvant in the treatment of empyema following pneumonectomy. A study compiling data from 9 papers concluded that the use of vacuum in these cases can reduce morbidity and length of hospital stay.[16]

Recently, Hofmann et al.[17] described a minimally invasive technique using a vacuum-assisted closure device that can be used as an alternative to thoracostomy in patients with phase III pleural empyema. The advantage of the technique is that it does not require rib resection, making the procedure less harmful from an aesthetic and functional standpoint. In addition, time to thoracostomy closure, which can also be regarded as time to resolution of the condition, appears to be shorter with the use of this minimally invasive technique. The disadvantage is the possible need for dressing changes and the high cost of using vacuum-assisted closure.

The same group[15] described a larger sample, consisting of 15 patients with postoperative or recurrent pleural empyema of parapneumonic etiology who underwent intrapleural vacuum-assisted closure without thoracoscopy. Study entry criterion was a Karnofsky performance status ≤ 50%, reflecting the frailty of that group of patients; patients with a bronchopleural fistula were excluded. The device used was a model that creates vacuum and also provides an antibiotic solution. Of those 15 patients, 7 had postoperative empyema. Overall, the results were as follows: resolution of the condition, in 11 patients; death, in 1; recurrence, in 1; and need for conversion to thoracostomy, in 2. The authors concluded that, considering the severity of those patients, the use of intrapleural vacuum-assisted closure provides a good response, with low morbidity and no deformities due to thoracostomy.

Despite the good results reported by the aforementioned studies, there have been no studies comparing the technique advocated by Hofmann et al.[17] with conventional thoracostomy in terms of effectiveness, duration of treatment, and incidence of complications.

Our group is responsible for treating a large number of patients with pleural empyema at various levels of severity. We consider vacuum-assisted closure, which is clearly less invasive than thoracostomy, an important item that should be included in our therapeutic arsenal, as long as the former is shown to have similar safety and efficacy to the latter. This study aims to analyze the efficacy and safety of vacuum-assisted closure in an initial sample of 3 patients, as well as discussing details about the technique.

The technique we standardized consists of placing the patient, under general anesthesia, in the supine position contralateral to the affected hemithorax and making a 5- to 6-cm incision like a mini-thoracotomy in the area defined by CT as the one with the largest cavity. The intercostal muscles are sectioned, and the pleural cavity is breached. To facilitate cleaning, we use a (30-degree) 10-mm endoscope and we aspirate secretions and remove debris with forceps and a pump; however, we emphasize that no attempt is made at performing decortication, in order not to cause air leakage (a possible contraindication to the use of vacuum). The cavity is washed with saline, and the volume of saline infused is used in the measurement. Subsequently, the vacuum-assisted closure sponge is introduced into the cavity, with care being taken to protect the skin, as well as the subcutaneous cellular tissue and muscle. Externally, the vacuum-assisted closure dressing is sealed with adhesive film. Finally, the dressing is connected to the vacuum-assisted closure tubing. The suction level is set to −125 mmHg (Figure 1). Patients are concomitantly treated with standard, culture-guided antibiotic therapy. Dressing changes are performed within 4-7 days—in the cases reported here, all dressing changes were performed on postoperative day 4—and the technique consists of removing the sponge, washing the cavity, measuring its volume with saline, and replacing the sponge into the cavity as described above. The parameters we use for consideration of closure are wound site status, assessed during dressing changes, and clinical improvement. For closure, we remove the sponge, wash and obliterate the cavity with saline plus gentamicin (in a procedure similar to that described by Clagett),[3] and close the skin. We do not use the video system for the dressing change or for closure.

Below, we describe the three cases.

Case 1: a 20-year-old male patient presented with a diagnosis of empyema secondary to retained pneumothorax. The patient underwent mini-thoracostomy with vacuum-assisted closure, a dressing change was performed on postoperative day 4, and the mini-thoracostomy was closed on postoperative day 7. There was a reduction in the volume of the residual cavity, from 200 mL to 30 mL. Hospital discharge occurred on postoperative day 8. The patient was asymptomatic at the outpatient follow-up visit six months later.

Case 2: a 44-year-old male patient presented with a diagnosis of parapneumonic empyema and no improvement of his condition following closed chest tube drainage. The patient underwent mini-thoracostomy with vacuum-assisted closure. A dressing change was performed on postoperative day 4, and the mini-thoracostomy was closed on postoperative day 7; there was a reduction in the residual cavity from 500 mL to 100 mL. The patient was discharged without symptoms on postoperative day 8 and had no complaints at the follow-up visit three months later.

Case 3: a 66-year-old male patient presented with a diagnosis of parapneumonic empyema. The patient underwent mini-thoracostomy with vacuum-assisted closure. A dressing change was performed on postoperative day 4, and the mini-thoracostomy was

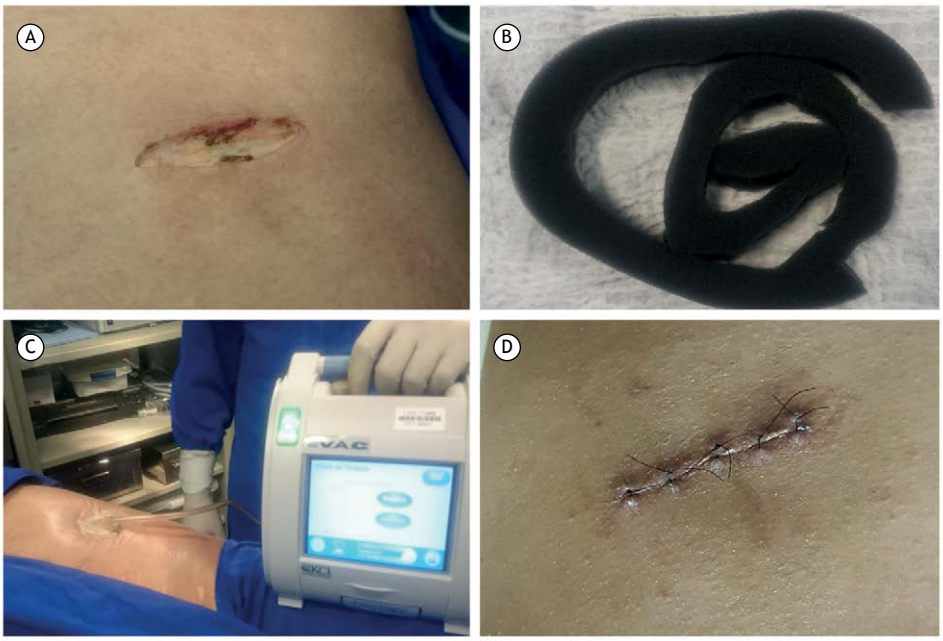

Figure 1. Photographs related to the technique. In A, incision; in B, sponge cut to fit the pleural cavity; in C, system connected to the patient and set to a pressure level of −125 mmHg; and, in D, final appearance after 15 days of closure.

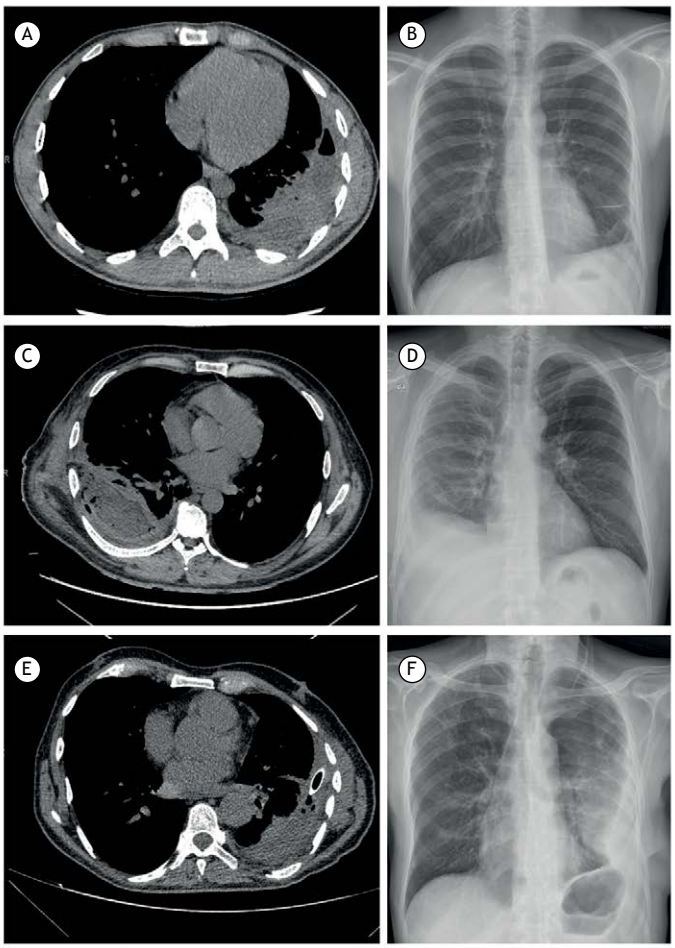

Figure 2. Preoperative chest CT scans and postoperative chest X-rays of cases 1 (in A and B), 2 (in C and D), and 3 (in E and F), respectively.

closed on postoperative day 7; there was a reduction in the residual cavity from 300 mL to 60 mL. The patient was discharged on postoperative day 11 after completing 7 days of antibiotic therapy. He had no complaints at the follow-up visit two months later.

In all of the cases, we achieved the primary goal of resolving infection. The length of hospital stay after the procedure ranged from 8 to 11 days, and the antibiotics were discontinued within 7 days in all of the cases. The shortest follow-up period was two months, and the patient showed no signs of recurrent infection. One characteristic we observed was that, contrary to our initial expectation, the vacuum-assisted closure failed to obliterate the entire cavity; however, it appears to promote rapid sterilization of the cavity, which allows closure, even with residual space (Figure 2).

With regard to safety issues, none of the patients developed complications that could be attributed to the procedure or the device. Pain during use of the vacuum-assisted closure, in all of the cases, was adequately controlled by analgesia with opioids (tramadol or codeine) and common analgesics (dipyrone). None of the patients had complaints of chronic pain during outpatient follow-up. To avoid re-exposure to radiation and reduce costs, we chose to follow patients with routine chest X-rays, eliminating the use of postoperative CT scans.

The impression derived from the observation of these three cases is that the technique is feasible, safe, and reasonably effective. Certainly, this small experience, even if combined with the findings of previously published studies, does not serve as conclusive evidence. Further, preferably comparative, studies are needed to determine the true place of this technique in the therapeutic arsenal against pleural empyema.

REFERENCES

1. Bouros D, Schiza S, Tzanakis N, Chalkiadakis G, Drositis J, Siafakas N. Intrapleural urokinase versus normal saline in the treatment of complicated parapneumonic effusions and empyema. A randomized, double-blind study. Am J Respir Crit Care Med. 1999;159(1):37-42. https://doi.org/10.1164/ajrccm.159.1.9803094
2. Andrews NC, Parker EF, Shaw RR, Wilson NJ, Webb WR. Management of nontuberculous empyema: a statement of the subcommittee on surgery. Am Rev Respir Dis. 1962;85:935-6.
3. Scarci M, Abah U, Solli P, Page A, Waller D, van Schil P, et al. EACTS expert consensus statement for surgical management of pleural empyema. Eur J Cardiothorac Surg. 2015;48(5):642-53. https://doi.org/10.1093/ejcts/ezv272
4. Schweigert M, Solymosi N, Dubecz A, Fernández MJ, Stadlhuber RJ, Ofner D, Stein HJ. Surgery for parapneumonic pleural empyema--What influence does the rising prevalence of multimorbidity and advanced age has on the current outcome? Surgeon. 2016;14(2):69-75. https://doi.org/10.1016/j.surge.2014.05.002
5. Eloesser L. An operation for tuberculous empyema. Chest. 1935;1(8):8-9, 23. https://doi.org/10.1378/chest.1.8.8
6. Morykwas MJ, Argenta LC, Shelton-Brown EI, McGuirt W. Vacuum-assisted closure: a new method for wound control and treatment: animal studies and basic foundation. Ann Plast Surg. 1997;38(6):553-62. https://doi.org/10.1097/00000637-199706000-00001
7. Lambert KV, Hayes P, McCarthy M. Vacuum assisted closure: a review of development and current applications. Eur J Vasc Endovasc Surg. 2005;29(3):219-26. https://doi.org/10.1016/j.ejvs.2004.12.017
8. Greer SE. Whither sub atmospheric dressing? Ann Plast Surg. 2000;45(3):332-4; discussion 335-6. https://doi.org/10.1097/00000637-200045030-00019
9. Willy C, Agarwal A, Andersen CA, Santis G, Gabriel A, Grauhan O, et al. Closed incision negative pressure therapy: international multidisciplinary consensus recommendations. Int Wound J. 2017;14(2):385-398. https://doi.org/10.1111/iwj.12612
10. Janssen AH, Mommers EH, Notter J, de Vries Reilingh TS, Wegdam JA. Negative pressure wound therapy versus standard wound care on quality of life: a systematic review. J Wound Care. 2016;25(3):154, 156-9. https://doi.org/10.12968/jowc.2016.25.3.154
11. Perathoner A, Klaus A, Mühlmann G, Oberwalder M, Margreiter R, Kafka-Ritsch R. Damage control with abdominal vacuum therapy (VAC) to manage perforated diverticulitis with advanced generalized peritonitis--a proof of concept. Int J Colorectal Dis. 2010;25(6):767-74. https://doi.org/10.1007/s00384-010-0887-8
12. Bleszynski MS, Chan T, Buczkowski AK. Open abdomen with negative pressure device vs primary abdominal closure for the management of surgical abdominal sepsis: a retrospective review. Am J Surg. 2016;211(5):926-32. https://doi.org/10.1016/j.amjsurg.2016.01.012
13. Sjögren J, Malmsjö M, Gustafsson R, Ingemansson R. Poststernotomy mediastinitis: a review of conventional surgical treatments, vacuum-assisted closure therapy and presentation of the Lund University Hospital mediastinitis algorithm. Eur J Cardiothorac Surg. 2006;30(6):898-905. https://doi.org/10.1016/j.ejcts.2006.09.020
14. Yu AW, Rippel RA, Smock E, Jarral OA. In patients with post-sternotomy mediastinitis is vacuum-assisted closure superior to conventional therapy? Interact Cardiovasc Thorac Surg. 2013;17(5):861-5. https://doi.org/10.1093/icvts/ivt326
15. Sziklavari Z, Ried M, Neu R, Schemm R, Grosser C, Szöke T, et al. Mini-open vacuum-assisted closure therapy with instillation for debilitated and septic patients with pleural empyema. Eur J Cardiothorac Surg. 2015;48(2):e9-16. https://doi.org/10.1093/ejcts/ezv186
16. Haghshenasskashani A, Rahnavardi M, Yan TD, McCaughan BC. Intrathoracic application of a vacuum-assisted closure device in managing pleural space infection after lung resection: is it an option? Interact Cardiovasc Thorac Surg. 2011;13(2):168-74. https://doi.org/10.1510/icvts.2011.267286
17. Hofmann HS, Neu R, Potzger T, Schemm R, Grosser C, Szöke T, et al. Minimally Invasive Vacuum-Assisted Closure Therapy With Instillation (Mini-VAC-Instill) for Pleural Empyema. Surg Innov. 2015;22(3):235-9. https://doi.org/10.1177/1553350614540811

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Characterization and outcomes of pulmonary alveolar proteinosis in Brazil: a case series

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ABSTRACT

Objective: Pulmonary alveolar proteinosis (PAP) is a rare disease, characterized by the alveolar accumulation of surfactant, which is composed of proteins and lipids. PAP is caused by a deficit of macrophage activity, for which the main treatment is whole-lung lavage (WLL). We report the experience at a referral center for PAP in Brazil. **Methods:** This was a retrospective study involving patients with PAP followed between 2002 and 2016. We analyzed information regarding clinical history, diagnostic methods, treatments, and outcomes, as well as data on lung function, survival, and complications. **Results:** We evaluated 12 patients (8 of whom were women). The mean age was 41 ± 15 years. Most of the patients were diagnosed by means of BAL and transbronchial biopsy. The mean number of WLLs performed per patient was 2.8 ± 2.5. One third of the patients never underwent WLL. Four patients (33.3%) had associated infections (cryptococcosis, in 2; nocardiosis, in 1; and tuberculosis, in 1), and 2 (16.6%) **died:** 1 due to lepidic adenocarcinoma and 1 due to complications during anesthesia prior to WLL. When we compared baseline data with those obtained at the end of the follow-up period, there were no significant differences in the functional data, although there was a trend toward an increase in SpO_2. The median follow-up period was 45 months (range, 1-184 months). The 5-year survival rate was 82%. **Conclusions:** To our knowledge, this is the largest case series of patients with PAP ever conducted in Brazil. The survival rate was similar to that found at other centers. For symptomatic, hypoxemic patients, the treatment of choice is still WLL. Precautions should be taken in order to avoid complications, especially opportunistic infections.

Keywords: Pulmonary alveolar proteinosis; Bronchoalveolar lavage; Opportunistic infections.

INTRODUCTION

Pulmonary alveolar proteinosis (PAP) is a rare disease, characterized by the alveolar accumulation of surfactant—which is composed of proteins and lipids—and caused by a deficit of macrophage activity.[1-3] Epidemiological data show that the estimated prevalence of PAP is 0.37 cases per 100,000 population, most (approximately 90%) of the cases having an autoimmune etiology. The mean age at diagnosis is in the fourth decade of life, PAP being more prevalent in men than in women and being associated with smoking.[3] The main symptoms are cough and dyspnea, and physical examination is usually unremarkable.[3,4] The initial diagnosis of PAP is based on imaging findings (preferably HRCT findings) consistent with the disease, the most common CT finding being the crazy-paving pattern (septal thickening superimposed on areas of ground-glass attenuation typically bilateral and widespread).[5] The diagnosis is then confirmed by the BAL fluid, which is typically milky in appearance. Although a diagnosis of PAP can be made without a surgical lung biopsy, the procedure is considered the gold standard for the diagnosis of PAP.[1,3,4]

On the basis of its etiology, PAP is classified as autoimmune PAP (formerly known as primary or idiopathic PAP), secondary PAP, or congenital PAP (also known as hereditary PAP). Autoimmune PAP is the most common of the three, being characterized by the presence of anti-GM-CSF antibodies. Secondary PAP is associated with hematologic diseases, neoplasms, toxic inhalations, and infections. Congenital PAP is the rarest form of PAP and usually occurs in children as a result of deficient surfactant production caused by mutations in the *SFTPB* gene, the *SFTPC* gene, the *ABCA3* gene, or the *NKX2-1* gene; changes in the GM-CSF receptor; or other mutations, such as *GATA2* and telomerase complex mutations.[1-4] Neutralizing anti-GM-CSF IgG antibodies can be found in the serum and BAL fluid of patients with autoimmune PAP. Autoantibodies neutralize alveolar macrophage activity and cause alveolar macrophage dysfunction, thus affecting surfactant catabolism and clearance from the distal air spaces. In cases of congenital PAP, defective surfactant clearance is primarily caused by mutations in genes encoding surfactant proteins or GM-CSF receptor chains, preventing GM-CSF from binding to its membrane

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receptor.[6] In contrast, secondary PAP occurs in several diseases involving reduced alveolar macrophage numbers or function, including myelodysplastic syndromes, leukemias, and lymphomas,[1,7-10] as well as solid tumors[11,12] and infections (including tuberculosis, nocardiosis, and pneumocystosis),[1,4,6,8,10,13-17] together with environmental or occupational exposure to substances such as silica, aluminum, titanium, and certain fertilizers.[1,3,4,6,8,13,18,19]

The course of PAP varies widely among individuals, ranging from spontaneous resolution to rapid progression to respiratory failure.[3,5,20,21] The treatment of PAP is variable, and, in cases of secondary PAP, the underlying cause should be treated. For patients with autoimmune PAP, available treatments include whole-lung lavage (WLL), GM-CSF replacement therapy, anti-CD20 monoclonal antibody (rituximab) use, and lung transplantation.[3,4] During WLL, the initial effluent is typically milky and the supernatant is foamy because of the proteinaceous material filling the alveoli; as the procedure progresses, the effluent becomes clearer, ideally acquiring the same appearance as that of the instilled fluid. The 5-year survival rate ranges from 75%[3] to 95%.[1,4,13] In 1991, Lorenzi-Filho et al.[22] reported a series of cases of patients who had been followed between 1983 and 1989 and in whom the diagnosis of PAP had been confirmed by biopsy, 3 patients having shown clinical and radiological improvement after WLL and 1 patient having achieved spontaneous remission. Below, we report the experience at a referral center for PAP in Brazil.

METHODS

This was a retrospective study involving PAP patients followed at our institution between 2002 and 2016, data being collected by reviewing patient medical records. We analyzed information regarding demographic characteristics, clinical history, diagnostic methods, treatments, and outcomes (including survival and complications).

Spirometry was performed with a calibrated pneumotachograph (Koko® PFT; nSpire Health Inc., Longmont, CO, USA). We collected data on the following variables: FVC, FEV_1, and FEV_1/FVC. The predicted values were derived from the reference values for the Brazilian population.[23,24] We also collected data on room-air pulse oximetry. We included no data on DLCO, because they were not consistently available for all patients at the time of the study. Given that arterial blood gas data were available for most of the patients who had undergone WLL, we evaluated pre- and post-WLL PaO_2 values and alveolar-arterial oxygen gradients.

Continuous variables with normal distribution were expressed as mean and standard deviation, whereas those with non-normal distribution were expressed as median and interquartile range. Categorical variables were expressed as proportions. A paired t-test was used in order to compare functional data at diagnosis with the latest available functional data. Values of $p < 0.05$ were considered significant. Survival was estimated by the Kaplan-Meier method. Data were analyzed with the program SigmaStat, version 3.5 (Systat Software, Inc., San Jose, CA, USA).

Table 1. Clinical and demographic characteristics of the study sample (N = 12).[a]

Variable	Result
Female gender	8 (66.7)
Age, years	41 ± 15
Dyspnea at diagnosis	12 (100)
Smokers (current or former)	2 (16.6)
Exposure	
Birds	3 (25.0)
Mold	1 (8.3)
Diagnosis	
BAL	9 (75.0)
Open lung biopsy	3 (25.0)

[a]Values expressed as n (%) or mean ± SD.

RESULTS

A total of 12 patients were included in the study. Their demographic and clinical characteristics are presented in Table 1. Most (66.7%) of the patients were female, and the mean age was 41 ± 15 years. Two patients were over 60 years of age. Most (75%) of the patients had been diagnosed with PAP by BAL and transbronchial biopsy. A body mass index > 25 kg/m^2 was a common finding, 4 patients being neither overweight nor obese. Despite having PAP, 1 young patient was a habitual cyclist. Treatments and primary outcomes are shown in Table 2. Pre- and post-WLL HRCT scans of the chest of 1 of the 12 patients in our series are shown in Figure 1, and the fluid collected during one of the WLL procedures performed is shown in Figure 2. One third of the patients never underwent WLL and remained clinically stable. In

Table 2. Treatments, major complications, and outcomes (N = 12).[a]

Variable	Result
WLL	
Number of patients undergoing WLL (n, %)	8 (66.7)
Number of procedures per patient	2.8 ± 2.5
Other forms of treatment	
GM-CSF replacement therapy	2 (16.6)
Anti-CD20 monoclonal antibody (rituximab)	2 (16.6)
Neoplasm	1 (8.3)
Infection	4 (33.3)
Tuberculosis	1 (8.3)
Nocardiosis	1 (8.3)
Cryptococcosis	2 (16.6)
Death	2 (16.6)
Neoplasm	1 (8.3)
WLL complications	1 (8.3)

WLL: whole-lung lavage. [a]Values expressed as n (%) or mean ± SD.

contrast, 8 patients underwent WLL multiple times (mean number of procedures per patient, 2.8 ± 2.5; highest number of procedures per patient, 7; lowest number of procedures per patient, 2). The longest interval between 2 WLL procedures was 7 years, the mean interval between procedures being 1.9 years. With regard to other forms of treatment, 2 patients received GM-CSF replacement therapy, which resulted in improvement for 4 months in 1, whereas another 2 received a single course of treatment with rituximab. Of the 12 patients studied, 4 (33%) had opportunistic infections—cryptococcosis, in 2; nocardiosis, in 1; and tuberculosis, in 1—none of which were related to the treatments received. During the follow-up period, 3 patients reported exposure to birds and 1 patient reported exposure to mold. Of the 12 patients studied, 2 died: 1 of lepidic adenocarcinoma and 1 of pre-WLL complications (cardiopulmonary arrest secondary to hypoxemia during induction of anesthesia). Table 3 shows data on lung function and SpO_2 at diagnosis, as well as the latest available data (for the period from diagnosis to death or the last visit). No significant differences were found between baseline functional data and the latest available functional data, although there was a trend toward an increase in SpO_2. Pre- and post-WLL arterial blood gas data were available for 5 patients. Mean PaO_2 values increased from 48 ± 10 mmHg to 69 ± 9 mmHg (p = 0.01), whereas mean alveolar-arterial oxygen gradients decreased from 47 ± 9 mmHg to 23 ± 5 mmHg (p = 0.03). The median follow-up period (from diagnosis to death or the last evaluation) was 45 months (range, 1-184 months). The 1-, 3-, and 5-year survival rates were 91%, 82%, and 82%, respectively (Figure 3).

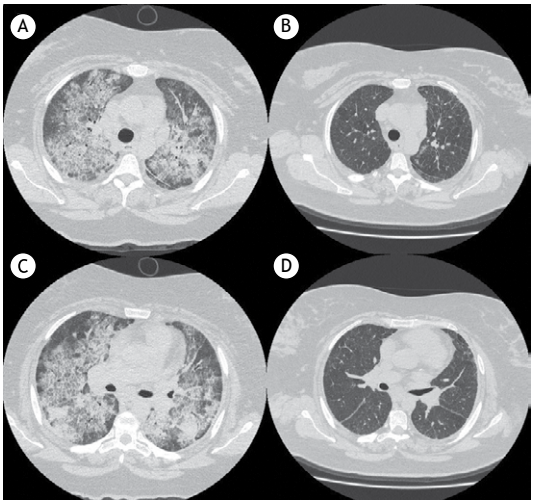

Figure 1. CT scans of the chest of a patient with pulmonary alveolar proteinosis, showing diffuse ground-glass opacities and interlobular septal thickening (the crazy-paving pattern). In A and C, chest CT scans performed before whole-lung lavage. In B and D, chest CT scans performed after the procedure, showing improvement.

Figure 2. Flasks containing alveolar lavage fluid from a patient with pulmonary alveolar proteinosis. Note that the fluid became progressively less turbid (from left to right).

DISCUSSION

Despite controversy, WLL remains the treatment of choice for PAP. The procedure is aimed at removing the surfactant material deposited in the alveoli as a result of macrophage dysfunction, thereby improving gas diffusion. More than 60% of patients undergoing WLL have been shown to respond well to two procedures per lung. Few patients require more than six WLL cycles, and less than 10% of patients do not respond to WLL.[25] Asymptomatic or oligosymptomatic patients with normal or near-normal lung function and without hypoxemia

Table 3. Lung function and SpO_2: baseline data and latest available data for the 2002-2016 period (n = 10).

Variable	Baseline data	Latest available data	p
FEV_1, L	2.11 ± 0.61	2.16 ± 0.43	0.66
FEV_1, % predicted	76 ± 20	77 ± 15	0.89
FVC, L	2.47 ± 0.74	2.62 ± 0.54	0.30
FVC, % predicted	75 ± 20	78 ± 15	0.55
FEV_1/FVC	0.85 ± 0.05	0.82 ± 0.03	0.18
SpO_2, %	87 ± 12	94 ± 7	0.08

[a]Values expressed as mean ± SD.

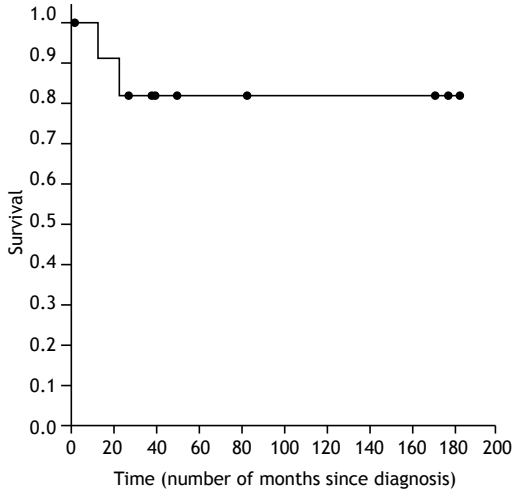

Figure 3. Kaplan-Meier survival curve.

require periodic evaluation rather than immediate treatment. Symptomatic patients with moderate to severe lung function impairment, hypoxemia, or both can undergo WLL; although there is no consensus regarding which PAP patients should undergo WLL, those with moderate or severe dyspnea at rest or dyspnea on exertion and a PaO_2 of < 60 mmHg at rest or an SpO_2 of < 90% during exercise testing are candidates for the procedure.[2,6] WLL is performed under general anesthesia, with the use of a double-lumen endotracheal tube and single-lung ventilation. Large saline volumes (of 10-15 L or more) are required, aliquots of 150-200 mL being infused. The initial returns are typically turbid, and the lavage should continue until the effluent becomes clear. A repeat WLL might be necessary during patient follow-up.[1-6,8,10,13,26] Some of our patients never underwent WLL and remained clinically stable, whereas others underwent multiple WLL procedures, findings that are consistent with the literature. In specific cases, segmental lung lavage is warranted.[1,4] If the symptoms recur, if there is no response to WLL, or if WLL is contraindicated, inhaled or subcutaneous GM-CSF is an option. Another option is to use rituximab, an anti-CD20 monoclonal antibody. Both options have shown promising results. In our case series, 2 patients received GM-CSF replacement therapy. Of those, 1 remained clinically stable for 4 months but required a repeat WLL during clinical follow-up. Another 2 patients received a single loading dose of rituximab, a medication that is not widely available at our institution. Neither patient responded satisfactorily to treatment, possibly because the medication was used for a short period of time. Lung transplantation is an option for patients with advanced PAP.[1,3,4]

Pulmonary function tests and exercise capacity tests play an important role in follow-up and therapeutic decisions. Although spirometry typically shows a restrictive pattern, results are normal in 10-30% of cases. Smokers can present with an obstructive pattern. The most common and significant changes are hypoxemia and reduced DLCO.[1] According to Borie et al.,[1] WLL results in symptomatic, radiological, and functional improvement in 85% of patients (mean improvement in FEV_1, 0.26 L; mean improvement in FVC, 0.5 L; mean improvement in DLCO, 4.4 mL/mmHg/min; and mean improvement in PaO_2, 20 mmHg). We found no significant changes in lung function when we compared the data obtained at baseline with those obtained during the last visit. Although baseline values were at the lower limits of normal, they did not worsen over time. However, there was a trend toward an increase in SpO_2. Arterial blood gas data were available for 5 patients. There was an increase in PaO_2 and a decrease in the alveolar-arterial oxygen gradient after WLL, findings that confirm the impact of WLL on gas exchange.

Two patients died: 1 of lepidic adenocarcinoma and 1 of pre-WLL complications (cardiopulmonary arrest secondary to hypoxemia during induction of anesthesia), the latter patient having presented with a difficult airway. However, fatal complications are rare.[4,10] Other possible complications include hydropneumothorax, pleural collections, endotracheal granuloma, stenosis due to multiple procedures, and surgical emphysema,[1,3,4,8,10] none of which were observed in any of our patients. Of the 12 patients in our series, 1 was lost to follow-up. She was followed at our institution for 1 month only and was lost to follow-up because she resided in another state. The mean 5-year survival rate was 82%, which is similar to those found in other studies (i.e., 75-95%).[1,3,4,13]

Precautions should be taken in order to avoid opportunistic infections in patients with PAP; macrophage deficiency, changes in surfactant proteins, and intra-alveolar accumulation of surfactant components result in a favorable environment for the growth of microorganisms.[3,4,8,10] Major pathogens include *Nocardia* spp., *Pneumocystis* spp., *Acinetobacter* spp., *Aspergillus* spp., and *Cladosporium* spp., as well as *Mycobacterium tuberculosis* and other mycobacteria.[3,4,8,10] Of the 12 patients in our series, 4 had opportunistic infections—cryptococcosis, in 2; nocardiosis, in 1; and tuberculosis, in 1—none of which were related to the treatments received. The infections were identified during the follow-up period, and all 4 patients responded well to pathogen-specific treatment.

Neoplastic diseases can cause secondary PAP, which is often associated with hematologic malignancies.[10,12] There are few reported cases of PAP associated with solid organ cancer, PAP having been reported to occur prior to or coincidentally with lung neoplasms—including squamous cell lung carcinoma, adenocarcinoma, mesothelioma, glioblastoma, and metastatic melanoma—or breast cancer.[10,12] With regard to autoimmunity, only 1 patient tested positive for ANF, rheumatoid factor, and anti-Ro antibodies. Although determination of serum levels of autoantibodies to GM-CSF is a simple and rapid test for autoimmune PAP, the sensitivity and specificity of which are nearly 100%, it is not widely available. In addition, normal individuals and those with hematologic malignancies, particularly acute myeloid leukemia, can present with low titers for isotypes IgA, IgG, and IgM. The test is performed by ELISA (which is the gold standard method) and cell culture. A concentration > 19 mg/mL is specific for autoimmune PAP, and values of < 10 mg/mL have a negative predictive value. No specific anti-GM-CSF autoantibody testing was performed in our sample.[1-3]

Occupational exposure (to silica, cellulose fibers, combustion products of plastics, aluminum, and titanium oxide) is known to contribute to the development of secondary PAP[3,4,8,18]; however, none of the individuals in our sample had a consistent history of exposure. Three patients (25%) reported exposure to birds, and 1 patient reported exposure to mold. One of the patients who reported exposure to birds was a 47-year-old female patient who had quit smoking 1 year before symptom onset (with a smoking history of

30 pack-years). She was obese (her body mass index was 35.6 kg/m^2), had had opportunistic nocardiosis, had undergone 7 WLL procedures (the longest interval between procedures being 6 months), and had received GM-CSF replacement therapy, having shown no clinical response. Clinical and functional improvement was achieved after the patient was separated from her pet bird (a cockatiel), which she had failed to mention. At this writing, no other intervention had been required, the patient having achieved remission 2 years prior. Her chest CT scans are shown in Figure 1, and the WLL fluid is shown in Figure 2. We found no studies examining this issue or reporting findings related to it. The association between PAP and smoking is also of note. Epidemiological data from other studies show that approximately 75% of patients have a history of smoking.[3,4] However, only 16% of the patients in our sample were smokers.

In 1991, Lorenzi-Filho et al. published a case series of 4 patients who were in the 27- to 52-year age bracket and who were followed between 1983 and 1989 in Brazil.[22] In all 4 patients, the diagnosis of PAP was confirmed by biopsy (transbronchial biopsy, in 3, and open lung biopsy, in 1). Three were smokers, and 1 had a history of occupational exposure to silica. There were no opportunistic infections. Of the 4 patients studied, 3 underwent WLL, showing clinical and radiological improvement, as well as improvement in functional parameters (saturation and DLCO); 1 patient achieved spontaneous remission after quitting smoking.[22]

Because of the size of our sample, we cannot accurately determine the impact of GM-CSF replacement therapy or rituximab use on patients with PAP, or their functional follow-up. In this context, the limitations of our study include the fact that secondary treatment options such as GM-CSF replacement therapy and rituximab use were used for a short period of time (because of their limited availability in Brazil), as well as the fact that pulmonary function testing did not include DLCO measurement, together with the fact that serum levels of anti-GM-CSF antibodies were not determined in our sample.

In summary, PAP is a rare and life-threatening disease. To our knowledge, this is the largest case series of patients with PAP ever conducted in Brazil. WLL remains the treatment of choice for symptomatic, hypoxemic patients; however, in some patients, treatment response is unsatisfactory, recurrence is common, or the procedure is contraindicated. For such patients, there are other treatment options, such as GM-CSF replacement therapy and rituximab use, although they are not widely available in Brazil and their roles in such cases have yet to be established. Precautions should be taken in order to avoid complications, especially opportunistic infections, which are common in patients with PAP.

REFERENCES

1. Borie R, Danel C, Debray MP, Taille C, Dombret MC, Aubier M, et al. Pulmonary alveolar proteinosis. Eur Respir Rev. 2011;20(120):98-107. https://doi.org/10.1183/09059180.00001311
2. Baldi BG, Pereira CA, Rubin AS, Santana AN, Costa AN, Carvalho CR, et al. Highlights of the Brazilian Thoracic Association guidelines for interstitial lung diseases. J Bras Pneumol. 2012;38(3):282-91. https://doi.org/10.1590/S1806-37132012000300002
3. Trapnell BC, Whitsett JA, Nakata K. Pulmonary alveolar proteinosis. N Engl J Med. 2003;349(26):2527-39. https://doi.org/10.1056/NEJMra023226
4. Jouneau S, Kerjouan M, Briens E, Lenormand JP, Meunier C, Letheulle J, et al. Pulmonary alveolar proteinosis [Article in French]. Rev Mal Respir. 2014;31(10):975-91. https://doi.org/10.1016/j.rmr.2014.08.009
5. Souza RC, Kanaan D, Martins HP, Vianna GA, Amorim VB, Marchiori E. Spontaneous regression of pulmonary alveolar proteinosis: a case report. Radiol Bras. 2012;45(5):294-6. https://doi.org/10.1590/S0100-39842012000500013
6. Rodríguez Portal JA. Treatment of Adult Primary Alveolar Proteinosis. Arch Bronconeumol. 2015;51(7):344-9. https://doi.org/10.1016/j.arbres.2015.02.003
7. Chaulagain CP, Pilichowska M, Brinckerhoff L, Tabba M, Erban JK. Secondary pulmonary alveolar proteinosis in hematologic malignancies. Hematol Oncol Stem Cell Ther. 2014;7(4):127-35. https://doi.org/10.1016/j.hemonc.2014.09.003
8. Juvet SC, Hwang D, Waddell TK, Downey GP. Rare lung disease II: pulmonary alveolar proteinosis. Can Respir J. 2008;15(4):203-10. https://doi.org/10.1155/2008/528948
9. Leth S, Bendstrup E, Vestergaard H, Hilberg O. Autoimmune pulmonary alveolar proteinosis: treatment options in year 2013. Respirology. 2013;18(1):82-91. https://doi.org/10.1111/j.1440-1843.2012.02274.x
10. Shah PL, Hansell D, Lawson PR, Reid KB, Morgan C. Pulmonary alveolar proteinosis: clinical aspects and current concepts on pathogenesis. Thorax. 2000;55(1):67-77. https://doi.org/10.1136/thorax.55.1.67
11. Sawai T, Umeyama Y, Yoshioka S, Matsuo N, Suyama N, Kohno S. Autoimmune pulmonary alveolar proteinosis co-existing with breast cancer: a case report. J Med Case Rep. 2014;8:279. https://doi.org/10.1186/1752-1947-8-279
12. Su KC, Lay SL, Perng RP, Chang SC, Chen YM. Lung cancer may develop subsequently or coincidently with pulmonary alveolar proteinosis. Lung Cancer. 2007;58(1):144-8. https://doi.org/10.1016/j.lungcan.2007.04.012
13. Ioachimescu O, Kavuru M. Pulmonary alveolar proteinosis. Chron Respir Dis. 2006;3(3):149-59. https://doi.org/10.1191/1479972306cd101rs
14. Pascual J, Gómez Aguinaga MA, Vidal R, Maudes A, Sureda A, Gómez Mampaso E, et al. Alveolar proteinosis and nocardiosis: a patient treated by bronchopulmonary lavage. Postgrad Med J. 1989;65(767):674-7. https://doi.org/10.1136/pgmj.65.767.674
15. Pereira-Silva JL, Marinho MM, Veloso TV, Coelho JC JC. Pulmonary alveolar proteinosis and tuberculosis in a diabetic patient: a rare or a seldom diagnosed association? Braz J Infect Dis. 2002;6(4):188-95. https://doi.org/10.1590/S1413-86702002000400006
16. Tekgül S, Bilaceroglu S, Ozkaya S, Coskun A, Komurcuoglu B, Cirak AK. Pulmonary alveolar proteinosis and superinfection with pulmonary tuberculosis in a case. Respir Med Case Rep. 2012;5:25-8. https://doi.org/10.1016/j.rmedc.2011.11.003
17. Sunderland WA, Campbell RA, Edwards MJ. Pulmonary alveolar proteinosis and pulmonary cryptococcosis in an adolescent boy. J Pediatr. 1972;80(3):450-6. https://doi.org/10.1016/S0022-3476(72)80503-1
18. Sauni R, Järvenpää R, Iivonen E, Nevalainen S, Uitti J. Pulmonary alveolar proteinosis induced by silica dust? Occup Med (Lond). 2007;57(3):221-4. https://doi.org/10.1093/occmed/kql162
19. Keller CA, Frost A, Cagle PT, Abraham JL. Pulmonary alveolar proteinosis in a painter with elevated pulmonary concentrations of titanium. Chest. 1995;108(1):277-80. https://doi.org/10.1378/chest.108.1.277
20. Patel NM, Diaz-Mendoza J, Valdiviezo EA, Ray C, Simoff MJ. A Case-Series Of pulmonary alveolar proteinosis Treated With Bilateral

Simultaneous Whole Lung Lavage : A Novel Treatment Modality. Am J Respir Crit Care Med. 2015;191:A4433.

21. Belchior I, Cerdeira AS, Santos M, Braga JS, Aragão I, Martins A. Successful pregnancy in a severely hypoxemic patient with pulmonary alveolar proteinosis [Article in Portuguese. Rev Port Pneumol. 2011;17(3):139-42. https://doi.org/10.1016/j.rppneu.2011.01.005
22. Lorenzi-Filho G, Carvalho CR, Dohlnikoff M, Travassos RR Jr. Proteinose alveolar: apresentação de quatro casos. Rev Hosp Clin Fac Med Sao Paulo. 1991;46(4):196-200.
23. 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. https://doi.org/10.1590/S1806-37132007000400008
24. 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
25. Thompson JC, Kishima M, Gomes MU, Menezes Mde A, Perandré Neto J, Pereira PT. Pulmonary alveolar proteinosis: four cases. J Bras Pneumol. 2006;32(3):261-6. https://doi.org/10.1590/S1806-37132006000300013
26. Khan A, Agarwal R. Pulmonary alveolar proteinosis. Respir Care. 2011;56(7):1016-28. https://doi.org/10.4187/respcare.01125

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http://dx.doi.org/10.1590/S1806-37562017000000204

REVIEW ARTICLE

Reperfusion in acute pulmonary thromboembolism

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ABSTRACT

Acute pulmonary thromboembolism (APTE) is a highly prevalent condition (104-183 cases per 100,000 person-years) and is potentially fatal. Approximately 20% of patients with APTE are hypotensive, being considered at high risk of death. In such patients, immediate lung reperfusion is necessary in order to reduce right ventricular afterload and to restore hemodynamic stability. To reduce pulmonary vascular resistance in APTE and, consequently, to improve right ventricular function, lung reperfusion strategies have been developed over time and widely studied in recent years. In this review, we focus on advances in the indication and use of systemic thrombolytic agents, as well as lung reperfusion via endovascular and classical surgical approaches, in APTE.

Keywords: Embolism; Shock; Hypotension; Thrombolytic therapy; Reperfusion; Hemorrhage.

INTRODUCTION

Acute pulmonary thromboembolism (APTE), the most severe form of venous thromboembolism (VTE), is a highly prevalent condition—104-183 cases per 100,000 person-years, similar to the prevalence of stroke[1]—and is potentially fatal,[2] currently being the third leading cause of cardiovascular death in the world, behind only acute myocardial infarction and stroke.[3] It is believed that, worldwide, more than three million people die annually from PTE.[4] A study conducted in Brazil identified approximately 100,000 deaths from PTE between 1989 and 2010, and, despite being impressive, that number is probably underestimated.[5] There are signs of pulmonary embolism in 18% of autopsies, and pulmonary embolism was the main or contributing cause of death in 70% of those cases.[6]

Although epidemiological data highlight the potential severity of PTE, a considerable proportion of patients with the disease are known to show a good evolution, becoming oligosymptomatic or even asymptomatic.[7] Scientists have long tried to understand the mechanism behind this constellation of such distinct presentations of the same disease: some patients evolve as asymptomatic; whereas others suffer hemodynamic instability, cardiogenic shock, and eventual death. The response of the right ventricle (RV) to PTE and to the acute increase in pulmonary vascular resistance (PVR) is currently believed to be the main determinant of patient evolution.

PHYSIOPATHOLOGY OF HEMODYNAMIC INSTABILITY IN APTE

The RV has certain anatomical and functional characteristics that determine its peculiar response to acute oscillations in the RV afterload. The RV has low muscle mass in comparison with the left ventricle (LV), and perfusion of the RV occurs during systole and diastole.[8] In APTE, there is a sudden increase in PVR, representing the ventricular afterload, by obstruction of the arterial lumen and by vasoconstriction, mediated by endothelial dysfunction induced by the presence of a clot.[9] The increase in arterial pulmonary pressure due to the increase in PVR is transmitted to the RV wall, leading to its dilation and consequent loss of its best position for distention, decreasing its contractile efficiency (the Frank-Starling mechanism).[10] The interventricular septum may also be affected by the acute increase in the afterload and in the pressure of the right chambers, altering its natural conformation and bulging into the interior of the LV, hindering the filling and contraction of the latter. Simultaneously, the increased tension in the RV wall increases the local demand for oxygen, causing relative ischemia of the RV and reducing its contractility.

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The interaction of these three factors results in reduced right cardiac output, with consequently reduced LV preload and, therefore, reduced LV cardiac output. This reduced cardiac output causes systemic hypotension and, subsequently, cardiogenic shock, and eventually death.[11] Therefore, the best strategy to predict the outcome of a patient with APTE is the evaluation of RV function, when that specific thromboembolic stimulus is present.[12]

The most recent consensus of the European Society of Cardiology, developed in conjunction with the European Respiratory Society, recognizes the central role of the RV and considers the evaluation of the RV to be the main focus of the risk stratification of patients with APTE.[13] The risk stratification model proposed jointly by the two societies can be seen in Table 1.

Once APTE has been diagnosed, the next step is to evaluate the clinical repercussions of the event. Significant clinical repercussions, identified by the application of a clinical score, such as the simplified Pulmonary Embolism Severity Index,[14] are not seen in low-risk patients. Patients that are not considered low risk by the simplified Pulmonary Embolism Severity Index should be further stratified. Intermediate-low-risk patients, despite some clinical repercussions, do not show signs of significant RV dysfunction, as evidenced by the absence of biochemical and radiological signs. Intermediate-high-risk patients show acute RV dysfunction, due to the increase in afterload, but can still maintain cardiac output and, consequently, arterial pressure, although that can result in myocardial injury (identified by the serum presence of markers of injury in association with signs of ventricular dysfunction visible by imaging tests, whether echocardiography or tomography), as depicted in Figure 1. Lastly, high-risk patients are hypotensive and, therefore, show pronounced RV failure.

The frequency of APTE, by severity, was evaluated in the International Cooperative Pulmonary Registry study.[15] In that study, 20% of the APTEs were classified as high risk, 48% were classified as low risk, and 32% were classified as intermediate risk. Therefore, although most patients do not show a severe form of the disease, a considerable proportion show some degree of RV dysfunction and are therefore at an increased risk of death. To reduce PVR in APTE and, consequently, to improve RV function, lung reperfusion strategies have been developed over time and widely studied in recent years. In this review, we focus on advances in the indication and use of systemic thrombolytic agents, as well as lung reperfusion via endovascular and classical surgical approaches, in APTE.

SYSTEMIC THROMBOLYTIC AGENTS

Since the 1960s, the use of intravenous or even oral anticoagulants has been effective in reducing the recurrence of VTE, as well as reducing mortality rates.[16] However, for a certain patient population this treatment was insufficient and mortality remained high. Systemic thrombolytic agents, already widely used for coronary reperfusion in acute myocardial infarction, were subsequently evaluated also for APTE. In 1971, Miller et al. demonstrated that the use of streptokinase, 72 h after the acute event, reduced the pulmonary artery systolic pressure, the

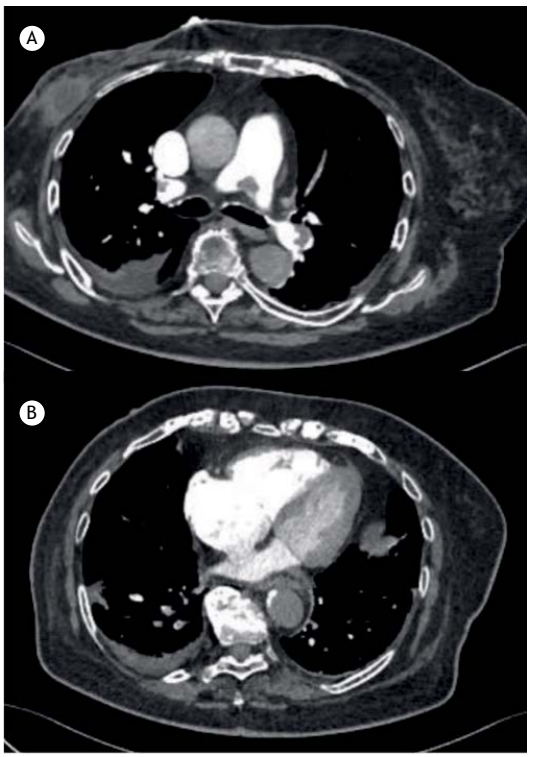

Figure 1. Contrast-enhanced computed tomography scan in a patient with intermediate-high-risk pulmonary thromboembolism. Note the presence of clot in the branch of the pulmonary artery (in A); and the dilation of the right ventricle and atrium, the narrowing of the interventricular septum, and the resulting compression of the left ventricle (in B).

Table 1. Risk stratification according to the European Society of Cardiology together with the European Respiratory Society.

Risk of early cardiovascular mortality (hospital mortality or 30-day mortality)	Shock or hypotension	PESI III-IV or sPESI > 1	RV dysfunction (imaging test)	Markers of myocardial injury
High	+	+	+	+
Intermediate-high	–	+	Both positive	
Intermediate-low	–	+	Either one (or none) positive	
Low	–	–	Assessment optional if both negative	

PESI: Pulmonary Embolism Severity Index; sPESI: simplified Pulmonary Embolism Severity Index; RV: right ventricular.

total pulmonary resistance, and the values of the angiographic severity index in PTE, in comparison with the use of heparin.[17] That information sparked enthusiasm for the use of thrombolytic agents in PTE. However, experience demonstrated two inconveniences in the use of thrombolytic agents. The first was that the comparison between thrombolytic agents and heparin as treatments for APTE showed them to be identical in terms of the rates of pulmonary reperfusion, evaluated by quantitative lung scintigraphy in the medium term (two weeks) and long term (one year).[18] In other words, despite acutely promoting a higher reperfusion rate and, therefore, acutely reducing PVR, the use of thrombolytic agents did not have a long-term effect on pulmonary reperfusion. The second inconvenience, which could affect the use of the new therapy, was the fact that the use of thrombolytic agents for PTE promoted significantly higher rates of bleeding than did that of conventional anticoagulants. Some studies reported rates of up to 22%[15] of clinically relevant bleeding with the use of thrombolytic agents. The rates of intracranial hemorrhage, 2-3%,[15,19] were particularly concerning, and the mortality in this population was up to 75%.

Two meta-analyses[20,21] demonstrated the role of systemic thrombolysis in high-risk APTE (hemodynamically unstable) patients. The first meta-analysis, published in 2004, evaluated a subgroup of 154 patients with PTE and hypotension, from several smaller studies, and showed that thrombolysis had a favorable impact on a compound outcome of death and recurrence of VTE, in comparison with heparin (9.4 vs. 19%; OR = 0.45; 95% CI: 0.22-0.92).[20] The second meta-analysis, published in 2012, evaluated a collective total of two million patients hospitalized with PTE.[21] In that study, 21,390 hemodynamically unstable patients received thrombolytic agents, and the mortality rate among those patients was 8.4%, compared with 42.0% among the 50,840 hemodynamically unstable patients who did not receive thrombolytic agents, for a variety of reasons. Therefore, the use of systemic thrombolytic agents in the presence of hemodynamic instability reduced the relative risk of death by 80% (95% CI: 0.19-0.22)[21]. Therefore, the use of systemic thrombolytic agents is considered an important alternative for reperfusion in patients with PTE and hemodynamic instability.[22] The benefit in terms of mortality is maintained even when thrombolytic therapy is implemented 14 days after the acute event. However, the maximum benefit occurs when therapy is implemented in the first 48 h after the initial clinical presentation.[23] The recommended agents and doses are described in Table 2.

Absolute contraindications to the use of thrombolytic agents are recent major surgery (less than 10 days), intracranial neoplasm, active bleeding, major trauma (less than two weeks), stroke in the last three months, any history of hemorrhagic stroke, and significant coagulopathy. These contraindications should be properly evaluated because there is a risk of fatal bleeding in these circumstances. However, studies demonstrate that up to two thirds of patients with PTE and hypotension do not receive fibrinolytic therapy.[24] Considering that the absolute contraindications cannot be present in all of those patients, it is clear that physicians fear bleeding. But such fear cannot justify not administering the best therapy available for patients with high-risk PTE. To better manage this condition and other conditions in patients with APTE, some institutions recently opted for the model of multidisciplinary care teams, known as rapid response teams (pulmonary embolism response teams).[25] Therefore, responsibility is shared among team members (pulmonologists, cardiologists, radiologists, intensivists, and surgeons) and the patient, all of whom must act in an assertive and timely manner, 24 h/day, in order to promote an individualized approach based on the best evidence in the field of pulmonary embolism research. This initiative began at Massachusetts General Hospital, in Boston, Massachusetts, and now extends to multiple centers in the United States and worldwide, with encouraging results.

SYSTEMIC THROMBOLYSIS IN INTERMEDIATE-HIGH-RISK PATIENTS

Even with the risk of bleeding previously described, in the case of APTE, given the imminent risk of death of a patient with pronounced RV insufficiency, the use of systemic fibrinolytic agents is indicated for patients with pulmonary embolism and hypotension.[22] However, in intermediate-high-risk cases, this indication is controversial. The pathophysiological mechanism previously described incites the tempting possibility of preventing circulatory collapse by reducing the RV afterload before the progression to pronounced ventricular insufficiency, thus improving the outlook for the patient. However, would this theoretical benefic supersede the risks of hemorrhage, which

Table 2. Thrombolytic agents and doses for high-risk pulmonary thromboembolism.

Agent	Dose
Urokinase (plasminogen activator)	4,400 IU/kg in 10 min, with additional 4,400 U/kg/h for 12 h
Streptokinase (polypeptide derived from cultures of beta-hemolytic streptococci, binds to plasminogen and activates plasmin)	250,000 IU in 30 min, with additional 100,000 IU/h for 24 h. (Risk of anaphylaxis and hypotension)
Tenecteplase (binds to fibrin, increasing affinity for plasmin)	30-50 mg in bolus, adjusted by weight (5 mg for each 10 kg, from 60 to 90 kg)
Alteplase (binds to fibrin, increasing affinity for plasmin)	100 mg in 2 h (10 mg in bolus, 50 mg in the first hour, and 40 mg in the second hour)

are already known for the use of fibrinolytic agents in other situations?

Dalla-Volta et al.[26] evaluated this question systematically in 1992. Thirty six patients with APTE and RV dysfunction, without shock, were randomized to receive alteplase or heparin. The study did not identify differences in terms of mortality or severe bleeding; however, there was a reduction in the pulmonary artery pressure and in the angiographic score. Could thrombolysis then have another effect, such as preventing the evolution of APTE to chronic thromboembolic pulmonary hypertension (CTEPH), a known complication of APTE, with its own high morbidity and mortality? In 2002, that possibility was suggested by Konstantinides et al. in a study evaluating 256 patients with APTE and RV dysfunction, without hypotension, receiving alteplase plus heparin or heparin only.[27] Although there was no difference between the two groups in terms of mortality, the rate of intracranial hemorrhage in that study was zero for both groups. In addition, at the end of the study, the pulmonary artery pressure, measured by echocardiography, was higher in the group that received heparin only. Could thrombolysis have reduced the risk of this population evolving to CTEPH?

The Pulmonary Embolism Thrombolysis trial[28] provided concrete answers to some of the questions that had arisen in the field of pulmonary embolism research. That multicenter study, conducted in 2014, evaluated 1,006 patients with APTE and RV dysfunction, without shock, and demonstrated that thrombolysis in that clinical situation (with the use of tenecteplase) had a positive effect on the combined outcome of mortality and hemodynamic instability/use of vasoactive drugs—2.6% of events in the thrombolysis group vs. 5.6% in the full anticoagulation only (control) group—with no isolated benefit in terms of mortality. However, that positive result occurred at a price[28]: the rate of intracranial bleeding was ten times higher in the thrombolysis group than in the full anticoagulation only group (2.0% vs. 0.2%). Another relevant aspect of the study was the extremely low mortality in the anticoagulation group (1.8%), only 3.4% of this group requiring rescue thrombolysis. Those results decreased the enthusiasm for thrombolysis in APTE without hemodynamic instability, although the question regarding the medium- and long-term effects of the use of fibrinolytic agents remained. Some limitations of that study should be noted.[28] The population included had a relatively high median age (70 years), therefore being more prone to bleeding, which increases the risks associated with the use of thrombolysis. Would an intervention for a younger population with less hemorrhagic risk be worth considering?

The long-term findings of the Pulmonary Embolism Thrombolysis trial were recently published,[28] and the use of thrombolysis was found to have no effect on two-year mortality (20.3 vs. 18%; p = 0.43) or on residual dyspnea (36.0 vs. 30.1%; p = 0.23). In the population screened for CTEPH (30% of cases), there was no difference in the identification of this diagnosis (2.1 vs. 3.2%; p = 0.79),[29] the incidences being comparable to those previously reported.[30] With modest short-term benefits, no long-term benefits, and a considerable risk of hemorrhage, the use of full-dose thrombolytic therapy in APTE is increasingly restricted to high-risk patients with hemodynamic instability. The current recommendation is close monitoring (preferably in the ICU) and, in case of instability, early implementation of thrombolysis.[13,22]

Alternative approaches to systemic thrombolysis in intermediate-high risk PTE, to minimize the risk of bleeding, have already been evaluated. In 2013, the Moderate Pulmonary Embolism Treated with Thrombolysis study[31] evaluated 121 patients randomized to receive alteplase (50 mg, corresponding to 50% of the usual dose) plus heparin, in comparison with patients receiving anticoagulation only. The reduced dose of the thrombolytic agent was found to be safe (no episodes of severe bleeding) and to reduce pulmonary artery pressure, not only acutely but also at six months after the initial event. However, that approach (using a reduced dose of a thrombolytic agent), albeit promising, cannot be routinely recommended until larger studies, with more robust outcomes, have been conducted.

ENDOVASCULAR APPROACH

Some patients with APTE and hemodynamic instability have an absolute contraindication to the administration of systemic fibrinolytic agents; for example, patients in the immediate postoperative period. In those situations, the endovascular approach to APTE is an alternative.[32] The objective of this approach is to promote mechanical removal of the clot, reducing the RV afterload. In general, the vascular access for this procedure is via the femoral vein.

Important studies in the field of APTE have been carried out in recent years. One study evaluated 59 patients with intermediate-high-risk APTE randomized for conventional heparinization or ultrasound-assisted catheter-directed thrombolysis.[33] The catheter fragments the thrombus by ultrasound vibration (Figure 2), exposing more clot surface, thus enabling better action of the fibrinolytic agent at a lower dose (in that study, 10-20 mg of alteplase, over 15 h). With the endovascular approach, there was an improvement in the relationship between the areas of the RV and LV, indicating acute hemodynamic improvement. However, when patients were evaluated at the end of the study (90 days), there was no difference in terms of mortality. There was no significant bleeding with any of the approaches.

Ultrasound-assisted catheter-directed thrombolysis was evaluated in another study,[34] involving 150 patients with high-risk APTE (n = 31) or intermediate-high-risk APTE (n = 119). The fibrinolytic agent used was alteplase, which was administered at a dose of 24 mg, 1 mg/h, for 24 h with the use of unilateral catheters

or for 12 h with the use of bilateral catheters. There was no control group in that study. The endovascular approach was effective in reducing the pulmonary artery pressure (51.4 mmHg vs. 36.9 mmHg; $p < 0.0001$) and improving the relationship between the areas of the RV and LV (1.55 vs. 1.13; $p < 0.0001$), 48 h after the acute event. In 10% of the patients, there was some type of moderate bleeding, although there was no intracranial bleeding.

A case series evaluating the combination of pharmacomechanical thrombolysis with a low-dose local fibrinolytic agent, published in 2015,[35] involved 101 patients with intermediate-high-risk APTE (n = 73) or high-risk APTE (n = 28). Reperfusion was considered successful in 85.7% of the high-risk APTE cases and in 97.3% of the intermediate-high-risk APTE cases. The mean pulmonary artery pressure decreased from 51.17 ± 14.06 to 37.23 ± 15.81 mmHg ($p < 0.0001$).[35] None of the patients evolved to major bleeding or intracranial bleeding.

Although evidence suggests some hemodynamic benefit of the vascular approach, current evidence does not justify its large-scale use in APTE. This approach should still be considered only for selected cases, at centers with expertise in this type of intervention. However, centers continue to gain experience, data of procedure records, such as those from the abovementioned study,[35] are increasingly more available, and ongoing randomized trials should endorse the dissemination of this type of procedure in the near future.

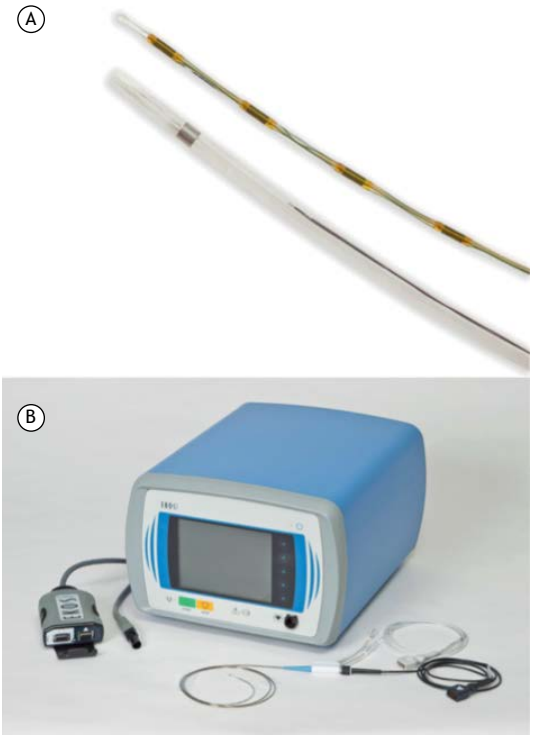

Figure 2. Catheter (in A) and Ekosonic Endovascular System (EKOS®; BTG Interventional Medicine, Bothell, WA, USA) device (in B) for endovascular reperfusion in acute pulmonary thromboembolism. The internal part of the catheter emits an ultrasonic pulse, vibrating and making the fibrin of the clot more porous, allowing the thrombus to be permeated by the fibrinolytic agent administered concomitantly at a low dose (images provided by the manufacturer).

SURGICAL EMBOLECTOMY

The surgical alternative, with the mechanical removal of the clot, reduction of the PVR, and recovery of the RV function, is another possible approach to high-risk APTE. In general, surgery is recommended when systemic thrombolysis is contraindicated and the center does not have the necessary infrastructure to apply the endovascular approach. Embolectomy is a major surgery, performed by median sternotomy, with extracorporeal circulation and deep hypothermia.[36] The surgery produces the best results when the thrombus causing the hemodynamic instability has a central location and can therefore be removed more effectively. Consequently, the use of transesophageal echocardiography is recommended in order to locate the appropriate thrombus.[37] The initial results of surgical embolectomy in APTE were very unsatisfactory, with high mortality rates, which in a certain way stigmatized the surgery. However, with the improvement of the surgical technique, of the knowledge of extracorporeal circulation, and of intensive care practices, together with the increase in experience at referral centers, significantly better results have been obtained.

In 2013, Aymard et al.[38] retrospectively evaluated 80 consecutive patients with high-risk APTE who were subjected to reperfusion via embolectomy (35%) or systemic fibrinolytic agent administration (65%) at a single center in Bern, Switzerland.[38] Of the patients who received the fibrinolytic agent, 21% required rescue embolectomy, because of persistent shock. Early mortality did not differ significantly between the embolectomy and thrombolysis groups (3.6% vs. 13.5%; $p = 0.25$). Early mortality was significantly higher in the thrombolysis group patients who underwent rescue embolectomy (26.5%, $p = 0.02$). The rates of severe bleeding after treatment were significantly higher in the thrombolysis group than in the embolectomy group (26.5% vs. 3.6%, $p = 0.013$). In the long-term follow-up (63 ± 21 months), the mortality rate was similar in both groups (17.9% in the embolectomy group vs. 23.1% in the thrombolysis group, $p = 0.6$).

Another relevant study in this field, published in 2017, was conducted by Lehnert et al.[39] In a prospective cohort study, the authors evaluated 136 patients with APTE (64 with high-risk APTE and 72 with intermediate-high-risk APTE), treated with surgical embolectomy or systemic thrombolysis at a single center in Copenhagen, Denmark. In the high-risk group, there was no statistical difference between those treated with embolectomy and those treated with thrombolysis in terms of 30-day mortality (14% vs. 31%; $p = 0.16$) or five-year mortality (32% vs. 49%; $p = 0.53$). Similar results were found in the

intermediate-high-risk group, with no difference between the two treatments. Secondary vascular outcomes, such as the extent of perfusion defect in lung scintigraphy and the reduction in diffusion, were evaluated, suggesting a smaller quantity of residual thrombus in the embolectomy group.

The studies cited above have shown reasonable results, given the severity of patients with PTE and hemodynamic instability, with an early mortality rate of 3.6%, underscoring the role of embolectomy in the treatment of this condition, especially at centers with experience in this type of surgery. We emphasize that the worst result occurred in the patients who underwent surgery because of refractory shock after administration of the thrombolytic agent. Therefore, if embolectomy can be performed, perhaps it should be an early option, rather than a rescue measure.

FINAL CONSIDERATIONS

APTE is a highly prevalent condition and is potentially fatal. Approximately 20% of patients with APTE are hypotensive, being considered at high risk of death. In such patients, immediate lung reperfusion is necessary in order to reduce RV afterload and to restore hemodynamic stability. Reperfusion can be performed in various ways (Figure 3): via the use of systemic thrombolytic agents (the most widely used method); with endovascular treatment (a method that is increasingly more widely used); or with surgical embolectomy (the most complex strategy; Figure 3). For the population of patients with intermediate-high-risk APTE (who maintain arterial pressure but show signs of RV injury, as well as radiological and biochemical signs), the benefit of reperfusion with thrombolytic agents is limited in the short term, whereas it is nonexistent in the long term, and there is a significant rate of intracranial bleeding. In order to define the best individualized approach and to improve the evaluation of the risk/benefit ratio of reperfusion therapies versus the risks of bleeding, some institutions have opted for the model of multidisciplinary, rapid-response teams, with encouraging results.

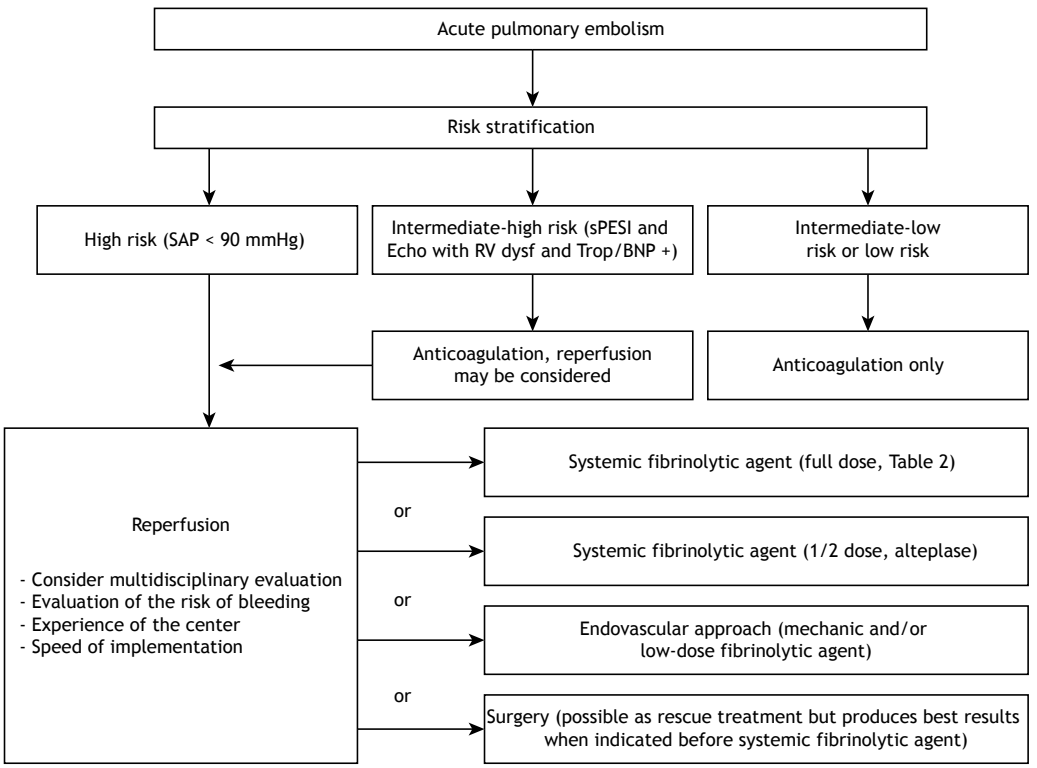

Figure 3. Management algorithm for reperfusion in acute pulmonary embolism. SAP: systemic arterial pressure; sPESI: simplified Pulmonary Embolism Severity Index; Echo: echocardiogram; RV dysf: right ventricular dysfunction; Trop: troponin, BNP: brain natriuretic peptide; and eval: evaluation..

REFERENCES

1. Heit JA. Epidemiology of venous thromboembolism. Nat Rev Cardiol. 2015;12(8):464-74. https://doi.org/10.1038/nrcardio.2015.83
2. Heit JA. The epidemiology of venous thromboembolism in the community. Arterioscler Thromb Vasc Biol. 2008;28(3):370-2. https://doi.org/10.1161/ATVBAHA.108.162545
3. Cohen AT, Agnelli G, Anderson FA, Arcelus JI, Bergqvist D, Brecht JG, et al. Venous thromboembolism (VTE) in Europe. The number of VTE events and associated morbidity and mortality. Thromb Haemost. 2007;98(4):756-64.
4. ISTH Steering Committee for World Thrombosis Day. Thrombosis: a

major contributor to the global disease burden. J Thromb Haemost. 2014;12(10):1580-90. https://doi.org/10.1111/jth.12698

5. Darze ES, Casqueiro JB, Ciuffo LA, Santos JM, Magalhães IR, Latado AL. Pulmonary Embolism Mortality in Brazil from 1989 to 2010: Gender and Regional Disparities. Arq Bras Cardiol. 2016;106(1):4-12. https://doi.org/10.5935/abc.20160001
6. Oger E. Incidence of venous thromboembolism: a community-based study in Western France. EPI-GETBP Study Group. Groupe d'Etude de la Thrombose de Bretagne Occidentale. Thromb Haemost. 2000;83(5):657-60. https://doi.org/10.1055/s-0037-1613887
7. Wood KE. Major pulmonary embolism: review of a pathophysiologic approach to the golden hour of hemodynamically significant pulmonary embolism. Chest. 2002;121(3):877-905. https://doi.org/10.1378/chest.121.3.877
8. Hoette S, Jardim C, Souza Rd. Diagnosis and treatment of pulmonary hypertension: an update. J Bras Pneumol. 2010;36(6):795-811. https://doi.org/10.1590/S1806-37132010000600018
9. Torbicki A. Acute and long term management of pulmonary embolism. Heart. 2010;96(17):1418-24. https://doi.org/10.1136/hrt.2008.153957
10. Sequeira V, van der Velden J. Historical perspective on heart function: the Frank-Starling Law. Biophys Rev. 2015;7(4):421-447. https://doi.org/10.1007/s12551-015-0184-4
11. Konstantinides S, Torbicki A. Management of venous thromboembolism: an update. Eur Heart J. 2014;35(41):2855-63. https://doi.org/10.1093/eurheartj/ehu243
12. Kasper W, Konstantinides S, Geibel A, Tiede N, Krause T, Just H. Prognostic significance of right ventricular afterload stress detected by echocardiography in patients with clinically suspected pulmonary embolism. Heart. 1997;77(4):346-9. https://doi.org/10.1136/hrt.77.4.346
13. Konstantinides SV. 2014 ESC Guidelines on the diagnosis and management of acute pulmonary embolism. Eur Heart J. 2014;35(45):3145-6.
14. Jiménez D, Aujesky D, Moores L, Gómez V, Lobo JL, Uresandi F, et al. Simplification of the pulmonary embolism severity index for prognostication in patients with acute symptomatic pulmonary embolism. Arch Intern Med. 2010;170(15):1383-9. https://doi.org/10.1001/archinternmed.2010.199
15. Goldhaber SZ, Visani L, De Rosa M. Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). Lancet. 1999;353(9162):1386-9. https://doi.org/10.1016/S0140-6736(98)07534-5
16. Fernandes CJ, Alves Júnior JL, Gavilanes F, Prada LF, Morinaga LK, Souza R. New anticoagulants for the treatment of venous thromboembolism. J Bras Pneumol. 2016;42(2):146-54. https://doi.org/10.1590/S1806-37562016042020068
17. Miller GA, Sutton GC, Kerr IH, Gibson RV, Honey M. Comparison of streptokinase and heparin in treatment of isolated acute massive pulmonary embolism. Br Heart J. 1971;33(4):616. https://doi.org/10.1136/bmj.2.5763.681
18. Bell WR, Simon TL, Stengle JM, Sherry S. The urokinase-streptokinase pulmonary embolism trial (phase II) results. Circulation. 1974;50(6):1070-1. https://doi.org/10.1161/01.CIR.50.6.1070
19. Dalen JE, Alpert JS, Hirsh J. Thrombolytic therapy for pulmonary embolism: is it effective? Is it safe? When is it indicated? Arch Intern Med. 1997;157(22):2550-6. https://doi.org/10.1001/archinte.1997.00440430026003
20. Wan S, Quinlan DJ, Agnelli G, Eikelboom JW. Thrombolysis compared with heparin for the initial treatment of pulmonary embolism: a meta-analysis of the randomized controlled trials. Circulation. 2004;110(6):744-9. https://doi.org/10.1161/01.CIR.0000137826.09715.9C
21. Stein PD, Matta F. Thrombolytic therapy in unstable patients with acute pulmonary embolism: saves lives but underused. Am J Med. 2012;125(5):465-70. https://doi.org/10.1016/j.amjmed.2011.10.015
22. Kearon C, Akl EA, Ornelas J, Blaivas A, Jimenez D, Bounameaux H, et al. Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report. Chest. 2016;149(2):315-352. https://doi.org/10.1016/j.chest.2015.11.026
23. Goldhaber SZ. Thrombolytic therapy. Adv Intern Med. 1999;44:311-25.
24. Moorjani N, Price S. Massive pulmonary embolism. Cardiol Clin. 2013;31(4):503-18, vii. https://doi.org/10.1016/j.ccl.2013.07.005
25. Kabrhel C, Rosovsky R, Channick R, Jaff MR, Weinberg I, Sundt T, et al. A Multidisciplinary Pulmonary Embolism Response Team: Initial 30-Month Experience With a Novel Approach to Delivery of Care to Patients With Submassive and Massive Pulmonary Embolism. Chest. 2016;150(2):384-93. https://doi.org/10.1016/j.chest.2016.03.011
26. Dalla-Volta S, Palla A, Santolicandro A, Giuntini C, Pengo V, Visioli O, et al. PAIMS 2: alteplase combined with heparin versus heparin in the treatment of acute pulmonary embolism. Plasminogen activator Italian multicenter study 2. J Am Coll Cardiol. 1992;20(3):520-6. https://doi.org/10.1016/0735-1097(92)90002-5
27. Konstantinides S, Geibel A, Heusel G, Heinrich F, Kasper W; Management Strategies and Prognosis of Pulmonary Embolism-3 Trial Investigators. Heparin plus alteplase compared with heparin alone in patients with submassive pulmonary embolism. N Engl J Med. 2002;347(15):1143-50. https://doi.org/10.1056/NEJMoa021274
28. Meyer G, Vicaut E, Danays T, Agnelli G, Becattini C, Beyer-Westendorf J, et al. Fibrinolysis for patients with intermediate-risk pulmonary embolism. N Engl J Med. 2014;370(15):1402-11. https://doi.org/10.1056/NEJMoa1302097
29. Konstantinides SV, Vicaut E, Danays T, Becattini C, Bertoletti L, Beyer-Westendorf J, et al. Impact of Thrombolytic Therapy on the Long-Term Outcome of Intermediate-Risk Pulmonary Embolism. J Am Coll Cardiol. 2017;69(12):1536-1544. https://doi.org/10.1016/j.jacc.2016.12.039
30. Hoeper MM, Humbert M, Souza R, Idrees M, Kawut SM, Sliwa-Hahnle K, et al. A global view of pulmonary hypertension. Lancet Respir Med. 2016;4(4):306-22. https://doi.org/10.1016/S2213-2600(15)00543-3
31. Sharifi M, Bay C, Skrocki L, Rahimi F, Mehdipour M; "MOPETT" Investigators. Moderate pulmonary embolism treated with thrombolysis (from the "MOPETT" Trial). Am J Cardiol. 2013;111(2):273-7. https://doi.org/10.1016/j.amjcard.2012.09.027
32. Kuo WT. Endovascular therapy for acute pulmonary embolism. J Vasc Interv Radiol. 2012;23(2):167-79 e4; quiz 179.
33. Kucher N, Boekstegers P, Müller OJ, Kupatt C, Beyer-Westendorf J, Heitzer T, et al. Randomized, controlled trial of ultrasound-assisted catheter-directed thrombolysis for acute intermediate-risk pulmonary embolism. Circulation. 2014;129(4):479-86. https://doi.org/10.1161/CIRCULATIONAHA.113.005544
34. Piazza G, Hohlfelder B, Jaff MR, Ouriel K, Engelhardt TC, Sterling KM, et al. A Prospective, Single-Arm, Multicenter Trial of Ultrasound-Facilitated, Catheter-Directed, Low-Dose Fibrinolysis for Acute Massive and Submassive Pulmonary Embolism: The SEATTLE II Study. JACC Cardiovasc Interv. 2015;8(10):1382-92. https://doi.org/10.1016/j.jcin.2015.04.020
35. Kuo WT, Banerjee A, Kim PS, DeMarco FJ Jr, Levy JR, Facchini FR, et al. Pulmonary Embolism Response to Fragmentation, Embolectomy, and Catheter Thrombolysis (PERFECT): Initial Results From a Prospective Multicenter Registry. Chest. 2015;148(3):667-673. https://doi.org/10.1378/chest.15-0119
36. Lazar HL, Farber HW. Early pulmonary embolectomy for acute pulmonary embolus: an operation whose time has come. J Card Surg. 2010;25(3):259-60. https://doi.org/10.1111/j.1540-8191.2010.01012.x
37. Le RD, Dewan NA. Pulmonary embolectomy: should it be offered earlier rather than later? Respir Care. 2009;54(3):390-2.
38. Aymard T, Kadner A, Widmer A, Basciani R, Tevaearai H, Weber A, et al. Massive pulmonary embolism: surgical embolectomy versus thrombolytic therapy–should surgical indications be revisited? Eur J Cardiothorac Surg. 2013;43(1):90-4; discussion 94. https://doi.org/10.1093/ejcts/ezs123
39. Lehnert P, Moller CH, Mortensen J, Kjaergaard J, Olsen PS, Carlsen J. Surgical embolectomy compared to thrombolysis in acute pulmonary embolism: morbidity and mortality. Eur J Cardiothorac Surg. 2017;51(2):354-361.

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Fat embolism syndrome: chest CT findings

Alessandro Graziani[1,a], Chiara Carli Moretti[2,b], Federica Mirici Cappa[3,c]

Fat embolism syndrome (FES), characterized by the combination of acute respiratory failure, central nervous system involvement, and petechiae, can occur after a trauma or secondary to a disease.[1,2] Here, we describe the case of a 72-year-old woman admitted to our hospital due to traumatic pertrochanteric fracture of the left femur. The patient had a medical history of systemic lupus erythematosus, positivity for antiphospholipid antibodies, deep vein thrombosis, use of a ventricular demand rate-responsive pacemaker, and aortic valve replacement due to severe stenosis. At admission, she was hemodynamically stable. Thirty-six hours after admission, she underwent orthopedic surgery involving the use of gamma nails (Stryker, Kalamazoo, MI, USA). On the first postoperative day, she presented with acute dyspnea, confusion, and agitation. Her vital signs were as follows: blood pressure, 100/60 mmHg; HR, 103 bpm; temperature, 37.1°C; RR, 26 breaths/min; and SpO_2, 75% on room air. Contrast-enhanced CT scans of the chest excluded pulmonary artery embolism and revealed peripherally located ground-glass opacities and bilateral patchy consolidations, as well as dilation of the pulmonary artery, right atrium, and right ventricle (Figures 1 and 2). Ten days later, a control CT scan showed complete regression of the lesions (Figure 3). Therefore, findings on CT scans can reflect the pathophysiology of FES and contribute to its diagnosis.[3]

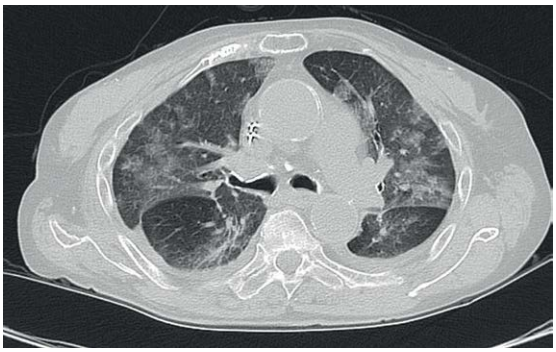

Figure 1. CT scan of the chest revealing peripherally located ground-glass opacities and bilateral patchy consolidations.

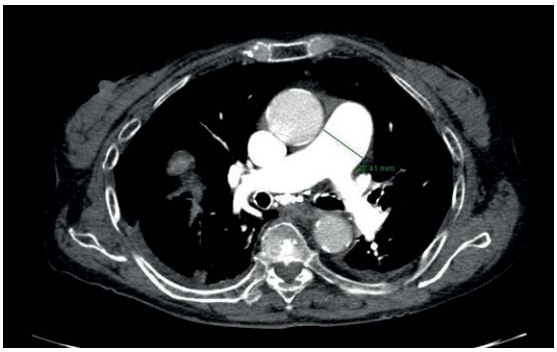

Figure 2. Contrast-enhanced CT scan of the chest showing dilation of the pulmonary artery.

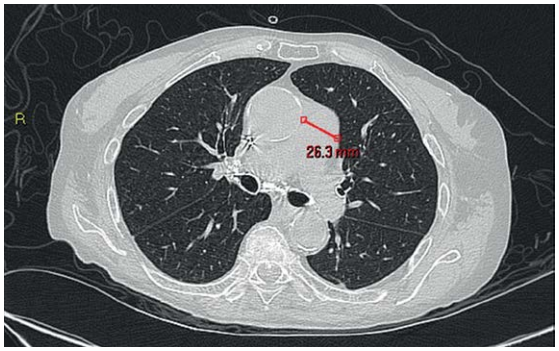

Figure 3. Control CT scan showing complete regression of the lesions.

REFERENCES

1. Akhtar S. Fat embolism. Anesthesiol Clin. 2009;27(3):533-50, table of contents. https://doi.org/10.1016/j.anclin.2009.07.018
2. Gurd AR, Wilson RI. The fat embolism syndrome. J Bone Joint Surg Br.1974;56B(3):408-16. https://doi.org/10.1302/0301-620X.56B3.408
3. Malagari K, Economopoulos N, Stoupis C, Daniil Z, Papiris S, Müller NL, et al. High-resolution CT findings in mild pulmonary fat embolism. Chest. 2003;123(4):1196-201. https://doi.org/10.1378/chest.123.4.1196

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Response to cytotoxic chemotherapy and overall survival in non-small cell lung cancer patients with positive or negative ERCC1 expression

Helen Naemi Honma[1,a], Maurício Wesley Perroud Jr[1,b], André Moreno Morcillo[2,c], José Vassallo[3,d], Lair Zambon[1,e]

TO THE EDITOR:

ERCC1 expression levels, as assessed by messenger RNA or protein levels in tumor cells, play a role in the repair of platinum-DNA adducts and influence the response to platinum-based chemotherapy in patients with non-small cell lung cancer (NSCLC).[1] Unlike patients with ERCC1-positive NSCLC, patients with ERCC1-negative NSCLC appear to benefit from cytotoxic chemotherapy; however, there is considerable controversy regarding high or low ERCC1 expression levels.[2] This study was aimed at examining the relationship of ERCC1 expression with resistance to chemotherapy with cisplatin plus paclitaxel and global survival. All procedures were performed in accordance with our institutional guidelines, and the study was approved by the local research ethics committee (CEP Protocol no. 550/2009 and CAAE Protocol no. 0442.0.146.0001-09).

Fifty patients with inoperable stage III or IV NSCLC received four cycles of platinum-based chemotherapy (with cisplatin [75 mg/m^2] or carboplatin [area under the curve, 5] and paclitaxel [200 mg/m^2] over a 21-day cycle) at our institution in the period between August of 2009 and June of 2012. Of those 50 patients, only 46 presented with enough tissue for immunohistochemical analysis of ERCC1 expression.

Before initiation of chemotherapy and one month after the end of the fourth cycle, patients underwent CT. Response Evaluation Criteria in Solid Tumors, version 1.1, were used in order to evaluate patient response to treatment.

Before chemotherapy, bronchoscopic biopsy specimens were analyzed for ERCC1 expression. Tissue sections were deparaffinized and rehydrated. Mouse anti-ERCC1 monoclonal antibody (clone 8F1; Thermo Fisher Scientific, Waltham, MA, USA) was used at 1:200. The primary antibody was visualized with HRP (Agilent Technologies, Inc., Santa Clara, CA, USA) and 3,3'-diaminobenzidine tetrahydrochloride (Agilent Technologies, Inc.). The sections were counterstained with Mayer's hematoxylin.

All immunohistochemical stains were evaluated by the same pathologist, immunoreactivity levels being assessed semiquantitatively under light microscopy. Representative images were acquired at a magnification of ×400 for each specimen. Scores were attributed to the proportion of positive cells (0%, 0; < 25%, 1; 25-50%, 2; 50-75%, 3; and > 75%, 4) and to staining intensity (no staining, 0; weak, 1; moderate, 2; and strong, 3), the final score being obtained by summing the two scores. A final score of 0-2 indicated negative ERCC1 expression, and a final score of 3-7 indicated positive ERCC1 expression.

Statistical analysis was performed with the Statistical Package for the Social Sciences, version 16.0 (SPSS Inc., Chicago, IL, USA). Data are presented as mean ± standard deviation. Associations between ERCC1 expression and clinicopathological characteristics were evaluated with the chi-square test or Fisher's exact test. The level of significance was set at $p < 0.05$. Overall survival was estimated by the Kaplan-Meier method, the log-rank test being used for comparisons. All survival data were analyzed 14 months after data on the last case had been collected.

Patient age ranged from 41 years to 76 years (mean, 61.9 ± 9.6 years). Most (65.2%) of the patients were male, and Whites predominated over non-Whites (84.8% vs. 15.2%). The vast majority of patients had stage IV NSCLC (67.4%) and a performance status of 0-1 (65.2%). In addition, smokers (i.e., current smokers plus former smokers) predominated over never smokers (78.3% vs. 21.7%).

Of the NSCLC patients with positive expression of ERCC1, 9 (64.3%) did not respond to platinum-based chemotherapy and 5 (35.7%) did. As can be seen in Table 1, there were no significant differences between patients with ERCC1-positive NSCLC and those with ERCC1-negative NSCLC regarding response to platinum-based chemotherapy ($p = 0.754$).

Median survival was 8.88 months for patients with positive expression of ERCC1 and 12.63 months for those with negative expression of ERCC1, showing that ERCC1 expression had no impact on overall survival in the present study ($p = 0.651$), a finding that is consistent with those of Lee et al.[3] In the present study, there were no significant differences in response to platinum-based chemotherapy or overall survival between NSCLC patients with positive ERCC1 expression and those with negative ERCC1 expression. There is considerable controversy regarding the relationship of ERCC1 expression with response to platinum-based chemotherapy and overall survival. Breen & Barlési[4] reported that patients with

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Table 1. Chemotherapy response in patients with positive or negative ERCC1 expression.[a]

ERCC1 expression	Chemotherapy		p	OR	95% CI
	NRs	Rs			
Positive	9 (64.3)	5 (35.7)	0.754	1.23	0.34-4.52
Negative	19 (59.4)	13 (40.6)	1.00		

NRs: nonresponders; and Rs: responders. [a]Values expressed as n (%).

negative ERCC1 expression responded favorably to platinum-based chemotherapy. Simon et al.[5] reported that overall survival was better in patients with high levels of ERCC1 expression than in those with low levels of ERCC1 expression. Lee et al.[6] found a median survival of 7.6 years among patients with high levels of ERCC1 expression and of 4 years among those with low levels of ERCC1 expression (p = 0.046). Future studies should employ methods that are more accurate in determining ERCC1 expression levels in order to determine the role of the ERCC1 protein as a predictive biomarker of response to platinum-based chemotherapy.

We would like to thank the thoracic surgery staff of the State University at Campinas for collecting endobronchial biopsy specimens. We would also like to thank Dr. Maurício S. T. Leme and Dr. Aristóteles S. Barbeiro for examining the CT scans. The present study received financial support from the *Fundação de Amparo à Pesquisa do Estado de São Paulo* (FAPESP, São Paulo Research Foundation; Grant no. 09/52574-5).

REFERENCES

1. Liao WY, Shih JY, Chang GC, Cheng YK, Yang JC, Chen YM, et al. Genetic polymorphism of XRCC1 Arg399Gln is associated with survival in non-small-cell-lung cancer patients treated with gemcitabine/platinum. J Thorac Oncol. 2012;7(6):973-81. https://doi.org/10.1097/JTO.0b013e31824fe98c
2. Maus MK, Mack PC, Astrow SH, Stephens CL, Zeger GD, Grimminger PP, et al. Histology-related associations of ERCC1, RRM1, and TS biomarkers in patients with non-small-cell lung cancer: implications for therapy. J Thorac Oncol. 2013;8(5):582-6. https://doi.org/10.1097/JTO.0b013e318287c3c5
3. Lee SM, Falzon M, Blackhall F, Spicer J, Nicolson M, Chaudhuri A et al. Randomized Prospective Biomarker Trial of ERCC1 for Comparing Platinum and Nonplatinum Therapy in Advanced Non-Small-Cell Lung Cancer: ERCC1 Trial (ET). J Clin Oncol. 2017;35(4):402-411. https://doi.org/10.1200/JCO.2016.68.1841
4. Breen D, Barlési F. The place of excision repair cross complementation 1 (ERCC1) in surgically treated non-small cell lung cancer. Eur J Cardiothorac Surg. 2008;33(5):805-11. https://doi.org/10.1016/j.ejcts.2008.01.067
5. Simon GR, Sharma S, Cantor A, Smith P, Bepler G. ERCC1 expression is a predictor of survival in resected patients with non-small cell lung cancer. Chest. 2005;127(3):978-83. https://doi.org/10.1378/chest.127.3.978
6. Lee KH, Min HS, Han SW, Oh DY, Lee SH, Kim DW, et al. ERCC1 expression by immunohistochemistry and EGFR mutations in resected non-small cell lung cancer. Lung Cancer. 2008;60(3):401-7. https://doi.org/10.1016/j.lungcan.2007.10.014

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Hemoptysis in recurrent respiratory papillomatosis: also think about aspergillosis

Giorgia Dalpiaz[1,a], Sofia Asioli[2,b], Stefania Damiani[2,c], Gaetano Rea[3,d], Edson Marchiori[4,e]

TO THE EDITOR:

A 24-year-old immunocompetent woman was admitted to the emergency room with sudden-onset pleuritic chest pain and hemoptysis. She had been diagnosed at birth with laryngeal and tracheal papillomatosis, having subsequently received treatment with antiviral agents and laser therapy until undergoing tracheal autotransplantation. CT revealed multiple nodular lesions of various sizes in both lungs. Most of the lesions were cavitated. In the right lower lobe, two adjacent cavities with central soft-tissue masses were surrounded by an air crescent sign, a finding that is consistent with mycetoma (Figure 1A). The patient was referred to our department for a bronchoscopy, a BAL, and a lung biopsy. The bronchoscopy showed no evidence of papillomatosis, and the BAL fluid was negative for neoplastic cells. The lung biopsy showed desquamative interstitial pneumonia with septate hyphae. After being diagnosed with fungal infection, the patient received antifungal therapy, but neither her clinical condition nor her radiological features improved. Therefore, she underwent right lower lobectomy. Gross examination of resected specimens revealed multiple cystic lesions filled with soft, greenish brown material (Figure 1B). Histological examination revealed that the cavities contained a conglomerate of septate hyphae, fibrin, and inflammatory cells (Figure 1C). Fungal staining (Grocott methenamine silver staining) confirmed the morphological diagnosis of respiratory aspergillosis (inset in Figure 1C). Numerous papillary structures filled the alveolar spaces (Figure 1D). These features were consistent with a diagnosis of respiratory papillomatosis with aspergillosis. In situ hybridization revealed that the squamous cells contained HPV-11 genome (inset in Figure 1D). The patient died 15 months later, of disease-related respiratory failure.

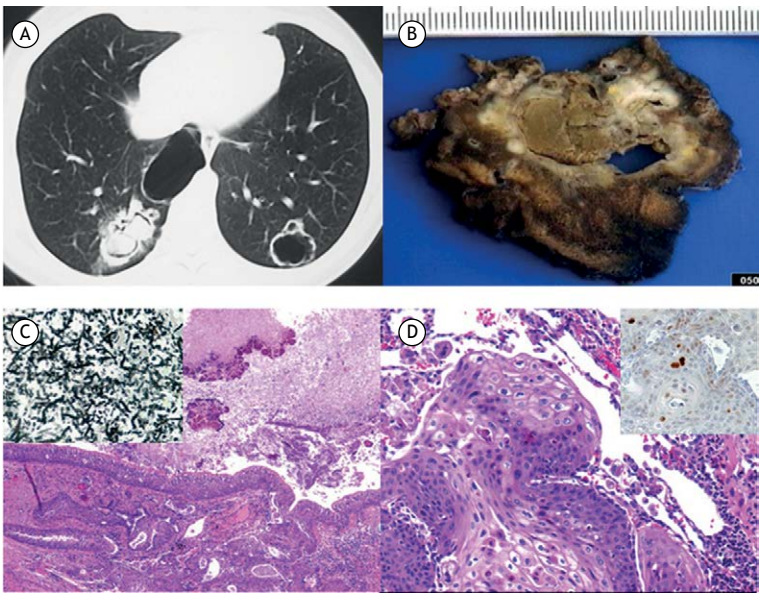

Figure 1. In A, axial CT scan of the chest showing two adjacent cavities with central soft-tissue masses surrounded by an air crescent sign in the right lower lobe, a finding that is consistent with mycetoma; a cystic lesion with thick, irregular walls is also present in the left lung. In B, right lower lobe specimen showing that the main cystic lesion was filled with soft, greenish brown material. In C, histopathology (H&E staining; magnification, ×40) showing that the cavity was filled with numerous septate hyphae displaying morphological features consistent with a colonizing form of respiratory aspergillosis (fungus ball). Fungal staining (Grocott methenamine silver staining; magnification, ×100; inset in C) confirmed the diagnosis of respiratory aspergillosis. In D, note papillary structures filling the alveolar spaces. In situ hybridization revealed that the squamous cells contained HPV-11 genome (inset in D).

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Recurrent respiratory papillomatosis (RRP) is a rare benign condition characterized by the growth of multiple papillomas in the upper respiratory tract. Dissemination to the lower airways is uncommon. The trachea and proximal bronchi are involved in 5% of cases, and less than 1% of cases show lung involvement. RRP is more common in children (juvenile-onset RRP) and in adults in the fourth decade of life (adult-onset RRP). It is caused by HPV, particularly HPV-6 and HPV-11. HPV-11 is more often associated with an aggressive course, ultimately leading to pulmonary dissemination, malignant transformation, or both. Various hypotheses have been proposed to explain the distal spread of laryngeal papillomatosis, including contiguous tumor spread, diffuse viral infection, and iatrogenic factors (e.g., those related to laryngoscopy, bronchoscopy, tracheostomy, and surgical manipulation). Clinically, RRP usually presents as nonspecific symptoms of airway involvement, including chronic cough, hoarseness, wheezing, voice change, stridor, and chronic dyspnea.[1,2]

Hemoptysis is common in cases of RRP complicated by recurrent pneumonia, obstructive atelectasis, tuberculosis, or malignant degeneration.[3] To our knowledge, there is only one reported case of RRP with hemoptysis due to aspergillosis.[4] In patients with RRP and hemoptysis, the air crescent sign on CT scans is suggestive of aspergillosis.

REFERENCES

1. Fortes HR, von Ranke FM, Escuissato DL, Araujo Neto CA, Zanetti G, Hochhegger B, et al. Recurrent respiratory papillomatosis: A state-of-the-art review. Respir Med. 2017;126:116-121. https://doi.org/10.1016/j.rmed.2017.03.030
2. Marchiori E, Araujo Neto Cd, Meirelles GS, Irion KL, Zanetti G, Missrie I,et al. Laryngotracheobronchial papillomatosis: findings on computed tomography scans of the chest. J. Bras Pneumol 2008;34(12):1084-9. https://doi.org/10.1590/S1806-37132008001200016
3. Dalpiaz G, Cancellieri A, editors. Atlas of Diffuse Lung Diseases. A Multidisciplinary Approach. New York: Springer; 2017. https://doi.org/10.1007/978-3-319-42752-2
4. Kuruvilla S, Saldanha R, Joseph LD. Recurrent respiratory papillomatosis complicated by aspergillosis: a case report with review of literature. J Postgrad Med. 2008;54(1):32-4. https://doi.org/10.4103/0022-3859.39188

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Reflections upon the article "Evaluation of the impact that the changes in tuberculosis treatment implemented in Brazil in 2009 have had on disease control in the country"

Ethel Leonor Maciel[1,a], José Ueleres Braga[2,3,b], Adelmo Inácio Bertolde[4,c], Eliana Zandonade[4,d]

TO THE EDITOR:

In the article by Rabahi et al.[1] published in volume 43, issue 6, of the JBP in 2017, the authors concluded that "The changes in tuberculosis treatment [fixed-dose combination implemented by the Brazilian Ministry of Health] were unable to contain the decrease in cure rates, the increase in treatment abandonment rates, and the increase in [multidrug-resistant tuberculosis] MDR-TB rates, being associated with increased mortality from pulmonary tuberculosis during the study period." Considering that this statement published in the major means of scientific dissemination of the Brazilian Thoracic Association may have a major impact not only on the Brazilian medical community but also on the health professionals engaged in the fight against tuberculosis, we would like this letter to be likewise published in the JBP. Some comments must be made about methodological issues that certainly influenced the conclusions of the aforementioned study.[1]

It is known that evaluation of the level of scientific evidence should be a routine activity of health professionals, but various barriers prevent this from happening. Studies on the impact of public health program interventions require the application of specific methods that consider both the use of an appropriate study design and well-constructed theoretical causal models. Since the discovery of *Mycobacterium tuberculosis* as the causal agent of tuberculosis, various models of disease determination have been proposed.[2] Initially, these models were uni-causal, based only on this etiologic agent. However, successive failures to control tuberculosis have led to the recognition of a broad range of potential disease determinants, and the uni-causal models have been replaced by complex models, which, in addition to the aspects related to the agent, include determinants ranging from those related to the person with tuberculosis to those related to the social and programmatic context that surrounds him or her.[2] Complex causal models have also been proposed to study interventions. Therefore, attributing solely to a new treatment the outcomes of an intervention, that is, stating a single cause relationship, is an important conceptual limitation since it disregards the multi-causal complexity at play, especially if observational studies are proposed instead of studies with experimental designs, such as randomized clinical trials or even cluster randomized trials.

Conversely, the use of interrupted time series analysis techniques requires meeting some conditions, the most important of which being that the only change affecting the outcome measure in the period is the intervention of interest.[3,4] An article by Linden,[5] which was used by Rabahi et al.[1] as a reference for performing interrupted time series analysis, also reinforces that caution is needed in drawing inferences when potential confounding factors, such as concomitant policies and programs, vary during the study period. It is known that, during the period studied by Rabahi et al.,[1] other important changes occurred that could affect treatment outcomes, such as the lack of nationwide use of tuberculin testing within the health care system; the improvement in diagnosis, with the implementation of the Xpert MTB/RIF assay[6]; and the economic crisis that unequally affected the population at highest risk for unfavorable treatment outcomes because of their social vulnerability.

In addition to the limitation that potential confounding factors were disregarded, there is the fact that the treatment was not implemented uniformly in Brazil, with implementation occurring early in some states and later in others. In the study by Rabahi et al.,[1] the intervention time frame chosen does not seem appropriate, given that the study that validated the implementation of the supervised treatment in the health care system was completed only in September 2010, in five cities surveyed.[7] Therefore, during data analysis, line fitting should consider heterogeneity in the treatment's adoption and use (whether treatment was supervised or not) and Family Health Program coverage by city, as well as socioeconomic variables.[8]

The inferences drawn by the authors must also be considered, since not detecting a relationship between an exposure and an outcome should not be interpreted as "there is no relationship between them." The study by Rabahi et al.[1] could not detect the impact of the new treatment on cure and treatment abandonment rates, and it is not correct to state that "the changes in tuberculosis treatment were unable to contain the decrease in cure rates, the increase in treatment abandonment rates, (. . .)" because the inability to verify this relationship may be due to the low statistical power of the study. Additionally,

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some results were presented in a format that is difficult to interpret, such as in Figure 2,[1] given that there are confidence intervals that include null values but show p values less than 0.05 (Figures 2C and 2G). Furthermore, Figure 2G presents a line with a positive slope and a negative estimate for the parameter.

Therefore, we consider that important methodological limitations and misinterpretation of results have led to conclusions with a low level of scientific evidence, and disseminating this knowledge without criticism is inconsistent with good practices of collective health and health research.

REFERENCES

1. Rabahi MF, da Silva Júnior JLRD, Conde MB. Evaluation of the impact that the changes in tuberculosis treatment implemented in Brazil in 2009 have had on disease control in the country. J Bras Pneumol. 2017;43(6):437-444. https://doi.org/10.1590/s1806-37562017000000004
2. Maciel EL, Reis-Santos B. Determinants of tuberculosis in Brazil: from conceptual framework to practical application. Rev Panam Salud Publica. 2015;38(1):28-34.
3. Penfold RB, Zhang F. Use of interrupted time series analysis in evaluating health care quality improvements. Acad Pediatr. 2013;13(6 Suppl):S38-44. https://doi.org/10.1016/j.acap.2013.08.002
4. Bernal JL, Cummins S, Gasparrini A. Interrupted time series regression for the evaluation of public health interventions: a tutorial. Int J Epidemiol. 2017;46(1):348-355. https://doi.org/10.1093/ije/dyw098
5. Linden A. Conducting interrupted time-series analysis for single-and multiple-group comparisons. Stata J. 2015;15(2):480-500.
6. Durovni B, Saraceni V, van den Hof S, Trajman A, Cordeiro-Santos M, Cavalcante S, et al. Impact of replacing smear microscopy with Xpert MTB/RIF for diagnosing tuberculosis in Brazil: A stepped-wedge cluster-randomized trial. PLoS Med. 2014;11(12):e1001766. https://doi.org/10.1371/journal.pmed.1001766
7. Braga JU, Trajman A. Effectiveness of RHZE-FDC (fixed-dose combination) compared to RH-FDC+Z for tuberculosis treatment in Brazil: a cohort study. BMC Infect Dis. 2015;15:81. https://doi.org/10.1186/s12879-015-0820-4
8. O Brasil pode alcançar os novos objetivos globais da OMS para o controle da TB? Rev Epidemiol Servico Saude. [Epub ahead of print]

Authors' reply

Marcelo Fouad Rabahi[1,a], José Laerte Rodrigues da Silva Júnior[2,3,b], Marcus Barreto Conde[4,5,c]

In the first part of our article, we presented the annual data for the period from January 2003 to December 2014 regarding all 861,901 reported cases of pulmonary tuberculosis (PTB) in individuals aged 10 years or older, as recorded in the Brazilian Ministry of Health National Case Registry Database on October 18, 2016.[1] These data showed a decrease in the total number of cases of PTB, a decrease in the number of new cases of PTB, and a continuous decrease in cure rates, as well as a steady increase in the rates of recurrence, multidrug-resistant TB, and mortality (death from tuberculosis among patients diagnosed with PTB), together with high rates of treatment abandonment.[1] There was no sample selection, and, therefore, selection bias is not possible. We included all available official data, that is, the entire population treated in the period.

Subsequently, we used interrupted time series analysis (ITSA) to determine whether or not there was an association between the irrefutable worsening in the figures regarding PTB and the changes in tuberculosis treatment implemented in 2009.[2,3] At no time did we use the word "causality" mentioned in the letter to the editor. The distinction between "association" and "causality" has been well described in the literature.[4]

The most important variable in assessing infectious disease treatment outcomes is the treatment itself. Therefore, this condition was met in our study. According to Linden,[5] when multiple observations of an outcome variable are available in the pre- and post-intervention periods, ITSA offers a quasi-experimental research design with a high degree of internal validity. According to the literature, one of the strengths of ITSA is the low interference from typical confounding variables that remain reasonably constant (e.g., socioeconomic variables) or change slowly (e.g., Family Health Program coverage or supervised treatment), because these variables are taken into consideration in the long-term trend model.[6] Naturally, the use of the entire population (rather than a sample) strengthened the validity of our study by allowing the control of confounding variables omitted from the statistical analysis, which rejects the low statistical power hypothesis. In fact, because of its robustness, ITSA is used to assess the effects of community interventions, public policies, and regulatory actions; in addition, systematic reviews of the literature have increasingly been including studies that used ITSA as a data analysis tool.[7]

The lack of tuberculin testing (which is used to diagnose latent tuberculosis) and the implementation of the Xpert MTB/RIF assay (which is used to diagnose tuberculosis in patients with negative sputum smear microscopy results) do not affect treatment outcomes in patients with active PTB.

In the "Methods" section of our study,[1] it can be seen that the time frame considered for the implementation of the changes in tuberculosis treatment was from December 2009 to December 2010 (three months after the implementation validation study's date of completion mentioned by the authors of the letter to the editor).

The suggestion that the inferences drawn in our article could not be drawn is in contrast with the literature.[8] In the interpretation of a statistical test, the rejection of the null hypothesis (i.e., when the p value is significant) means that the variables are not independent (i.e., there is a relationship among them), and therefore the opposite is true.[8] Thus, the terms used regarding the inference used in our text are entirely appropriate and correct.

The observation that there are confidence intervals that include null values but show p values less than 0.05 (Figures 2C and 2G) is valid.[1] However, the conclusion from this observation is wrong. It can be easily perceived that there was a misprint (a minus sign is missing before "4.76"). This can be proved by calculating the p value from the confidence interval.[9] When placing a minus sign ($\beta = -8.20$; 95% CI: -11.58 to -4.76), we find a p value of 0.000003300, that is, $p < 0.0001$, as described in our study; this shows that the reported interval does not include null values. The same is true for Figure 2G and for the slope of the line where the parameters are positive ($p = 0.00001356$, i.e., $p < 0.0001$). Therefore, there were no misinterpretations or methodological limitations in our study, and the data analyzed allow all of the inferences and conclusions drawn in our article.

We thank the authors of the letter to the editor for the critical review of our article. The review allowed us to dispel doubts, clarify concepts, address aspects that we had not addressed, and contribute to the better understanding of ITSA, thereby significantly increasing the strength of the evidence that we presented.

REFERENCES

1. Rabahi MF, da Silva Júnior JLRD, Conde MB. Evaluation of the impact that the changes in tuberculosis treatment implemented in Brazil in 2009 have had on disease control in the country. J Bras Pneumol. 2017;43(6):437-444. https://doi.org/10.1590/s1806-37562017000000004

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2. Soumerai SB, Starr D, Majumdar SR. How Do You Know Which Health Care Effectiveness Research You Can Trust? A Guide to Study Design for the Perplexed. Prev Chronic Dis. 2015;12:E101. https://doi.org/10.5888/pcd12.150187
3. Wagner AK, Soumerai SB, Zhang F, Ross-Degnan D. Segmented regression analysis of interrupted time series studies in medication use research. J Clin Pharm Ther. 2002;27(4):299-309. https://doi.org/10.1046/j.1365-2710.2002.00430.x
4. Gordis L. Epidemiology. 2nd ed. Philadelphia: Elsevier Saunders; 2000.
5. Linden A. Conducting interrupted time series analysis for single-and multiple-group comparisons. Stata J. 2015;15(2):480-500.
6. Bernal JL, Cummins S, Gasparrini A. Interrupted time series regression for the evaluation of public health interventions: a tutorial. Int J Epidemiol. 2017;46(1):348-355. https://doi.org/10.1093/ije/dyw098
7. Cochrane Effective Practice and Organisation of Care (EPOC). London: EPOC; c2018 [cited 2018 May 20]. EPOC Resources for review authors, Interrupted time series (ITS) analyses. Available from: http://epoc.cochrane.org/epoc-specific-resources-review-authors
8. Smith LF, Gratz ZS, Bousquet SG. The Chi-Square Test: Hypothesis Tests for Frequencies. In: Smith LF, Gratz ZS, Bousquet SG, editors. The Art and Practice of Statistics. 1st ed. Belmont: Wadsworth Cengage Learning; 2009. p. 407-20.
9. Altman DG, Bland JM. How to obtain the confidence interval from a P value. BMJ. 2011;343:d2090. https://doi.org/10.1136/bmj.d2090

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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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