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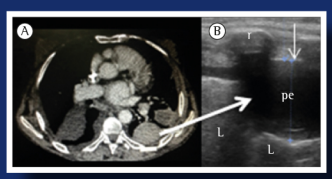
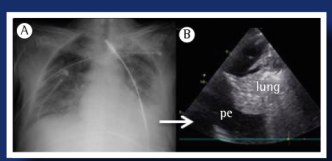
HIGHLIGHT

Ultrasonography in pleural effusion





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Sumário/Contents

Lung ultrasound in the evaluation of pleural effusion

Ultrassom de pulmão na avaliação de derrame pleural

Elena Prina, Antoni Torres, Carlos Roberto Ribeiro Carvalho

In recent years, there has been an increasing interest in the use of ultrasound for the evaluation of chest diseases, especially for the study of bedridden, critically ill patients. In fact, the ultrasound method presents various advantages: it uses no radiation; it is inexpensive; it can be used at the bedside; it is noninvasive; and it can be repeated as necessary. In addition, ultrasound is starting to be a method used by professionals, other than radiologists, who have specific clinical questions,[1] having become an important tool for the pulmonary physician. In this context, the utility of ultrasound for the diagnosis and management of pleural effusion is well documented.

In the present issue of the Brazilian Journal of Pulmonology, Perazzo et al.[2] present a randomized controlled trial aimed at assessing whether ultrasound-assisted thoracentesis, in contrast with a blinded method, would reduce the rate of pneumothorax. The authors also aimed to assess whether ultrasound improves the efficacy of the procedure (in terms of the number of successful fluid removal procedures and the amount of fluid removed). It is of note that, in that study, experienced operators performed both methods, following a standardized protocol, in order to focus attention on the influence of using ultrasound or not, and removed other factors that could be responsible for complications. For these purposes, 160 inpatients and outpatients with pleural effusion requiring pleural puncture were randomized into two groups. In the study group (comprising 80 patients), thoracentesis was performed with the use of ultrasound, whereas it was performed without ultrasound in the control group (also comprising 80 patients). In comparing the study and control groups, the authors observed that the former had a significantly lower pneumothorax rate (1.25% vs. 12.5%; $p = 0.009$; OR = 0.09), a higher number of patients with successful drainage (79/80 vs. 72/80), and a higher amount of fluid drained (mean ± SD: 960 ± 500 mL vs. 770 ± 480 mL). They concluded that the use of ultrasound during thoracentesis reduced the number of cases of pneumothorax and increased the efficiency of the procedure.

The findings of Perazzo et al.[2] corroborate data already described in the literature—thoracentesis involving the use of ultrasound is safer than is the blinded approach. Nevertheless, the study is interesting because it confirms the idea that ultrasound can provide advantages even to more experienced operators. In addition, the study is a randomized controlled trial, which increases the power of their findings.

Despite its utility, ultrasound presents some limitations. Soft tissue edema, subcutaneous emphysema, or obesity can reduce the quality of the images. We also think that physicians need adequate training in order to avoid misreading ultrasound images and, consequently, to avoid mistakes.

Ultrasound and diagnosis of pleural effusion

The first step in the evaluation of patients with suspected pleural effusion is to confirm the diagnosis, especially in the case of a white hemithorax on chest X-rays. Ultrasound is a useful method for these purposes because it allows the distinction between effusion and lung consolidations[3] and has a higher accuracy in detecting pleural effusion in comparison with bedside chest X-rays (93% vs. 47%).[4] In fact, chest X-rays can detect the presence of pleural effusion in patients in the orthostatic position only if the volume of the effusion is at least 200 mL,[5] and the sensitivity of this method decreases in the supine position, whereas ultrasound can detect effusions as small as 20 mL.[6]

The ultrasound evaluation of a patient in a sitting position is better because it allows a more precise quantification of pleural effusion. In this position, the free fluid will collect in the dependent space, whereas it will be found in a posterior location with the patient in the supine position. In addition, ultrasound allows the identification of adjacent structures: chest

wall, hemidiaphragm (over the liver or spleen), and visceral pleural surface. This is important, especially in the case of an invasive procedure, in order to avoid organ injury (Figure 1).

A second step is the distinction between transudative and exudative pleural effusions. The aspect of pleural effusion on ultrasound can suggest the nature of the fluid, although a definitive diagnosis requires a thoracentesis in order to allow physical, chemical, and microbiological studies. According to the characteristics of the pleural effusion on ultrasound, it can appear as anechoic (black), complex nonseptated (black with white strands), complex septated (black with white septa), or homogeneously echogenic (white).[7] In general, the presence of complex pleural effusion suggests exudative effusion, whereas an anechogenic effusion might be transudative. However, in contrast to what we expect, transudative effusion can also appear as complex nonseptated effusion[8]; this is due to the fact that transudates are not pure water, having various components (i.e., cells, proteins, and lipids), and exudative effusions can also appear as anechogenic effusion. Homogeneous echogenic effusions are the result of hemorrhagic effusions or empyema (Table 1).

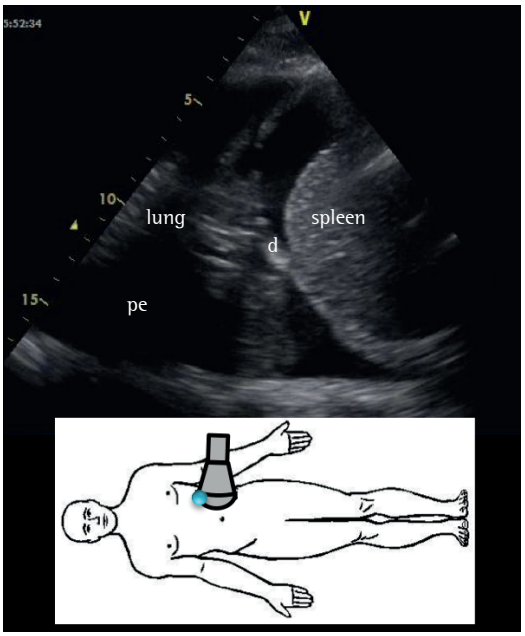

Figure 1 - Ultrasound identification of pleural effusion at a specific site (lower image). pe: pleural effusion; d: diaphragm; and c: chest wall.

In some cases, ultrasound images other than those of the effusion can help assess the nature of the pleural effusion. For example, the presence of thickened pleura or of a pulmonary consolidation with dynamic air bronchogram (suggestive of an infectious origin) is usually indicative of an exudate. The presence of a diffuse sign of lung congestion (B lines) suggests transudative effusion during heart failure.

Laing & Filly[9] reported that nearly 20% of the anechogenic images of the pleura revealed a solid lesion, not the presence of fluid. Therefore, especially in cases of small or loculated pleural effusion (Figure 2), or when thoracentesis is requested, it is important to focus on the differential diagnosis. One aspect that can facilitate the diagnosis is that pleural effusions are associated with a typical movement of the adjacent structure that determines a change in the shape of the effusion—the movement of the collapsed lung into the effusion or that of particles inside the fluid. The use of the M mode can help in the visualization of the sinusoidal movement of the collapsed lung in the fluid (sinusoid sign).[10] However, very dense or loculated pleural effusions might present no variation in the shape.

Although various ultrasound methods have been described for the quantification of the volume of pleural effusions,[11] they all require several measurements. We believe that knowledge of the exact amount of fluid has limited usefulness in clinical practice. Therefore, we prefer a qualitative approach, which is summarized in Table 2. In addition, ultrasound can help estimate the effect of pleural effusion on the lung parenchyma by enabling the visualization of different degrees

Table 1 - Ultrasound patterns and the nature of pleural effusion.

Pattern	Transudative	Exudative	Hemorrhagic
Anechogenic	✓	✓	
Complex nonseptated	✓	✓	
Complex septated		✓	
Echogenic		✓	✓

of collapse. This information, combined with clinical judgment, can help physicians in the decision-making process regarding thoracentesis (Figure 3).

Ultrasound and thoracentesis

The use of ultrasound in thoracentesis reduces the rate of complications (i.e., pneumothorax) and increases the successfulness of fluid removal when compared with traditional methods.[12] Ultrasound is especially useful when the pleural effusion is small or loculated.

Ultrasound allows the identification of the best site to perform the puncture and the measurement of the depth of the adjacent organs in order to avoid organ injury. For experts, ultrasound allows the study of the intercostal spaces prior to needle insertion, in order to identify aberrantly positioned intercostal vessels, thus avoiding vascular injury.

On ultrasound images, the appearance of pleural effusion can also provide clues to the necessary intervention: for example, a complex septated effusion could require the use of a larger catheter. There are two different techniques employed in thoracentesis with the use of ultrasound: the landmark-based method, in which ultrasound is used in order to identify the best site of the puncture; and the ultrasound-guided method, in which the procedure is closely monitored in real time by continuous visualization of the needle. This second method requires the involvement of a professional who is more experienced in the use of ultrasound.

Ultrasound and pneumothorax

The use of ultrasound reduces the risk of pneumothorax following thoracocentesis from 18% to 3%.[13]. As shown in one retrospective study,[13] that is especially true when the ultrasound-guided method is used, the rates of pneumothorax being significantly lower than when the landmark-based method is used (4% vs. 10%). In addition, Weingardt et al.[14] demonstrated that ultrasound can be an effective rescue method in 88% of cases in which blind thoracocentesis is unsuccessful. The authors noted that, in 69% of those cases, the site of puncture chosen in the blind approach was below the diaphragm. Interestingly, ultrasound-guided thoracentesis resulted safe for use in mechanically ventilated patients as well.[15]

Ultrasound is also a more useful method to detect pneumothorax after thoracentesis than are chest X-rays using a supine anterior approach. The sensitivity of these two methods is 78.6% and 39.8%, respectively, whereas their specificity is 98.4% and 99.3%, respectively.[16]

As shown in Figure 4, the major ultrasonographic signs for the diagnosis of pneumothorax are the absence of lung sliding—movement of the pleura during respiratory excursion—which is more evident using the M mode with the stratosphere sign; the absence

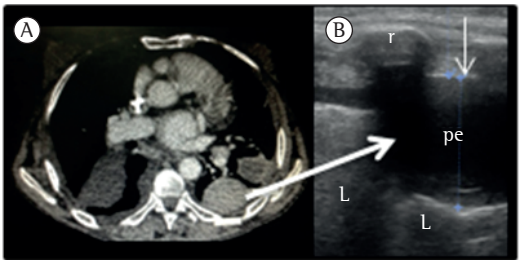

Figure 2 - CT (in A) and ultrasound (in B) revealing loculated pleural effusion. pe: pleural effusion; L: lung; and r: rib. The thin arrow indicates the parietal pleural line.

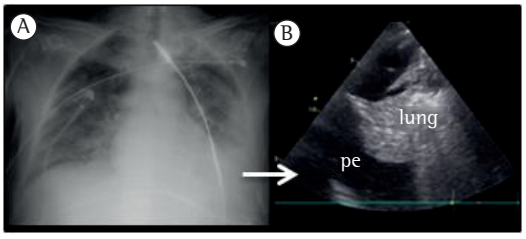

Figure 3 - X-ray (in A) and ultrasound (in B) revealing pleural effusion and lung collapse. pe: pleural effusion.

Table 2 - Ultrasound quantification of pleural effusion.

Quantification	Ultrasound visualization	Volume estimation, mL
Minimal	Costophrenic angle	≤ 100
Small	Range, one probe	100-500
Moderate	Range, two probes	500-1,500
Large or massive	Range, three or more probes	>1,500

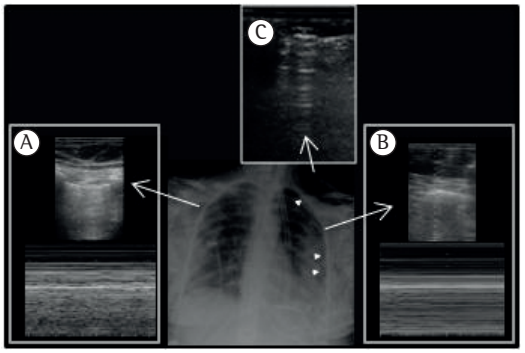

Figure 4 - Ultrasound signs of pneumothorax. In A, normal lung, showing the seashore sign in M mode. In B, pneumothorax, showing the stratosphere sign in M mode. In C, subcutaneous emphysema. Arrowheads indicate the pneumothorax.

of B lines (negative predictive value: 100%); and the presence of the lung point (positive predictive value: 100%) in the absence of massive pneumothorax.

In summary, ultrasound represents a highly useful tool for the evaluation of patients with pleural effusion during the diagnostic phase and in combination with invasive procedures.

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References

1. Koenig SJ, Narasimhan M, Mayo PH. Thoracic ultrasonography for the pulmonary specialist. Chest. 2011;140(5):1332-41. http://dx.doi.org/10.1378/chest.11-0348
2. Perazzo A, Gatto P, Barlascini C, Ferrari-Bravo M, Nicolini A. Can ultrasound guidance reduce the risk of pneumothorax following thoracentesis? J Bras Pneumol. 2014;40(1):6-12.
3. Yu CJ, Yang PC, Wu HD, Chang DB, Kuo SH, Luh KT. Ultrasound study in unilateral hemithorax opacification. Image comparison with computed tomography. Am Rev Respir Dis. 1993;147(2):430-4. http://dx.doi.org/10.1164/ajrccm/147.2.430
4. Lichtenstein D, Goldstein I, Mourgeon E, Cluzel P, Grenier P, Rouby JJ. Comparative diagnostic performances of auscultation, chest radiography, and lung ultrasonography in acute respiratory distress syndrome. Anesthesiology. 2004;100(1):9-15. http://dx.doi.org/10.1097/00000542-200401000-00006
5. Blackmore CC, Black WC, Dallas RV, Crow HC. Pleural fluid volume estimation: a chest radiograph prediction rule. Acad Radiol. 1996;3(2):103-9. http://dx.doi.org/10.1016/S1076-6332(05)80373-3
6. Rahman NM, Singanayagam A, Davies HE, Wrightson JM, Mishra EK, Lee YC, et al. Diagnostic accuracy, safety and utilisation of respiratory physician-delivered thoracic ultrasound. Thorax. 2010;65(5):449-53. http://dx.doi.org/10.1136/thx.2009.128496
7. Lomas DJ, Padley SG, Flower CD. The sonographic appearances of pleural fluid. Br J Radiol. 1993;66(787):619-24. http://dx.doi.org/10.1259/0007-1285-66-787-619
8. Chen HJ, Tu CY, Ling SJ, Chen W, Chiu KL, Hsia TC, et al. Sonographic appearances in transudative pleural effusions: not always an anechoic pattern. Ultrasound Med Biol. 2008;34(3): 362-9. http://dx.doi.org/10.1016/j.ultrasmedbio.2007.09.009
9. Laing FC, Filly RA. Problems in the application of ultrasonography for the evaluation of pleural opacities. Radiology. 1978;126(1):211-4.
10. Lichtenstein DA. Lung ultrasound in the critically ill. Ann Intensive Care. 2014;4(1):1. http://dx.doi.org/10.1186/2110-5820-4-1
11. Remérand F, Dellamonica J, Mao Z, Ferrari F, Bouhemad B, Jianxin Y, et al. Multiplane ultrasound approach to quantify pleural effusion at the bedside. Intensive Care Med. 2010;36(4):656-64. http://dx.doi.org/10.1007/s00134-010-1769-9
12. Diacon AH, Brutsche MH, Solèr M. Accuracy of pleural puncture sites: a prospective comparison of clinical

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examination with ultrasound. Chest. 2003;123(2):436-41. http://dx.doi.org/10.1378/chest.123.2.436
13. Barnes TW, Morgenthaler TI, Olson EJ, Hesley GK, Decker PA, Ryu JH. Sonographically guided thoracentesis and rate of pneumothorax. J Clin Ultrasound. 2005;33(9):442-6. http://dx.doi.org/10.1002/jcu.20163
14. Weingardt JP, Guico RR, Nemcek AA Jr, Li YP, Chiu ST. Ultrasound findings following failed, clinically directed thoracenteses. J Clin Ultrasound. 1994;22(7):419-26. http://dx.doi.org/10.1002/jcu.1870220702
15. Lichtenstein D, Hulot JS, Rabiller A, Tostivint I, Mezière G. Feasibility and safety of ultrasound-aided thoracentesis in mechanically ventilated patients. Intensive Care Med. 1999;25(9):955-8. http://dx.doi.org/10.1007/s001340050988
16. Alrajab S, Youssef AM, Akkus NI, Caldito G. Pleural ultrasonography versus chest radiography for the diagnosis of pneumothorax: review of the literature and meta-analysis. Crit Care. 2013;17(5):R208. http://dx.doi.org/10.1186/cc13016

Can ultrasound guidance reduce the risk of pneumothorax following thoracentesis?*,**

A ultrassonografia pode reduzir o risco de pneumotórax após toracocentese?

Alessandro Perazzo, Piergiorgio Gatto, Cornelius Barlascini, Maura Ferrari-Bravo, Antonello Nicolini

Abstract

Objective: Thoracentesis is one of the bedside procedures most commonly associated with iatrogenic complications, particularly pneumothorax. Various risk factors for complications associated with thoracentesis have recently been identified, including an inexperienced operator; an inadequate or inexperienced support team; the lack of a standardized protocol; and the lack of ultrasound guidance. We sought to determine whether ultrasound-guided thoracentesis can reduce the risk of pneumothorax and improve outcomes (fewer procedures without fluid removal and greater volumes of fluid removed during the procedures). In our comparison of thoracentesis with and without ultrasound guidance, all procedures were performed by a team of expert pulmonologists, using the same standardized protocol in both conditions. **Methods:** A total of 160 participants were randomly allocated to undergo thoracentesis with or without ultrasound guidance (n = 80 per group). The primary outcome was pneumothorax following thoracentesis. Secondary outcomes included the number of procedures without fluid removal and the volume of fluid drained during the procedure. **Results:** Pneumothorax occurred in 1 of the 80 patients who underwent ultrasound-guided thoracentesis and in 10 of the 80 patients who underwent thoracentesis without ultrasound guidance, the difference being statistically significant (p = 0.009). Fluid was removed in 79 of the 80 procedures performed with ultrasound guidance and in 72 of the 80 procedures performed without it. The mean volume of fluid drained was larger during the former than during the latter (960 ± 500 mL vs. 770 ± 480 mL), the difference being statistically significant (p = 0.03). **Conclusions:** Ultrasound guidance increases the yield of thoracentesis and reduces the risk of post-procedure pneumothorax.
(Chinese Clinical Trial Registry identifier: ChiCTR-TRC-12002174 [http://www.chictr.org/en/])

Keywords: Pneumothorax; Ultrasonography; Thoracic surgical procedures.

Resumo

Objetivo: Dentre os procedimentos realizados à beira do leito, a toracocentese é um dos mais comumente associados a complicações iatrogênicas, particularmente pneumotórax. Foram recentemente identificados vários fatores de risco de complicações associadas à toracocentese: a inexperiência do operador, a inadequação ou inexperiência da equipe de apoio, a ausência de um protocolo padronizado e a ausência de ultrassonografia para guiar o procedimento. Nosso objetivo foi determinar se a toracocentese guiada por ultrassonografia pode reduzir o risco de pneumotórax e melhorar os desfechos (menos procedimentos sem remoção de líquido e maior volume de líquido removido durante os procedimentos). Para compararmos a toracocentese guiada por ultrassonografia à toracocentese sem ultrassonografia, todos os procedimentos foram realizados pela mesma equipe de pneumologistas especialistas, os quais usaram o mesmo protocolo padronizado em ambas as condições. **Métodos:** Cento e sessenta pacientes foram aleatoriamente divididos em dois grupos: toracocentese guiada por ultrassonografia e toracocentese sem ultrassonografia (n = 80 por grupo). O desfecho primário foi pneumotórax após a toracocentese. Os desfechos secundários foram o número de procedimentos sem remoção de líquido e o volume de líquido drenado durante o procedimento. **Resultados:** Houve pneumotórax em 1 dos 80 pacientes submetidos a toracocentese guiada por ultrassonografia e em 10 dos 80 submetidos a toracocentese sem ultrassonografia; a diferença foi estatisticamente significante (p = 0,009). Líquido foi removido em 79 dos 80 procedimentos guiados por ultrassonografia e em 72 dos 80 que não o foram. A média do volume de líquido drenado foi maior nos procedimentos guiados por ultrassonografia do que naqueles que não o foram (960 ± 500 mL vs. 770 ± 480 mL); a diferença foi estatisticamente significante (p = 0,03). **Conclusões:** A ultrassonografia aumenta o rendimento da toracocentese e reduz o risco de pneumotórax após o procedimento.
(Chinese Clinical Trial Registry identifier: ChiCTR-TRC-12002174 [http://www.chictr.org/en/])

Descritores: Pneumotórax; Ultrassonografia; Procedimentos cirúrgicos torácicos.

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Introduction

In the United States, pleural effusion is diagnosed in approximately 1.5 million patients each year, and therapeutic thoracentesis is therefore a common medical procedure.[1] In addition, thoracentesis is one of the bedside procedures most commonly associated with iatrogenic complications, particularly pneumothorax.[2] A systematic review and meta-analysis of 24 studies, including a total of 6,605 thoracenteses, showed a 6.0% overall incidence of pneumothorax, one third of the cases of pneumothorax requiring chest tube insertion.[2]

The safety of thoracentesis has been directly associated with the technical skills of the operator.[2] Within the past several years, system and procedural variables, including a lack of real-time ultrasound imaging, operator inexperience, drainage of large volumes of fluid, and repeated thoracentesis, have been shown to increase the likelihood of complications.[2-4] An optimal thoracentesis protocol should include the use of the best available techniques (in order to minimize procedural errors and complications) in combination with a system that improves the technical skills of the operator.[1,5] Various risk factors for complications associated with thoracentesis (particularly pneumothorax) were described in a recent study[5] and are displayed in Chart 1. Those risk factors include an inexperienced or poorly trained operator, an inadequate or inexperienced support team, nonstandardized systems, and lack of ultrasound guidance.[2,5]

Chart 1 - Risk factors for complications associated with thoracentesis.

Patient-related factors
Small effusion (< 250 mL)
Multiloculated effusion
Obesity
Patient position (supine position)
Mechanical ventilation
Procedure-related factors
Inexperienced or poorly trained operator
Lack of ultrasound guidance
Drainage of large volumes (> 1,500 mL) of fluid
System-related factors
Inadequate or inexperienced support team
Nonstandardized system
Lack of standards of quality
Lack of routine review of physician-specific procedural outcomes

In view of these considerations, we sought to determine whether ultrasound guidance reduces the risk of pneumothorax following thoracentesis.

The primary outcome measure of the present study was to determine whether the incidence of pneumothorax following thoracentesis differed between two conditions: thoracentesis performed under ultrasound guidance by a team of expert pulmonologists (with 20 years of experience, specific physician training in the procedure, more than 500 thoracenteses performed, and training in chest ultrasound)[6] using a standardized protocol and standard equipment; and thoracentesis performed without ultrasound guidance by the same team using the same protocol and equipment. Secondary outcome measures included the number of procedures during which no fluid was removed, the volume of fluid removed during each procedure, and the need for chest tube placement.

Methods

This was a prospective randomized study conducted between May of 2012 and October of 2012, involving consecutive inpatients and outpatients with pleural effusion treated in the Department of Respiratory Diseases (respiratory monitoring section, respiratory ward, or day hospital) of the Sestri Levante General Hospital, in the municipality of Sestri Levante, Italy. The inclusion criteria were as follows: presenting with pleural effusion visible on chest X-rays and requiring pleural puncture (diagnostic or therapeutic thoracentesis) on the basis of previously published criteria[7]; and being in the 18-85 year age bracket. We enrolled a total of 197 patients with pleural effusion due to various causes, including neoplasms, chronic heart failure, rheumatic diseases, pneumonia, and tuberculosis. Of those 197 patients, 34 declined to participate and 3 were excluded for other reasons (not recorded). Therefore, 160 patients were randomly allocated to undergo thoracentesis with ultrasound guidance (ultrasound-guided thoracentesis group) or without ultrasound guidance (control group). A flowchart of the study is shown in Figure 1.

A statistician who was not involved in the present study devised a randomization plan using a computerized random number generator. The randomization plan was given to each recruiting physician in a sealed envelope. The patients

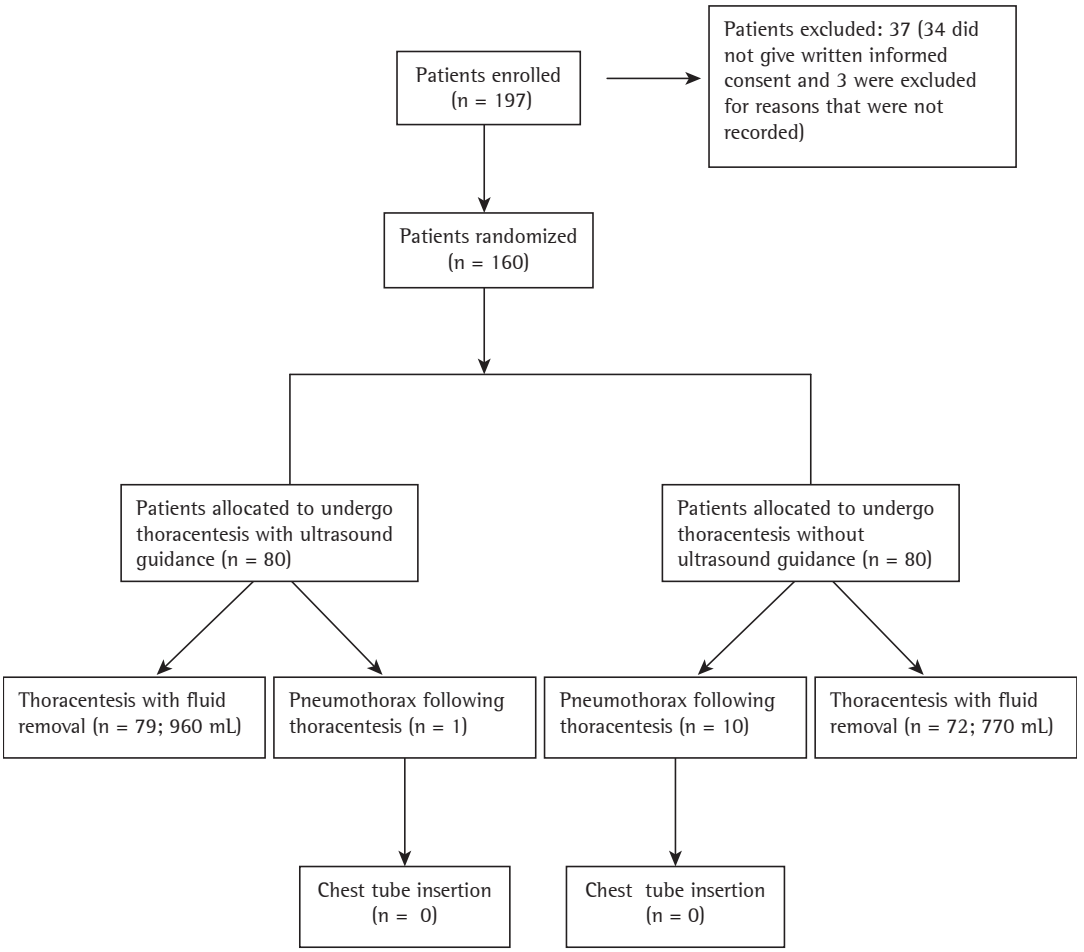

Figure 1 - Flowchart of the study.

underwent thoracentesis with or without ultrasound guidance on the basis of the randomization plan. Ultrasound was not used for real-time guidance; rather, it was used immediately before the procedure in order to identify the appropriate site. Thoracentesis was performed immediately after the site had been marked. We employed a portable ultrasound system (LOGIQ P5; GE Healthcare, Chalfont, UK) with a convex probe (3.5-5.0 MHz).

Thoracentesis was performed by one of three pulmonologists, with the patient in the sitting position, following a local protocol written in accordance with the 2010 British Thoracic Society Pleural Disease Guideline.[5] In addition, we used a thoracentesis set (Chimed s.r.l., Livorno, Italy) consisting of a three-way stopcock, a large (60-mL) syringe, a 2,000-mL vacuum-free collection bag, and a 50-mm, 18-G needle. Fluid was drained either by passive drainage or by active drainage with the 60-mL syringe connected to the three-way stopcock.

Fluid removal was terminated when there was chest pain, excessive cough, a vasovagal event, shortness of breath, or air suction. Drainage was stopped when 1.5 L of pleural fluid had been removed. Within 60 min after the procedure, posteroanterior and lateral decubitus chest X-rays were performed. The occurrence of pneumothorax was determined on the basis of the British Thoracic Society guidelines.[8] The investigators involved in the analysis of the data were blinded to the complications. The primary outcome measure of the present study was the incidence of pneumothorax following thoracentesis. Secondary outcome measures included the need for chest tube drainage and the volume of fluid drained. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Research Ethics Committee of *Azienda Sanitaria Locale*

no. 4 Chiavarese, Liguria, Italy. All participating patients gave written informed consent.

The main objectives of the present study were to compare the incidence of pneumothorax following thoracentesis performed under ultrasound guidance with that of pneumothorax following thoracentesis performed without ultrasound guidance and to determine the diagnostic value (i.e., the number of procedures during which fluid was removed and the volume of fluid removed) of ultrasound-guided thoracentesis. We used logistic regression for categorical variables (incidence of pneumothorax and secondary outcomes of thoracentesis) and analysis of covariance for continuous variables. All data were analyzed with the R software, version 2.13.2 (The R Foundation for Statistical Computing, Vienna, Austria). Values of $p \leq 0.05$ were considered statistically significant.

Results

All 160 patients evaluated (122 males and 38 females) completed the study. All of the patients were in the 32-84 year age bracket (mean age, 67.8 ± 14.9 years).

The causes of pleural effusion were as follows: pleural mesothelioma, in 11 patients; metastatic pleural neoplasm, in 90 patients; rheumatic disease, in 6 patients; chronic heart failure, in 23 patients; pneumonia, in 20 patients; and tuberculosis, in 10 patients (Table 1). A total of 80 thoracenteses were performed without ultrasound guidance. Of those, 8 were suspended because of complications: chest pain (in 4); air suction (in 3); and excessive cough with dyspnea (in 1). Of the 80 thoracenteses performed under ultrasound guidance, only 1 was suspended (because of chest pain and shortness of breath).

Pneumothorax following thoracentesis occurred in 1 of the 80 patients submitted to the procedure performed under ultrasound guidance and in 10 of the 80 patients submitted to the procedure performed without ultrasound guidance, the difference being statistically significant (p = 0.009). None of the 11 cases of pneumothorax required chest tube placement.

Table 1 - Causes of pleural effusion in the 160 patients under study.

Cause	Patient	
	n	%
Pleural mesothelioma	11	6.87
Metastatic pleural neoplasm	90	56.25
Rheumatic diseases	6	3.75
Chronic heart failure	23	14.37
Pneumonia	20	12.50
Tuberculosis	10	6.25

As can be seen in Table 2, 79 of the 80 ultrasound-guided procedures were successful, as were 72 of the 80 procedures performed without ultrasound guidance. As can be seen in Figure 2, the mean volume of fluid drained during the former procedures was larger than was that drained during the latter procedures (960 ± 500 mL vs. 770 ± 480 mL), the difference being statistically significant (p = 0.03).

In 8 of the patients in the control group, no fluid was removed during the procedure. An ultrasound-guided thoracentesis was performed in 4 of those 8 patients, pleural fluid being successfully removed (240 ± 30 mL).

The probability of success (i.e., fluid removal) was approximately nine times higher in the patients who underwent ultrasound-guided thoracentesis than in those who underwent thoracentesis without ultrasound guidance (OR = 8.8). In addition, the risk of pneumothorax was 90% lower in the former than in the latter (OR = 0.09). Patient data and the results are reported in Table 2.

Discussion

The purpose of the present study was to determine whether the incidence of pneumothorax following thoracentesis decreases when most of the risk factors (mechanical ventilation use, an inexperienced team, and an inexperienced operator) are absent and ultrasound guidance is used. We have demonstrated that ultrasound-guided thoracentesis is a very safe procedure, which was associated with a very low (1.25%) incidence of pneumothorax in our sample (1 case among the 80 patients in the ultrasound-guided thoracentesis group). In fact, ultrasound guidance reduced the risk of pneumothorax by 90% (OR = 0.09; 95% CI: 0.005-0.5; p = 0.009). Although there was no difference between the two groups in terms of the need for chest tube drainage, the amount of fluid drained was significantly greater in the ultrasound-guided thoracentesis group than in the control group (p = 0.0014).

The strength of the present study lies in the fact that it was performed by skilled pulmonologists using carefully standardized procedures to evaluate

Table 2 - Patient data and results (including statistics) in the patients submitted to thoracentesis performed under ultrasound guidance (the ultrasound-guided thoracentesis group) and in those submitted to thoracentesis performed without ultrasound guidance (the control group).

Variable	Ultrasound-guided thoracentesis group	Control group	Statistics
Thoracentesis	80	80	
Successful (fluid removal)	79/80	72/80	p > 0.03 (OR = 8.8*)
Unsuccessful (no fluid removal)	1/80	8/80	p > 0.03*
Pneumothorax	1/80	10/80	p > 0.009 (OR = 0.09*)
Pneumothorax rate	1.25%	12.5%	
Mean volume of fluid drained	960 mL	770 mL	p > 0.014**

*Logistic regression. **Analysis of covariance.

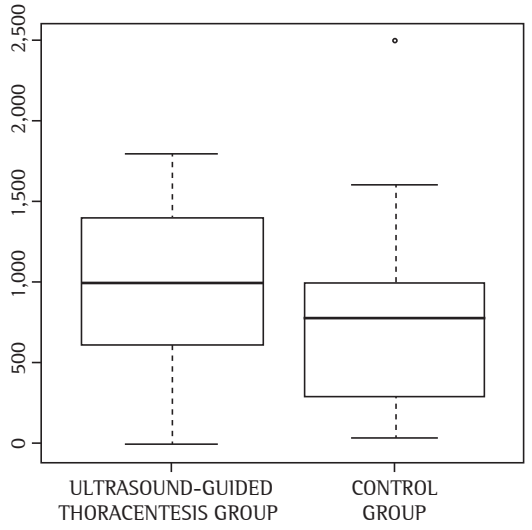

Figure 2 - Mean volume of pleural fluid removed during thoracentesis in the patients who underwent the procedure performed under ultrasound guidance (ultrasound-guided thoracentesis group) and in those who underwent the procedure performed without ultrasound guidance (control group). The difference between the two groups was statistically significant (p = 0.014).

the benefit of ultrasound guidance without any bias. To our knowledge, this is the first study of its kind. We are aware of the limitations of our study, which include the fact that patients on mechanical ventilation were not enrolled and the fact that real-time ultrasound guidance was not performed (ultrasound being used only to mark the site before thoracentesis was performed). Real-time ultrasound guidance allows clinicians to visualize the needle and important adjacent structures and therefore avoid accidental punctures, as well as allowing a further reduction in the risk of pneumothorax following thoracentesis. Nevertheless, its routine use at the bedside remains low, although it is considered the standard of care in safely locating, characterizing, and draining pleural fluid. Ultrasound is highly sensitive for detecting pleural effusions, even when chest X-rays are normal. Chest X-rays can miss up to 500 mL of pleural effusion in cases of interlobar and loculated pleural effusion. Lung ultrasound can detect as little as 20 mL of pleural fluid, whereas an upright posteroanterior chest X-ray cannot detect blunting of the costophrenic angle unless there is at least 100 mL of fluid.[6,9] Ultrasound-guided thoracentesis has been associated with lower total hospital costs and a lower incidence of pneumothorax and hemorrhage.[9] The overall incidence of pneumothorax varies from 4.0% to 30.3%,[10,11] and chest tube insertion is required in 1.7% of all thoracenteses, in order to evacuate symptomatic pneumothoraces; therefore, 20-50% of all pneumothoraces following thoracentesis require chest tube insertion.[2,11] The reported incidence of pneumothorax is significantly lower in studies published after 2000 than in earlier studies (4.6% vs. 8.7%).[11,12]

There are four reasons why pneumothorax develops in patients undergoing thoracentesis. First, air can flow from the atmosphere into the pleural space, as occurs when the negative pressure of the pleural space communicates freely with the atmosphere. This most often occurs as the syringe is removed from a needle or catheter, particularly when the individual performing the procedure is inexperienced.[10] Second, the thoracentesis needle can lacerate the lung and allow air to enter the pleural space from the alveoli.[10,11] Third, the decrease in pleural pressure can lead to a rupture of the visceral pleura.[10,11] Fourth, trapped lung or lung entrapment develops as a result of transitory pleuropulmonary fistula.[10,11] Multiple risk factors

for pneumothorax following thoracentesis have been identified, including the type of needle used,[11,13-15] operator inexperience,[16,17] the presence of emphysema,[11,18] having previously undergone thoracentesis,[19] being on mechanical ventilation,[20,21] and even the lack of ultrasound guidance.[10,22] The training of chest ultrasound technicians is task-specific and is aimed at developing the skill of identifying pleural fluid and surrounding organs, as well as that of providing an unobstructed view of the pleural fluid. These simple and well-defined skills can be readily acquired by pulmonologists and can avoid other complications during most thoracentesis procedures.[23,24] In addition, ultrasound-guided thoracentesis is a procedure that most pulmonologists can perform after short-term training.[23-25] We believe that meticulous adherence to sonographic criteria and avoidance of patient movement during the time elapsed between ultrasound examination and fluid removal are key factors responsible for the low rate of pneumothorax following thoracentesis and the larger volume of fluid removed during the procedure.[12,22-24]

In conclusion, ultrasound guidance can increase patient safety and the amount of fluid removed during thoracentesis. Ultrasonography is an easily learned technique that not only enhances the physical examination but also has the distinct advantage of being a portable imaging technique for the evaluation of the pleural space. Ultrasound is currently used in a limited number of thoracenteses, and the present study provides evidence supporting the more widespread use of this technique.[25]

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References

1. Light RW. Clinical practice. Pleural effusion. N Engl J Med. 2002;346(25):1971-7. http://dx.doi.org/10.1056/NEJMcp010731 PMid:12075059
2. Daniels CE, Ryu JH. Improving the safety of thoracentesis. Curr Opin Pulm Med. 2011;17(4):232-6. http://dx.doi.org/10.1097/MCP.0b013e328345160b PMid:21346571
3. Gordon CE, Feller-Kopman D, Balk EM, Smetana GW. Pneumothorax following thoracentesis: a systematic review and meta-analysis. Arch Intern Med. 2010;170(4):332-9. http://dx.doi.org/10.1001/archinternmed.2009.548 PMid:20177035
4. Duncan DR, Morgenthaler TI, Ryu JH, Daniels CE. Reducing iatrogenic risk in thoracentesis: establishing best practice via experiential training in a zero-risk environment. Chest. 2009;135(5):1315-20. http://dx.doi.org/10.1378/chest.08-1227 PMid:19017865
5. Havelock T, Teoh R, Laws D, Gleeson F; BTS Pleural Disease Guideline Group. Pleural procedures and thoracic ultrasound: British Thoracic Society Pleural Disease Guideline 2010. Thorax. 2010;65 Suppl 2:ii61-76. http://dx.doi.org/10.1136/thx.2010.137026 PMid:20696688
6. Rahman NM, Singanayagam A, Davies HE, Wrightson JM, Mishra EK, Lee YC, et al. Diagnostic accuracy, safety and utilisation of respiratory physician-delivered thoracic ultrasound. Thorax. 2010;65(5):449-53. http://dx.doi.org/10.1136/thx.2009.128496 PMid:20435870
7. Villena Garrido V, Ferrer Sancho J, Hernández Blasco L, de Pablo Gafas A, Pérez Rodríguez E, Rodríguez Panadero F, et al. Diagnosis and treatment of pleural effusion [Article in Spanish]. Arch Bronconeumol. 2006;42(7):349-72. http://dx.doi.org/10.1157/13090586 PMid:16945266
8. MacDuff A, Arnold A, Harvey J; BTS Pleural Disease Guideline Group. Management of spontaneous pneumothorax: British Thoracic Society Pleural Disease Guideline 2010. Thorax. 2010;65 Suppl 2:ii18-31. http://dx.doi.org/10.1136/thx.2010.136986 PMid:20696690
9. Turner JP, Dankoff J. Thoracic ultrasound. Emerg Med Clin North Am. 2012;30(2):451-73, ix. http://dx.doi.org/10.1016/j.emc.2011.12.003 PMid:22487114
10. Patel PA, Ernst FR, Gunnarsson CL. Ultrasonography guidance reduces complications and costs associated with thoracentesis procedures. J Clin Ultrasound. 2012;40(3):135-41. http://dx.doi.org/10.1002/jcu.20884 PMid:21994047
11. Jones PW, Moyers JP, Rogers JT, Rodriguez RM, Lee YC, Light RW. Ultrasound-guided thoracentesis: is it a safer method? Chest. 2003;123(2):418-23. http://dx.doi.org/10.1378/chest.123.2.418 PMid:12576360
12. Gordon CE, Feller-Kopman D, Balk EM, Smetana GW. Pneumothorax following thoracentesis: a systematic review and meta-analysis. Arch Intern Med. 2010;170(4):332-9. http://dx.doi.org/10.1001/archinternmed.2009.548 PMid:20177035
13. Gervais DA, Petersein A, Lee MJ, Hahn PF, Saini S, Mueller PR. US-guided thoracentesis: requirement for postprocedure chest radiography in patients who receive mechanical ventilation versus patients who breathe spontaneously. Radiology. 1997;204(2):503-6. PMid:9240544
14. Jenkins DW Jr, McKinney MK, Szpak MW, Booker JL Jr. Veres needle in the pleural space. South Med J. 1983;76(11):1383-5. http://dx.doi.org/10.1097/00007611-198311000-00014
15. Khorasani A, Appavu SK, Nader AM, Saatee S. Tuohy needle and loss of resistance technique: a safer approach for thoracentesis. Anesthesiology. 1999;90(1):339-40. http://dx.doi.org/10.1097/00000542-199901000-00072 PMid:9915362
16. Collins TR, Sahn SA. Thoracocentesis. Clinical value, complications, technical problems, and patient experience. Chest. 1987;91(6):817-22. http://dx.doi.org/10.1378/chest.91.6.817
17. Bartter T, Mayo PD, Pratter MR, Santarelli RJ, Leeds WM, Akers SM. Lower risk and higher yield for thoracentesis when performed by experienced operators. Chest.

1993;103(6):1873-6. http://dx.doi.org/10.1378/chest.103.6.1873 PMid:8404116
18. Brandstetter RD, Karetzky M, Rastogi R, Lolis JD. Pneumothorax after thoracentesis in chronic obstructive pulmonary disease. Heart Lung. 1994;23(1):67-70. PMid:8150647
19. Colt HG, Brewer N, Barbur E. Evaluation of patient-related and procedure-related factors contributing to pneumothorax following thoracentesis. Chest. 1999;116(1):134-8. http://dx.doi.org/10.1378/chest.116.1.134 PMid:10424516
20. Lichtenstein D, Hulot JS, Rabiller A, Tostivint I, Mezière G. Feasibility and safety of ultrasound-aided thoracentesis in mechanically ventilated patients. Intensive Care Med. 1999;25(9):955-8. http://dx.doi.org/10.1007/s001340050988 PMid:10501751
21. Mayo PH, Goltz HR, Tafreshi M, Doelken P. Safety of ultrasound-guided thoracentesis in patients receiving mechanical ventilation. Chest. 2004;125(3):1059-62. http://dx.doi.org/10.1378/chest.125.3.1059 PMid:15006969
22. Petersen WG, Zimmerman R. Limited utility of chest radiograph after thoracentesis. Chest. 2000;117(4):1038-42. http://dx.doi.org/10.1378/chest.117.4.1038
23. Tsang TS, Enriquez-Sarano M, Freeman WK, Barnes ME, Sinak LJ, Gersh BJ, et al. Consecutive 1127 therapeutic echocardiographically guided pericardiocenteses: clinical profile, practice patterns, and outcomes spanning 21 years. Mayo Clin Proc. 2002;77(5):429-36. PMid:12004992
24. Soldati G, Smargiassi A, Inchingolo R, Sher S, Valente S, Corbo GM. Ultrasound-guided pleural puncture in supine or recumbent lateral position - feasibility study. Multidiscip Respir Med. 2013;8(1):18. http://dx.doi.org/10.1186/2049-6958-8-18 PMid:23497643 PMCid:PMC3605139
25. Mercaldi CJ, Lanes SF. Ultrasound guidance decreases complications and improves the cost of care among patients undergoing thoracentesis and paracentesis. Chest. 2013;143(2):532-8. http://dx.doi.org/10.1378/chest.12-0447 PMid:23381318

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Factors related to the incorrect use of inhalers by asthma patients*

Fatores relacionados ao uso incorreto dos dispositivos inalatórios em pacientes asmáticos

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Abstract

Objective: To evaluate inhaler technique in outpatients with asthma and to determine associations between the correctness of that technique and the level of asthma control. **Methods:** This was a cross-sectional study involving patients ≥ 14 years of age with physician-diagnosed asthma. The patients were recruited from the Asthma Outpatient Clinic of the *Hospital de Clínicas de Porto Alegre*, in the city of Porto Alegre, Brazil. The patients completed two questionnaires (a general questionnaire and an asthma control questionnaire based on the 2011 Global Initiative for Asthma guidelines), demonstrated their inhaler technique, and performed pulmonary function tests. Incorrect inhaler technique was defined as the incorrect execution of at least two of the predefined steps. **Results:** We included 268 patients. Of those, 81 (30.2%) showed incorrect inhaler technique, which was associated with poor asthma control (p = 0.002). Logistic regression analysis identified the following factors associated with incorrect inhaler technique: being widowed (OR = 5.01; 95% CI, 1.74-14.41; p = 0.003); using metered dose inhalers (OR = 1.58; 95% CI, 1.35-1.85; p < 0.001); having a monthly family income < 3 times the minimum wage (OR = 2.67; 95% CI, 1.35-1.85; p = 0.008), and having ≥ 2 comorbidities (OR = 3.80; 95% CI, 1.03-14.02; p = 0.045). **Conclusions:** In the sample studied, incorrect inhaler technique was associated with poor asthma control. Widowhood, use of metered dose inhalers, low socioeconomic level, and the presence of ≥ 2 comorbidities were associated with incorrect inhaler technique.

Keywords: Metered dose inhalers; Dry powder inhalers; Asthma/therapy.

Resumo

Objetivo: Avaliar a técnica inalatória em pacientes com asma atendidos ambulatorialmente, estabelecendo associações dessa com o grau de controle da doença. **Métodos:** Estudo transversal envolvendo pacientes com idade ≥ 14 anos e diagnóstico médico de asma, recrutados no Ambulatório de Asma do Hospital de Clínicas de Porto Alegre, na cidade de Porto Alegre (RS). Os pacientes completaram dois questionários (um geral e um questionário de controle da asma baseado nas diretrizes da *Global Initiative for Asthma* de 2011). Os pacientes demonstraram a técnica inalatória e realizaram testes de função pulmonar. A técnica inalatória incorreta foi definida como a execução incorreta de pelo menos duas etapas da avaliação. **Resultados:** Foram incluídos 268 pacientes. Desses, 81 (30,2%) apresentaram técnica inalatória incorreta, que foi associada com falta de controle da asma (p = 0,002). A regressão logística identificou os seguintes fatores associados com a técnica inalatória incorreta: ser viúvo (OR = 5,01; IC95%, 1,74-14,41; p = 0,003); utilizar inalador pressurizado (OR = 1,58; IC95%, 1,35-1,85; p < 0,001); ter renda familiar mensal < 3 salários mínimos (OR = 2,67; IC95%, 1,35-1,85; p = 0,008); e ter ≥ 2 comorbidades (OR = 3,80; IC95%, 1,03-14,02; p = 0,045). **Conclusões:** Na amostra estudada, a técnica inalatória incorreta se associou com a falta de controle da asma. Viuvez, uso de inalador pressurizado, baixo nível socioeconômico e presença de ≥ 2 comorbidades se associaram à técnica inalatória incorreta.

Descritores: Inaladores dosimetrados; Inaladores de pó seco; Asma/terapia.

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Introduction

Asthma is one of the most common chronic conditions. Although the results of clinical findings have shown that asthma control can be achieved in most patients, epidemiological evidence suggests that there is a significant gap between treatment goals and the actual level of control achieved with treatment in the general population.[1] Therefore, there remains the challenge of identifying the factors that are related to poor asthma control and of developing strategies to ensure that asthma control is achieved and maintained.[2]

Inhaled drugs are the primary treatment for asthma.[3] Incorrect handling of inhalers and inappropriate inhaler technique result in low bronchial deposition of the drug and can contribute to poor asthma control.[4] Understanding the frequency and type of inhaler technique errors, as well as their associations with the level of asthma control, may allow the development of educational strategies to help reduce the morbidity of the disease.[5]

The objective of the present article was to assess inhaler technique in outpatients with asthma and to determine associations between the correctness of that technique and the level of asthma control.

Methods

This was a cross-sectional study. The study protocol was approved by the Research Ethics Committee of the *Hospital de Clínicas de Porto Alegre* (HCPA, Porto Alegre *Hospital de Clínicas*), located in the city of Porto Alegre, Brazil. Written informed consent was obtained from all patients or their legal guardians, in the case of those under 18 years of age. The study population consisted of patients treated at the HCPA outpatient clinics specializing in asthma. Individuals aged 18 years or older who had a previous diagnosis of asthma were sequentially recruited. A physician who was a member of the research team confirmed the diagnosis on the basis of the following criteria[6]: symptoms consistent with asthma, accompanied by reversible airflow obstruction (an increase in $FEV_1 \geq 12\%$ and ≥ 200 mL after administration of an inhaled short-acting β_2 agonist) or by hyperresponsiveness to a bronchial challenge agent. Patients should have made two prior visits to one of the outpatient clinics mentioned above, and the pharmacological treatment regimen should have already been adjusted to the level of asthma severity. Patients should be receiving inhaled corticosteroids alone or in combination with long-acting β_2 agonists.

The exclusion criteria were declining to participate in the study, having another chronic lung disease (emphysema, chronic bronchitis, or bronchiectasis), not using inhaled drugs, and failing to complete all of the evaluations required by the study protocol.

The questionnaire used to interview patients included a checklist for assessing patient handling of the device used to inhale the corticosteroid. Prior to the study outset, the principal investigator trained all members of the research team on the correct use of each device and on how to score each stage of the evaluation process. Patients were asked to demonstrate their inhaler technique, using placebo. For metered dose inhalers, patients were assessed for their performance of the following steps: a) shaking the inhaler before using it; b) exhaling normally before using the inhaler; c) holding the inhaler at an appropriate distance (3-5 cm) from the lips if a spacer is not used or, if a spacer is used, placing the inhaler in the mouth and creating an adequate seal with the lips; d) inhaling slowly and deeply after squeezing the inhaler; and e) performing a breath-hold of at least 10 seconds (after inhalation). For dry powder inhalers, patients were assessed for their performance of the following steps: a) exhaling normally before using the inhaler; b) placing the inhaler in the mouth and creating an adequate seal with the lips; c) inhaling as forcefully and deeply as possible; and d) performing a breath-hold of at least 10 seconds (after inhalation).

Asthma severity was categorized on the basis of the daily medication regimen in use, as proposed in the Global Initiative for Asthma (GINA) guidelines.[3]

The level of asthma control was assessed in accordance with the classification proposed in the 2011 GINA guidelines (Chart 1).[3]

Pulmonary function was assessed with a computerized spirometer (MasterScreen v4.31; Jaeger, Würzburg, Germany). We recorded FVC, FEV_1, and the FEV_1/FVC ratio. All parameters are expressed as a percentage of the predicted value for age, gender, and height.[7]

Measurements of PEF were performed with a portable peak flow monitor (Vitalograph; Boehringer Ingelheim, Ingelheim am Rhein,

Chart 1 - Criteria for assessing the level of asthma control.[a]

Level of asthma control		
Controlled (presence of all criteria)	Partially controlled (presence of any criteria in any given week)	Uncontrolled (presence of any criteria)
• Daytime symptoms twice a week or less	• Daytime symptoms twice a week or less	• 3 or more criteria of partially controlled asthma in any given week
• No limitation of activities	• Any limitation of activities	
• No nocturnal symptoms/ awakenings	• Any nocturnal symptom/ awakening	• Exacerbation requiring the use of oral corticosteroids in any given week
• Rescue medication twice a week or less	• Rescue medication more than twice a week	
• Normal pulmonary function	• Pulmonary function < 80% of the predicted value or of the personal best value, if known	• Hospitalization/emergency room admission for asthma in the last 12 months

[a]In accordance with the Global Initiative for Asthma.[4]

Germany). The results are expressed as a percentage of the predicted value for age, gender, and height.[8]

For the statistical analysis, we used the Statistical Package for the Social Sciences, version 18.0 (SPSS Inc., Chicago, IL, USA). Data are expressed as number (percentage) of cases, mean ± SD, or median (interquartile range).

For each patient, the number of inhaler technique errors was recorded. In the present sample, the association between the number of errors (dichotomized into one or more errors and two or more errors) and the level of asthma control (controlled, partially controlled, and uncontrolled) was analyzed by the chi-square test. We found that the cut-off point of one or more errors was not significantly associated with the level of asthma control ($p = 0.07$), whereas the cut-off point of two or more errors was significantly associated with the level of asthma control ($p = 0.002$). Therefore, correct inhaler technique was defined as making less than two inhaler technique errors, whereas incorrect inhaler technique was defined as making two or more errors.

Patients with correct inhaler technique and patients with incorrect inhaler technique were compared for categorical variables using the chi-square test with adjusted standardized residuals and, when necessary, Yates' correction or Fisher's exact test. Continuous variables were compared by the independent sample t-test or the Mann-Whitney U test.

A binary logistic regression model (enter method) was used to identify characteristics predictive of incorrect inhaler technique. Variables with a significance level less than 0.1 in univariate analysis, adjusted for gender and age, were included in a logistic regression model.

All statistical tests were two-tailed. The level of significance was set at 5%.

Results

A total of 334 eligible patients were examined. Thirty patients declined to participate, 27 patients were excluded because they had another chronic lung disease, 7 patients were excluded because they did not use the prescribed inhaled drug, and 2 patients were excluded because they failed to complete all of the evaluations required by the study protocol. Therefore, 268 individuals completed the study. Of those, 187 patients showed correct inhaler technique and 81 (30.2%) showed incorrect technique.

Table 1 shows the general characteristics of the study patients. One hundred and ninety-nine patients (74.3%) were female, and 223 (83.2%) were White. The mean age was 50.9 ± 16.5 years. Most patients (60.1%) had had 8 years of schooling or less, and 186 (69.4%) had a monthly family income of less than three times the national minimum wage. Asthma severity was classified as mild persistent in 37 (13.8%) of the patients, as moderate persistent in 89 (33.2%), and as severe persistent in 142 (53.0%). Asthma was classified as controlled in 47 (17.5%) of the patients, as partially controlled in 74 (27.6%), and as uncontrolled in 147 (54.9%).

Table 2 shows the comparison between groups formed on the basis of inhaler technique assessment. Statistically significant differences

Table 1 - General characteristics of the 268 study patients.[a]

Variable	Result
Gender	
Female	199 (74.3)
Male	69 (25.7)
Age, years	50.9 ± 16.5
Ethnicity	
White	223 (83.2)
Non-White	45 (16.8)
Marital status	
Married/spouse	142 (53.0)
Divorced/separated	34 (12.7)
Widowed	26 (9.7)
Single	66 (24.6)
Level of education	
< 9 years of schooling	161 (60.1)
= 9 years of schooling	88 (32.8)
College	19 (7.1)
Monthly family income, number of times the national minimum wage	
< 3	186 (69.4)
3-10	79 (29.5)
> 10	3 (1.1)
Smoking status	
Never smoker	162 (60.4)
Former smoker	97 (36.2)
Smoker	9 (3.4)
Comorbidities	
0	160 (59.7)
1	94 (35.1)
≥ 2	14 (5.2)
Level of asthma severity (GINA)	
Mild persistent	37 (13.8)
Moderate persistent	89 (33.2)
Severe persistent	142 (53.0)
Level of asthma control (GINA)	
Controlled	47 (17.5)
Partially controlled	74 (27.6)
Uncontrolled	147 (54.9)
FVC, % of predicted	83.7 ± 21.0
FEV_1, % of predicted	68.8 ± 22.9
FVC/FEV_1, % of predicted	80.9 ± 14.3

GINA: Global Initiative for Asthma. [a]Values expressed as n (%), except where otherwise indicated. [b]Values expressed as mean ± SD.

were found for the following variables: marital status (p = 0.002), the proportion of widowed patients being higher among those with incorrect inhaler technique; level of education (p = 0.023), the proportion of patients who had had 8 years of schooling or less being higher among those with incorrect inhaler technique; monthly family income (p = 0.016), the proportion of patients with an income of less than three times the national minimum wage being higher among those with incorrect inhaler technique; and level of asthma control (p = 0.007), the proportion of patients with uncontrolled asthma being higher among those with incorrect inhaler technique.

Table 3 shows that there was a statistically significant difference in type of inhaler used (p < 0.001) between the two groups formed on the basis of inhaler technique assessment, the proportion of patients with correct technique being higher among those using dry powder inhalers than among those using metered dose inhalers. In addition, the proportion of patients with correct inhaler technique differed significantly among each specific type of inhaler used (p < 0.001), the proportion of patients with correct inhaler technique being higher among those using Aerolizer® or Turbuhaler®. In contrast, we found a higher proportion of patients with incorrect technique among those using metered dose inhalers without spacers.

Table 4 shows the logistic regression for factors related to incorrect inhaler technique. The following variables were independently associated with incorrect inhaler technique: being widowed (OR = 5.01; 95% CI, 1.74-14.41; p = 0.003); using metered dose inhalers (OR = 1.58; 95% CI, 1.35-1.85; p < 0.001); having a monthly family income of less than three times the national minimum wage (OR = 2.67; 95% CI, 1.35-1.85; p = 0.008), and having two or more comorbidities (OR = 3.80; 95% CI, 1.03-14.02; p = 0.045).

Discussion

The present study showed that the number of inhaler technique errors has a significant impact on the level of asthma control. The variables that were associated with incorrect inhaler technique were being widowed, using metered dose inhalers, having a monthly family income of less than three times the national minimum wage, and having two or more comorbidities.

Incorrect inhaler technique in asthma treatment can substantially reduce lung deposition of the drug, undermining the effectiveness of asthma treatment. In the present study, incorrect inhaler technique (i.e., making 2 or more errors) was

Table 2 - Comparison between groups formed on the basis of inhaler technique assessment.[a]

Variable	Groups[b]		p
	Correct technique (n = 187)	Incorrect technique (n = 81)	
Gender			0.474
Female	136 (72.7)	63 (77.8)	
Male	51 (27.3)	18 (22.2)	
Age, years[c]	50.4 ± 16.5	52.7 ± 16.8	0.296
Ethnicity			0.971
White	155 (82.9)	68 (84.0)	
Non-White	32 (17.1)	13 (16.0)	
Age at diagnosis of asthma, years[d]	26.0 (71.0)	24.0 (40.0)	0.966
Marital status			0.002
Married/spouse	106 (56.7)	36 (44.4)	
Divorced/separated	22 (11.8)	12 (14.8)	
Widowed	10 (5.3)*	16 (19.8)*	
Single	49 (26.2)	17 (21.0)	
Level of education			0.023
< 9 years of schooling	105 (56.1)*	56 (69.1)*	
= 9 years of schooling	64 (34.2)	24 (29.6)	
College	18 (9.6)*	1 (1.2)*	
Monthly family income, number of times the national minimum wage			0.016
< 3	120 (64.2)*	66 (81.5)*	
3-10	65 (34.8)*	14 (17.3)*	
> 10	2 (1.1)	1 (1.2)	
Smoking status			0.226
Never smoker	119 (63.6)	43 (53.1)	
Former smoker	63 (33.7)	34 (42.0)	
Smoker	5 (2.7)	4 (4.9)	
Comorbidities			0.055
0	117 (62.6)	43 (53.1)	
1	64 (34.2)	30 (37.0)	
≥ 2	6 (3.2)	8 (9.9)	
Level of asthma severity (GINA)			0.094
Mild intermittent or persistent	31 (16.6)	6 (7.4)	
Moderate persistent	63 (33.7)	26 (32.1)	
Severe persistent	93 (49.7)	49 (60.5)	
Level of asthma control (GINA)			0.007
Controlled	39 (20.9)*	8 (9.9)*	
Partially controlled	57 (30.5)	17 (21.0)	
Uncontrolled	91 (48.7)*	56 (69.1)*	
FVC, % of predicted[c]	83.5 ± 20.8	84.5 ± 22.0	0.748
FEV_1, % of predicted[c]	68.0 ± 23.7	71.2 ± 21.5	0.337
FVC/FEV_1, % of predicted[c]	65.8 ± 13.2	66.8 ± 11.1	0.605
PEF, % of predicted[c]	64.9 ± 22.9	61.3 ± 20.2	0.232

GINA: Global Initiative for Asthma. [a]Values expressed as n (%), except where otherwise indicated. [b]Correct technique was defined as making < 2 inhaler technique errors; incorrect technique was defined as making ≥ 2 inhaler technique errors. [c]Values expressed as mean ± SD. [d]Value expressed as median (interquartile range). *Statistically significant adjusted standardized residuals (< −1.96 or > 1.96). The independent sample t-test was used for variables with normal distribution; the Mann-Whitney U test was used for variables without normal distribution; and the chi-square test was used for categorical variables.

associated with poor asthma control. It is of note that a previous study,[9] in which incorrect inhaler technique was defined as making one or more errors, found no association between the correctness of inhaler technique and the level of asthma control.

Table 3 - Inhaler technique and type of inhaler used.[a]

Variable	Groups[b]		p*
	Correct technique	Incorrect technique	
	(n = 187)	(n = 81)	
Type of inhaler			
Metered dose inhaler	61 (32.6)*	59 (72.8)*	< 0.001
Aerolizer®	89 (47.6)*	18 (22.2)*	
Turbuhaler®	20 (10.7)*	1 (1.2)*	
Diskus®	15 (8.0)	3 (3.7)	
Pulvinal®	2 (1.1)	0 (0.0)	

[a]Values expressed as n (%). [b]Correct technique was defined as making < 2 inhaler technique errors; incorrect technique was defined as making ≥ 2 inhaler technique errors. *Statistically significant adjusted standardized residuals (< −1.96 or > 1.96). *Chi-square test.

Table 4 - Binary logistic regression for factors related to incorrect inhaler technique.

Variable	b	Wald	p	OR	95% CI
Age	0.003	0.09	0.770	1.00	0.98-1.02
Male gender	−0.54	2.12	0.145	0.58	0.28-1.20
Being widowed	−1.61	8.93	0.003	5.01	1.74-14.41
Using metered dose inhalers	0.45	31.75	< 0.001	1.58	1.35-1.85
Having had < 9 years of schooling	0.41	1.55	0.213	1.51	0.79-2.90
Having a monthly family income < 3 times the national minimum wage	0.98	7.03	0.008	2.67	1.35-1.85
Having ≥ 2 comorbidities	1.34	4.02	0.045	3.80	1.03-14.02
Constant	−4.14	10.33	0.001	0.016	-

Studies have suggested that 32% to 96% of asthma patients make errors when using their inhalers, and that, in 28% to 68% of cases, those errors are important to the point of undermining the effects of treatment.[10,11] In the present study, 30.2% of the patients made two or more inhaler technique errors, and this cut-off point was associated with asthma control. In contrast to these findings, in a study conducted in Brazil, Coelho et al.[12] evaluated handling of inhaler devices by 467 patients with severe asthma who were followed at a center in the state of Bahia and observed that most patients showed appropriate inhaler technique, a finding that was attributed to the intense educational intervention that those patients received at a referral center.

Performing the inhaler technique correctly depends on the type of inhaler. A systematic review[11] has shown that patients using dry powder inhalers had lower rates of inhaler technique errors than did those using metered dose inhalers. The present study adds to the evidence that the proportion of patients with inappropriate inhaler technique is higher among patients using metered dose inhalers than among those using dry powder inhalers. This difference is even greater when patients using metered dose inhalers without spacers are considered. Metered dose inhalers are more difficult to use, because they require greater motor coordination. The use of a spacer reduces the need for greater motor coordination, but, despite that, metered dose inhalers remain more difficult to use than dry powder inhalers, which leads to a higher proportion of inhaler technique errors.[11,13] However, one factor to be considered in the present study is that the number of inhaler technique steps assessed was greater for metered dose inhaler use (five steps) than for dry powder inhaler use (four steps). This may indicate a bias in the present study, with the requirement for classifying the technique as correct being more stringent for individuals using metered dose inhalers. However, this is more likely to represent the greater complexity of performing the inhaler technique with metered dose inhalers than with dry powder inhalers.

In the present study, a higher proportion of patients with inappropriate technique were found among those with a monthly family income of less than three times the national minimum wage. A previous study has shown that, to ensure appropriate treatment and reduce asthma

morbidity, it is necessary that socioeconomically disadvantaged patients receive a more intense educational approach.[14]

The level of support provided by family members or caregivers can also contribute to the appropriate performance of the inhaler technique.[15] In our study, we found that inappropriate inhaler technique was more common among widowed patients. Widowhood can contribute to a varying degree of social isolation and loneliness that can negatively impact the treatment of chronic diseases.[16]

The physical or mental impairment induced by the presence of other diseases can negatively impact the use of inhalers. Conditions such as tremors, vision impairment, hearing impairment, arthritis, mood disorders, and cognitive disorders can impair learning of the inhaler technique or its appropriate performance.[14] In the present study, the presence of two or more comorbidities was associated with inappropriate inhaler technique. However, we did not specifically address which diseases were more prevalent in this association.

Since the present study found a large proportion of patients with uncontrolled asthma (69.1%), it is important to highlight the fact that a previous study[9] conducted in Brazil showed that the level of asthma control was associated with asthma severity, access to medication, and appropriate use of inhaled corticosteroids. Therefore, since our study was carried out at a public tertiary care center, it is natural that cases that are more difficult to control will be referred there for treatment and that, in contrast, controlled asthma cases will be sent back for treatment at public primary care clinics.

The present study has some limitations to consider. First, it was a cross-sectional study and, therefore, it does not allow the establishment of a temporal sequence between the quality of the patients' performance of the inhaler technique and their level of asthma control. Second, the study was carried out at a single center that provides care within the public health system. Consequently, the study population consisted of individuals who had a low monthly family income and a low educational level, and this may limit the generalization of results.

The clinical implications of this study lie primarily in the demonstration of the fact that two or more inhaler technique errors affect the level of asthma control, with 30.2% of the patients studied showing inappropriate inhaler technique on the basis of this definition. In addition, our findings indicate that target group patients such as widowed patients, patients using metered dose inhalers, patients with a monthly family income of less than three times the national minimum wage, and patients with two or more comorbidities require special attention in terms of inhaler technique education. Therefore, it is important that educational strategies for asthma patients be developed to improve their performance of the inhaler technique and increase their level of asthma control.

References

1. Bateman ED, Boushey HA, Bousquet J, Busse WW, Clark TJ, Pauwels RA, et al. Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma ControL study. Am J Respir Crit Care Med. 2004;170(8):836-44. http://dx.doi.org/10.1164/rccm.200401-033OC PMid:15256389
2. Cazzoletti L, Marcon A, Janson C, Corsico A, Jarvis D, Pin I, et al. Asthma control in Europe: a real-world evaluation based on an international population-based study. J Allergy Clin Immunol. 2007;120(6):1360-7. http://dx.doi.org/10.1016/j.jaci.2007.09.019 PMid:17981317
3. Global Initiative for Asthma. Global strategy for asthma management and prevention. Bethesda: National Institutes of Health; 2011.
4. Molimard M, Raherison C, Lignot S, Depont F, Abouelfath A, Moore N, et al. Assessment of handling of inhaler devices in real life: an observational study in 3811 patients in primary care. J Aerosol Med. 2003;16(3):249-54. http://dx.doi.org/10.1089/089426803769017613 PMid:14572322
5. Roy A, Battle K, Lurslurchachai L, Halm EA, Wisnivesky JP. Inhaler device, administration technique, and adherence to inhaled corticosteroids in patients with asthma. Prim Care Respir J. 2011;20(2):148-54. http://dx.doi.org/10.4104/pcrj.2011.00022 PMid:21437565
6. IV Brazilian Guidelines for the management of asthma [Article in Portuguese]. J Bras Pneumol. 2006;32 Suppl 7:S447-74. PMid:17420905
7. Pereira CA, Barreto SP, Simões JG, Pereira FW, Gerstler JG, Nakatani J. Valores de referência para espirometria em uma amostra da população brasileira adulta. J Pneumol. 1992;18(1):10-22.
8. Gregg I, Nunn AJ. Peak expiratory flow in normal subjects. Br Med J. 1973;3(5874):282-4. http://dx.doi.org/10.1136/bmj.3.5874.282
9. Dalcin PT, Menegotto DM, Zanonato A, Franciscatto L, Soliman F, Figueiredo M, et al. Factors associated with uncontrolled asthma in Porto Alegre, Brazil. Braz J Med Biol Res. 2009;42(11):1097-103. http://dx.doi.org/10.1590/S0100-879X2009005000035 PMid:19820883
10. Chrystyn H, Price D. Not all asthma inhalers are the same: factors to consider when prescribing an inhaler. Prim Care Respir J. 2009;18(4):243-9. http://dx.doi.org/10.4104/pcrj.2009.00029 PMid:19513494
11. Cochrane MG, Bala MV, Downs KE, Mauskopf J, Ben-Joseph RH. Inhaled corticosteroids for asthma therapy: patient compliance, devices, and inhalation

technique. Chest. 2000;117(2):542-50. http://dx.doi.org/10.1378/chest.117.2.542 PMid:10669701
12. Coelho AC, Souza-Machado A, Leite M, Almeida P, Castro L, Cruz CS, et al. Use of inhaler devices and asthma control in severe asthma patients at a referral center in the city of Salvador, Brazil. J Bras Pneumol. 2011;37(6):720-8. PMid:22241028
13. Khassawneh BY, Al-Ali MK, Alzoubi KH, Batarseh MZ, Al-Safi SA, Sharara AM, et al. Handling of inhaler devices in actual pulmonary practice: metered-dose inhaler versus dry powder inhalers. Respir Care. 2008;53(3):324-8. PMid:18291048
14. Yawn BP, Colice GL, Hodder R. Practical aspects of inhaler use in the management of chronic obstructive pulmonary disease in the primary care setting. Int J Chron Obstruct Pulmon Dis. 2012;7:495-502. http://dx.doi.org/10.2147/COPD.S32674 PMid:22888221 PMCid:PMC3413176
15. de Oliveira MA, Faresin SM, Bruno VF, de Bittencourt AR, Fernandes AL. Evaluation of an educational programme for socially deprived asthma patients. Eur Respir J. 1999;14(4):908-14. http://dx.doi.org/10.1034/j.1399-3003.1999.14d30.x PMid:10573241
16. Aartsen MJ, Van Tilburg T, Smits CH, Comijs HC, Knipscheer KC. Does widowhood affect memory performance of older persons? Psychol Med. 2005;35(2):217-26. http://dx.doi.org/10.1017/S0033291704002831 PMid:15841679

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Morbidity, mortality, and categorization of the risk of perioperative complications in lung cancer patients*

Mortalidade, morbidade e categorização de risco para complicações perioperatórias em pacientes com câncer de pulmão

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Abstract

Objective: To determine morbidity and mortality rates by risk category in accordance with the American College of Chest Physicians guidelines, to determine what role pulmonary function tests play in this categorization process, and to identify risk factors for perioperative complications (PCs). **Methods:** This was a historical cohort study based on preoperative and postoperative data collected for cases of lung cancer diagnosed or suspected between 2001 and 2010. **Results:** Of the 239 patients evaluated, only 13 (5.4%) were classified as being at high risk of PCs. Predicted postoperative FEV_1 (FEV_1ppo) was sufficient to define the risk level in 156 patients (65.3%); however, cardiopulmonary exercise testing (CPET) was necessary for identifying those at high risk. Lung resection was performed in 145 patients. Overall morbidity and mortality rates were similar to those reported in other studies. However, morbidity and mortality rates for patients at an acceptable risk of PCs were 31.6% and 4.3%, respectively, whereas those for patients at high risk were 83.3% and 33.3%. Advanced age, COPD, lobe resection, and lower FEV_1ppo were correlated with PCs. **Conclusions:** Although spirometry was sufficient for risk assessment in the majority of the population studied, CPET played a key role in the identification of high-risk patients, among whom the mortality rate was seven times higher than was that observed for those at an acceptable risk of PCs. The risk factors related to PCs coincided with those reported in previous studies.

Keywords: Algorithms; Lung neoplasms; Postoperative complications.

Resumo

Objetivo: Determinar as taxas de morbidade e mortalidade por categoria de risco conforme as diretrizes do *American College of Chest Physicians*, verificar como exames funcionais participaram dessa categorização e identificar fatores de risco para complicações perioperatórias (CPOs). **Métodos:** Estudo de coorte histórica a partir de avaliações pré e pós-operatórias de casos diagnosticados ou suspeitos de câncer de pulmão avaliados entre 2001 e 2010. **Resultados:** Dos 239 pacientes avaliados, apenas 13 (5,4%) foram considerados como de alto risco para CPOs. O cálculo do VEF_1 previsto para o pós-operatório (VEF_1ppo) foi suficiente para a estratificação do risco em 156 pacientes (65,3%); entretanto, o teste de exercício cardiopulmonar (TECP) foi necessário para a identificação de alto risco. Foram operados 145 pacientes, e as taxas globais de morbidade e mortalidade encontradas foram semelhantes às de outros estudos. Entretanto, as taxas de morbidade e mortalidade para aqueles com risco aceitável foram de 31,6% e 4,3%, respectivamente, enquanto as taxas para aqueles com alto risco foram de 83,3% e 33,3%. Idade mais avançada, presença da DPOC, ressecção de um ou mais lobos e VEF_1ppo mais baixo estiveram relacionados à ocorrência de CPOs. **Conclusões:** Embora a espirometria tenha sido suficiente para a determinação de risco na maioria da população estudada, o TECP teve papel fundamental na identificação de pacientes com risco alto, que apresentaram uma taxa de mortalidade sete vezes maior que os de risco aceitável. Os fatores de risco relacionados a CPOs coincidiram aos relatados em outros estudos.

Descritores: Algoritmos; Neoplasias pulmonares; Complicações pós-operatórias.

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Introduction

Functional evaluation of candidates for lung resection for the treatment of lung cancer can be guided by various algorithms, of which the most known are those proposed by the consensus guidelines of the American College of Chest Physicians (ACCP)[1] and the European Respiratory Society/European Society of Thoracic Surgeons.[2] Although the use of these tools would potentially reduce morbidity and mortality rates, their application is compromised, because tests that are not readily available for most physicians, such as DLCO measurement and, especially, cardiopulmonary exercise testing (CPET), are required.[3-5]

The main difference between the two algorithms lies in the referral for those tests, although there have been no studies comparing the superiority of one over the other. However, it has been reported that, when no algorithm was used, evaluation errors were common, with the highest frequency of these errors occurring among less experienced physicians.[5,6]

Having been published before the European algorithm, the ACCP algorithm has been used in the preoperative evaluation center of the Federal University of São Paulo in the last 10 years. The objective of this study was to share our experience by providing morbidity and mortality rates by risk category, as well as to report the role played by DLCO measurement and CPET in this categorization process and the risk factors associated with perioperative complications (PCs).

Methods

This was a historical cohort study of a database of preoperative evaluations of patients diagnosed with or clinically suspected of having lung cancer, performed at the *Hospital São Paulo*, located in the city of São Paulo, Brazil, between January 1, 2001 and December 31, 2010. The project was approved by the Research Ethics Committee of the Federal University of São Paulo (Protocol no. 1487/11).

The evaluation algorithm proposed by the ACCP consensus guidelines was applied after patients had achieved their best clinical and functional status. Figure 1 illustrates the algorithm and the surgical risk categorization. All patients underwent spirometry, and referral for DLCO measurement occurred when there was clinical and radiological suspicion of concomitant interstitial disease, when there was a history of neoadjuvant chemotherapy, or when the intensity of dyspnea reported was disproportionate to the measured FEV_1 as a percentage of the predicted value. Referral for CPET occurred when either predicted postoperative FEV_1 (FEV_1ppo) or predicted postoperative DLCO (DLCOppo) was less than 40%, or when the patient was unable to perform acceptable DLCO measurement maneuvers. Patients who were unable to perform CPET properly were classified as being at high risk.

In the post-operative period, patients received physical therapy and pain management from specialized teams until they were discharged from the hospital.

The outcome measures analyzed, i.e., morbidity and mortality rates, included events occurring by postoperative day 30. Described in a previous study,[7] the definitions of PCs were as follows: respiratory or cardiovascular events causing intraoperative instability; lower respiratory tract infection; atelectasis; acute respiratory failure; acute myocardial infarction; atrial arrhythmia requiring treatment; congestive heart failure; bronchopleural fistula; pleural empyema; air leak lasting 7 days or longer; hemothorax; reoperation; and need for oxygen therapy on postoperative day 30.

In the statistical analysis, morbidity and mortality rates are expressed as simple percentages. In order to determine whether the functional values were associated with PCs, we had to recalculate them, adjusting them to the extent of the resection performed rather than maintaining them in accordance with the planned resection. The resulting values were called true FEV_1ppo and true DLCOppo. In order to identify which variables were correlated with PCs, we used Pearson's chi-square test and the Student's t-test.

Results

Of the 262 who were eligible for the study, 239 (91.2%) underwent all steps of the ACCP algorithm, whereas 23 (8.8%) did not. The clinical and functional characteristics of those 239 patients are shown in Table 1.

In 156 patients (65.3%), FEV_1 was $\geq$ 80% or FEV_1ppo was $\geq$ 40%, and no other tests were needed to complete the evaluation. However, 8 patients (3.3%) had a FEV_1ppo $\leq$ 40% and were therefore referred for CPET.

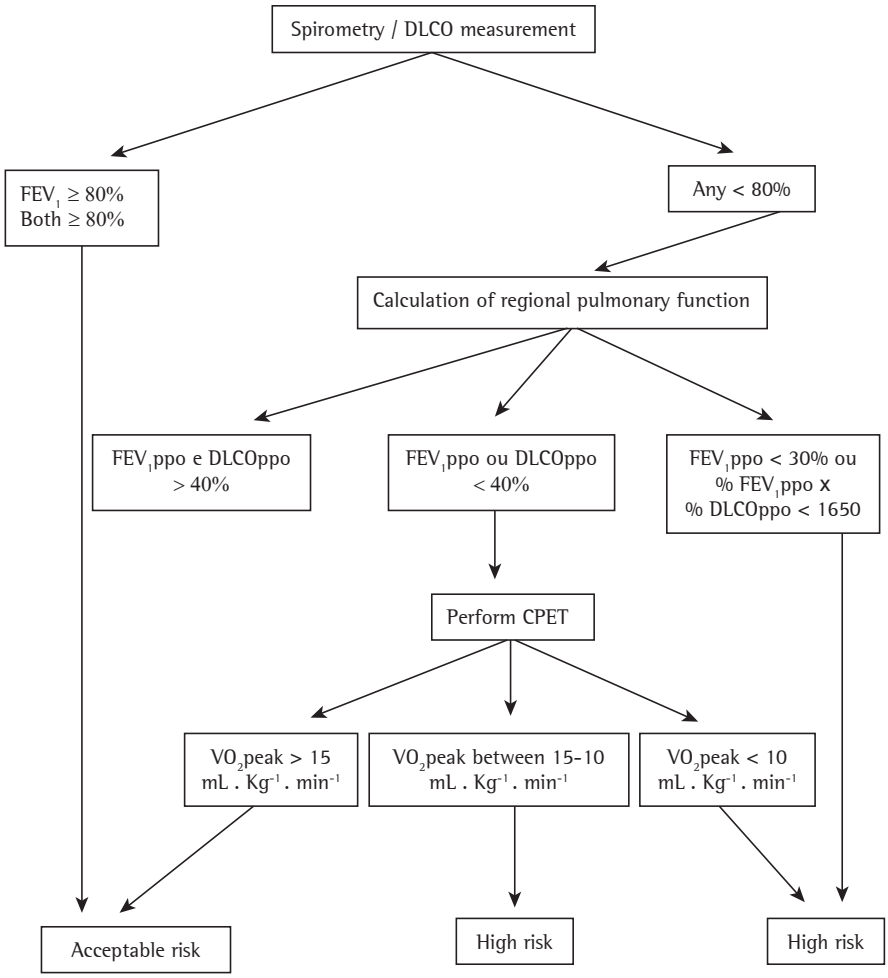

Figure 1 - Algorithm proposed by the American College of Chest Physicians. ppo: predicted postoperative; CPET: cardiopulmonary exercise testing; and VO_2peak: peak oxygen uptake.

Table 1 - Demographic, clinical, and pulmonary function data of the 239 candidates evaluated.[a]

Variable	Result
Age, years[b]	59.0 ± 12.0
Neoadjuvant chemotherapy	17 (7.1)
COPD	78 (32.6)
Other comorbidities	104 (43.5)
Systemic arterial hypertension	93 (89.4)
Diabetes mellitus	35 (33.6)
Coronary artery disease	7 (6.7)
Chronic renal disease	5 (4.8)
Heart failure	2 (1.9)
FEV_1, % of predicted[b]	86.2 ± 20.8
DLCO, % of predicted[b]	67.6 ± 18.3

[a]Values expressed as n (%), except where otherwise indicated. [b]Values expressed as mean ± SD.

Of the 239 patients, 82 (34.3%) were referred for DLCO measurement. However, 6 of those 82 did not undergo DLCO measurement because they were unable to perform acceptable maneuvers. Of the 76 remaining patients, 60 (73.2%) had FEV_1ppo and DLCOppo values > 40% predicted

and were classified, at the end of the preoperative evaluation, as being at an acceptable risk of PCs. Of the 14 patients who had a DLCOppo < 40%, 13 had a FEV_1ppo > 40%. A total of 23 patients (9.6%) were referred for CPET, and 13 (56.5%) of them were classified as being at high risk for the following reasons: having a peak oxygen uptake ≤ 15 mL • kg^{-1} • min^{-1} (6 patients); performing submaximal exercise or being unable to pedal (4 patients); not having undergone CPET because of an unknown reason (2 patients); and not having undergone CPET because the machine was broken (1 patient). Figure 2 illustrates the application of the algorithm, which classified 13 patients (5.4%) as being at high risk of PCs and 226 (94.6%) as being at an acceptable risk.

One hundred and fifty-one patients (63.2%) were operated on. Six of them did not undergo resection of lung parenchyma and were therefore disregarded in the remaining analyses. Of the remainder, 139 and 6 were classified as being at an acceptable and high risk, respectively. In 49.6% of those procedures, the amount of parenchyma resected was smaller than planned; in most cases, because malignant disease was ruled out by intraoperative frozen-section analysis. In 9.3%, a greater amount of tissue was resected because of the progression of cancer. The following procedures were performed: lobectomy (in 38.6% of the cases); resection of less than one segment (in 29.0%); segmentectomy (in 17.9%); pneumonectomy (in 8.3%); bilobectomy (in 4.8%); and bisegmentectomy (in 1.4%).

Of the 145 patients operated on, 49 had PCs, the morbidity rate being 33.8% and the overall mortality rate being 5.5% (8 deaths). There were 101 PCs, the most common being prolonged air leak (in 19.8%), lower airway respiratory infection (in 19.8%), and acute respiratory failure (in 17.8%), followed by cardiac arrhythmia (in 7.9%), need for reoperation (in 5.9%), home oxygen therapy (in 5.9%), pleural empyema (in 5.9%), atelectasis (in 5.0%), acute myocardial infarction (in 5.0%), bronchopleural fistula (in 4.0%), and intraoperative events (in 3.0%).

There were no statistically significant differences between operated and non-operated patients in terms of age, prevalence of comorbidities, prevalence of COPD, or FEV_1 as a percentage of the predicted value. The most common reasons preventing surgical treatment were progression of cancer, treatment discontinuation or dropout, and a diagnosis of benign disease by a method other than the initially planned surgery.

A diagnosis of malignancy was confirmed in 105 operated patients (72.4%), adenocarcinoma being the most common histological type (in 40.0%). In 27.6% of the patients, the histological diagnoses were benign, the majority (59.5%) corresponding to nonspecific benign lesions and tuberculomas.

Morbidity and mortality rates for patients classified preoperatively as being at an acceptable risk of PCs were, respectively, 31.6% and 4.3% (6 deaths), whereas those for patients at high risk were 83.3% and 33.3% (2 deaths). In the reclassification of patients by extent of the procedure, 4 of the 139 patients classified as being at an acceptable risk would be referred for CPET so that the evaluation could be completed. Of the 6 patients classified as being at high risk, 4 remained so and 2 were reclassified as being at an acceptable risk. After recalculation, morbidity and mortality rates were, respectively, 31.4% and 3.6% for those at an acceptable risk and 100% and 50.0% for those at high risk. Table 2 shows the morbidity and mortality rates of patients classified as being at an acceptable risk, by tests performed.

In a comparison of patients who had PCs with those who did not, statistically significant differences were found in the following variables: age; lobe resection; true FEV_1ppo as a percentage of the predicted value; and COPD (Table 3).

Discussion

The use of the ACCP algorithm showed that, among patients classified as being at high risk of PCs, the mortality rate was seven to thirteen times higher than was that observed for those classified as being at an acceptable risk. This difference occurred in the context of overall morbidity and mortality rates being consistent with those reported by other health care facilities.[8-10] This finding revealed that the algorithm provided a good prediction of patient risk, identifying those who require more attention and investment both before and after the procedure.

Whereas only calculation of FEV_1ppo was needed in the evaluation of the majority of the study population, who had a favorable postoperative course, a DLCOppo value < 40% determined the need for CPET five times more often than did a FEV_1ppo value < 40%.

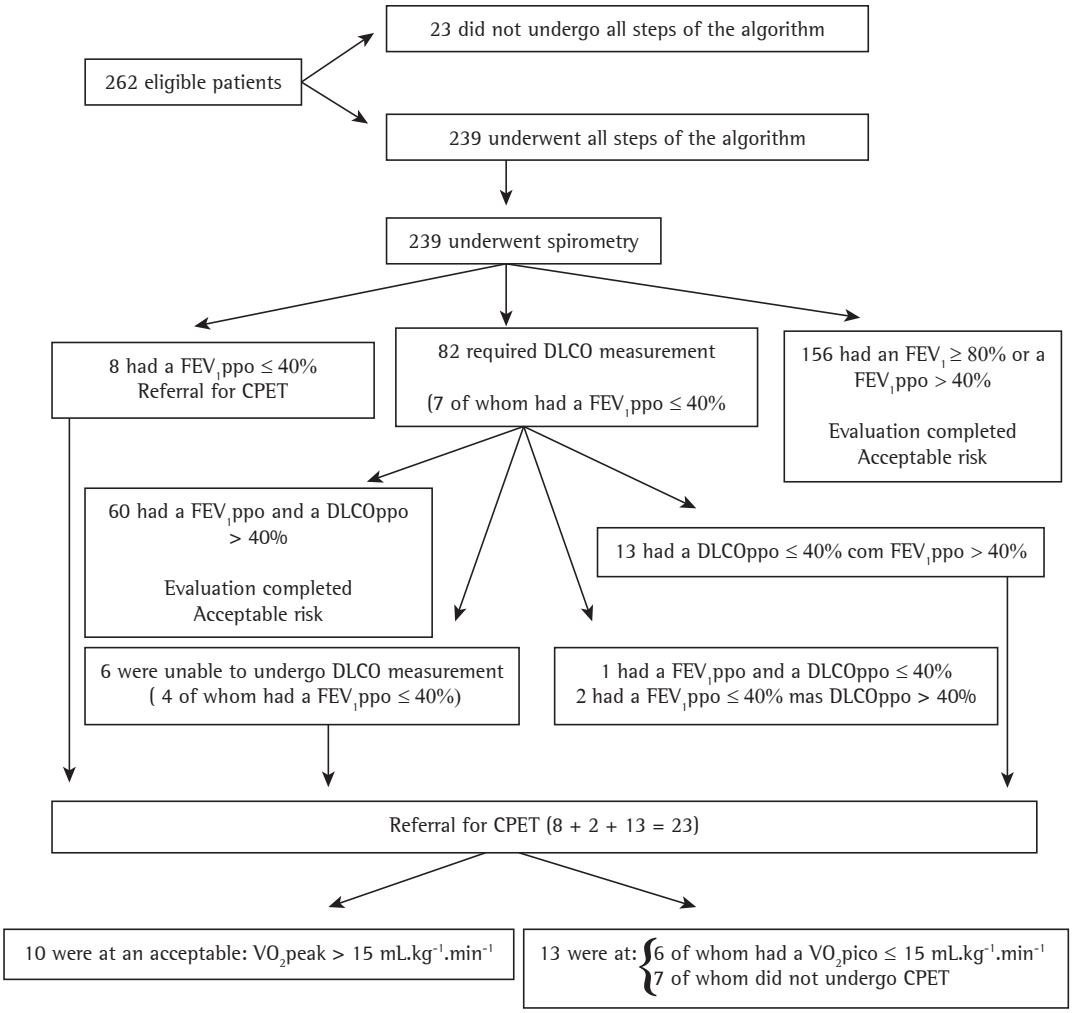

Figure 2 - Preoperative evaluation of 239 lung resection candidates as per the American College of Chest Physicians algorithm guidelines. ppo: predicted postoperative; CPET: cardiopulmonary exercise testing; and VO_2peak: peak oxygen uptake.

Table 2 - Morbidity and mortality rates of the 137 patients reclassified as being at an acceptable risk of perioperative complications after the surgical procedure, by tests performed.

Tests performed	Patients	Morbidity rate	Mortality rate
	n (%)	(%)	(%)
Spirometry	101 (73.7)	26.7	4.0
Spirometry + DLCO measurement	30 (21.9)	33.3	0.0
Spirometry + DLCO measurement + CPET	6 (4.4)	83.3	16.7

CPET: cardiopulmonary exercise testing.

However, considering the subgroup of patients who underwent this test, the risk level did not change in 75% of the cases. This result was unexpected, given that DLCO has gained much prominence in postoperative evaluation in recent years, with several studies demonstrating that DLCO is more accurate for predicting risk of PCs than is FEV_1.[11-13] A likely explanation for this is loss of discriminatory power of DLCO when DLCO is included in an algorithm that classifies patients into only two categories. However, it should also be considered that, if our sample was bigger or if all patients had undergone DLCO measurement, the results could perhaps

Table 3 - Comparison between the groups of patients with and without perioperative complications in terms of age, presence of COPD, presence of other comorbidities, size of resection, and pulmonary function parameters.

Variable	Group		p*
	With PCs	Without PCs	
Age, years	57.6 ± 11.5	61.8 ± 12.0	0.044
COPD	25.0	54.2	0.001
Other comorbidities	52.1	36.7	0.080
Lobe resection	44.8	65.3	0.003
True FEV_1ppo	81.4 ± 22.3	67.9 ± 22.5	0.001

PCs: perioperative complications; and ppo: % of predicted, postoperative. *Pearson's chi-square test and the Student's t-test.

be different, allowing even the creation of other categories, such as the moderate risk category.

Certainly, CPET is the method of choice for surgical risk stratification even outside the field of thoracic surgery; however, it is not widely available.[14,15] Our results showed that, when CPET is used after a series of tests that identified a patient as having limited reserve, which corresponded to only 9.6% of our population, the risk would be high in 56.6% of the cases. However, it is necessary to consider that the observed rates of PCs and mortality were very high. In our view, the algorithm used was designed in such a way that the high-risk category corresponded to "very high risk", and, therefore, the algorithm should be improved by the inclusion of intermediate-risk categories.

According to the European algorithm, CPET should be performed when the predicted FEV_1 or DLCO value is below 80%, i.e., in the initial phase of the evaluation. This recommendation was based primarily on the studies by Bolliger et al.,[3,4] who had this test available at their facility and developed an algorithm on the basis of it. In contrast, the cost-effectiveness of this approach as compared with that of simpler evaluation strategies, especially in low-risk patients, is unknown. If we had applied the European algorithm to our sample, 81.7% of the population should have undergone CPET. A recent study conducted in Spain showed that, when six hospitals used that algorithm, of the 92 patients (53.2%) of the study sample who had been referred for CPET, only 68 underwent the test. In most cases, the test was not performed because of a lack of technical infrastructure.[16]

During the review process of our manuscript, the third revision of the ACCP guidelines for the evaluation of lung resection candidates was published.[17] A new algorithm, extrapolated from a number of studies, was proposed, but, unfortunately, it was not validated in a large, multicenter, prospective study. In comparison with the 2007 guidelines, these new guidelines agree with the European algorithm that all resection candidates should undergo DLCO measurement, as well as including the use of submaximal exercise tests before CPET, the development of new parameters for categorizing low risk, and the creation of a moderate-risk category. Therefore, when FEV_1ppo and DLCOppo were above 60%, patients would be classified as being at low risk. If either of these parameters was between 30% and 60%, patients would be referred for the shuttle test or the stair-climbing test. Depending on the results obtained, patients would undergo CPET, the results of which would determine whether the patient would be classified into the low-risk, moderate-risk, or high-risk category.

In an attempt to simplify the dynamic evaluation of cardiopulmonary reserve, much research has been conducted on submaximal exercise tests, such as the stair-climbing test, the six-minute walk test (6MWT), and the shuttle test.[18-20] Despite the satisfactory findings reported, some negative points have been observed. The lack of standardization of the stair-climbing test, the low level of evidence of the 6MWT, the variability of effort exerted during the tests, and, first and foremost, the fact that none of these tests measure more complex metabolic and cardiopulmonary parameters reserved for them the role of ascertaining if the patient really was at low risk of PCs. The European consensus guidelines and the ACCP consensus guidelines agree that patients who perform poorly on these tests should undergo CPET. It is likely that further studies will discuss whether or not the strategy of using submaximal exercise tests within the new

algorithm will prove sufficiently discriminatory and cost-effective.

Given these findings, we suspect that the major problem may lie in the proposed algorithms rather than in the availability of the tests. In an attempt to verify this suspicion, our suggestion would be to start the investigative process after determining which PCs would be considered significant for this type of procedure, in order to determine the morbidity rate. Goals would then be set on the basis of morbidity and mortality rates considered tolerable for each risk category. Investigations would identify which tests and which results would be needed in order to achieve each goal, determining how much accuracy would be gained by including more sophisticated tests in each category. An algorithm designed in such a way would perhaps give greater assurance to the surgeon and the patient, as well as resulting in better use of more complex tests and of multidisciplinary teams as risk increased. This reasoning results from the difficulty we face in comparing the rates of PCs and death found in the present study with those reported in other studies, as well as from the hypothesis formulated on the basis of our findings, i.e., CPET plays a more decisive role in differentiating between the high-risk and very high-risk categories and in clinical treatment.

Although CPET is available at our facility, we will continue to recommend it only for patients with limited reserve, because, since ours is a public health care facility, we do not have sufficient resources or logistics capacity to meet the demand generated by the use of the European algorithm. In addition, as seen in Table 2, the morbidity and mortality rates obtained for the acceptable-risk category by using spirometry and DLCO measurement were satisfactory.

The occurrence of PCs is always a cause for concern. For patients, it means longer hospital stays, a greater delay in resuming work and social activities, and higher medical and hospital expenses, as well as adding to the risk of sequelae or death. As in recent studies, the rate of observed cardiac complications was lower than that of pulmonary complications.[9,21] One possible explanation could be care in recognizing and treating cardiac comorbidities prior to evaluation for resection, a recommendation made by both the ACCP algorithm and the European algorithm. Studies have shown that the implementation of a preoperative cardiac evaluation algorithm contributed to proper use of tests and therapeutic strategies, reducing cardiac morbidity rates.[22,23] Another contributing factor would be advances in the diagnosis and treatment of dyslipidemia, systemic arterial hypertension, diabetes mellitus, and coronary artery disease, reducing the systemic inflammatory state.

It remains controversial whether advanced age alone is a risk factor for PCs[24,25] or whether the severity and number of comorbidities that affect older patients are responsible for these complications.[9,26-28] The prevalence rate of comorbidities found in our study was similar to or lower than those reported in other studies,[8,9,29] as well as being similar between the groups with and without PCs. The opposite was true for the presence of COPD and the extent of resection, which are known to be the two most important risk factors related to PCs.[4,9,24]

The present study had some limitations. The first of these limitations was the study's retrospective design. Therefore, we prioritized addressing complications that have the greatest impact, have established definitions, and had been used in other studies conducted at out facility, such as pulmonary infection, acute respiratory failure, and bronchopleural fistula. The second limitation was the modest number of patients studied, which precluded more complex statistical analysis. However, this is the first report of the use of the ACCP algorithm in Brazil. The third limitation was the possibility that critically ill patients were not referred to our outpatient clinic because they had previously been considered as being at very high risk. Therefore, the findings of the present study should not be generalized.

In conclusion, the use of the ACCP algorithm allowed the identification of a group of patients whose morbidity and mortality rates were considerably higher, requiring more attention throughout the perioperative period. The majority of our population was evaluated on the basis of spirometry alone and had acceptable morbidity and mortality rates. However, CPET played an important role in the identification of high-risk patients. In agreement with published studies, advanced age, COPD, lobe resection, and poorer pulmonary function were correlated with PCs.

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References

1. Colice GL, Shafazand S, Griffin JP, Keenan R, Bolliger CT; American College of Chest Physicians. Physiologic evaluation of the patient with lung cancer being considered for resectional surgery: ACCP evidenced-based clinical practice guidelines (2nd edition). Chest. 2007;132(3 Suppl):161S-77S.
2. Brunelli A, Charloux A, Bolliger CT, Rocco G, Sculier JP, Varela G, et al. ERS/ESTS clinical guidelines on fitness for radical therapy in lung cancer patients (surgery and chemo-radiotherapy). Eur Respir J. 2009;34(1):17-41. Erratum in: Eur Respir J. 2009;34(3):782. http://dx.doi.org/10.1183/09031936.00184308 PMid:19567600
3. Bolliger CT, Jordan P, Solèr M, Stulz P, Grädel E, Skarvan K, et al. Exercise capacity as a predictor of postoperative complications in lung resection candidates. Am J Respir Crit Care Med. 1995;151(5):1472-80. http://dx.doi.org/10.1164/ajrccm.151.5.7735602 PMid:7735602
4. Wyser C, Stulz P, Solèr M, Tamm M, Müller-Brand J, Habicht J, et al. Prospective evaluation of an algorithm for the functional assessment of lung resection candidates. Am J Respir Crit Care Med. 1999;159(5 Pt 1):1450-6. http://dx.doi.org/10.1164/ajrccm.159.5.9809107 PMid:10228110
5. Charloux A, Brunelli A, Bolliger CT, Rocco G, Sculier JP, Varela G, et al. Lung function evaluation before surgery in lung cancer patients: how are recent advances put into practice? A survey among members of the European Society of Thoracic Surgeons (ESTS) and of the Thoracic Oncology Section of the European Respiratory Society (ERS). Interact Cardiovasc Thorac Surg. 2009;9(6):925-31. http://dx.doi.org/10.1510/icvts.2009.211219 PMid:19752152
6. Ferguson MK, Stromberg JD, Celauro AD. Estimating lung resection risk: a pilot study of trainee and practicing surgeons. Ann Thorac Surg. 2010;89(4):1037-42; discussion 1042-3. http://dx.doi.org/10.1016/j.athoracsur.2009.12.068 PMid:20338304
7. Stanzani F, Oliveira MA, Forte V, Faresin SM. Torrington and Henderson and Epstein risk assessment scales: applicability and effectiveness in lung resection. J Bras Pneumol. 2005;31(4):292-9. http://dx.doi.org/10.1590/S1806-37132005000400005
8. Harpole DH Jr, DeCamp MM Jr, Daley J, Hur K, Oprian CA, Henderson WG, et al. Prognostic models of thirty-day mortality and morbidity after major pulmonary resection. J Thorac Cardiovasc Surg. 1999;117(5):969-79. http://dx.doi.org/10.1016/S0022-5223(99)70378-8
9. Boffa DJ, Allen MS, Grab JD, Gaissert HA, Harpole DH, Wright CD. Data from The Society of Thoracic Surgeons General Thoracic Surgery database: the surgical management of primary lung tumors. J Thorac Cardiovasc Surg. 2008;135(2):247-54. http://dx.doi.org/10.1016/j.jtcvs.2007.07.060 PMid:18242243
10. Sánchez PG, Vendrame GS, Madke GR, Pilla ES, Camargo Jde J, Andrade CF, et al. Lobectomy for treating bronchial carcinoma: analysis of comorbidities and their impact on postoperative morbidity and mortality. J Bras Pneumol. 2006;32(6):495-504. http://dx.doi.org/10.1590/S1806-37132006000600005 PMid:17435899
11. Ferguson MK, Little L, Rizzo L, Popovich KJ, Glonek GF, Leff A, et al. Diffusing capacity predicts morbidity and mortality after pulmonary resection. J Thorac Cardiovasc Surg. 1988;96(6):894-900. PMid:3193801
12. Ferguson MK, Gaissert HA, Grab JD, Sheng S. Pulmonary complications after lung resection in the absence of chronic obstructive pulmonary disease: the predictive role of diffusing capacity. J Thorac Cardiovasc Surg. 2009;138(6):1297-302. http://dx.doi.org/10.1016/j.jtcvs.2009.05.045 PMid:19783010
13. Brunelli A, Refai MA, Salati M, Sabbatini A, Morgan-Hughes NJ, Rocco G. Carbon monoxide lung diffusion capacity improves risk stratification in patients without airflow limitation: evidence for systematic measurement before lung resection. Eur J Cardiothorac Surg. 2006;29(4):567-70. http://dx.doi.org/10.1016/j.ejcts.2006.01.014 PMid:16481190
14. Smith TB, Stonell C, Purkayastha S, Paraskevas P. Cardiopulmonary exercise testing as a risk assessment method in non cardio-pulmonary surgery: a systematic review. Anaesthesia. 2009;64(8):883-93. http://dx.doi.org/10.1111/j.1365-2044.2009.05983.x PMid:19604193
15. Older P, Smith R, Hall A, French C. Preoperative cardiopulmonary risk assessment by cardiopulmonary exercise testing. Crit Care Resusc. 2000;2(3):198-208. PMid:16599898
16. Novoa NM, Ramos J, Jiménez MF, González-Ruiz JM, Varela G. The initial phase for validating the European algorithm for functional assessment prior to lung resection: quantifying compliance with the recommendations in actual clinical practice. Arch Bronconeumol. 2012;48(7):229-33. http://dx.doi.org/10.1016/j.arbr.2012.05.001 PMid:22513266
17. Brunelli A, Kim AW, Berger KI, Addrizzo-Harris DJ. Physiologic evaluation of the patient with lung cancer being considered for resectional surgery: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013;143(5 Suppl):e166S-90S.
18. Brunelli A, Refai M, Xiumé F, Salati M, Sciarra V, Socci L, et al. Performance at symptom-limited stair-climbing test is associated with increased cardiopulmonary complications, mortality, and costs after major lung resection. Ann Thorac Surg. 2008;86(1):240-7; discussion 247-8. http://dx.doi.org/10.1016/j.athoracsur.2008.03.025 PMid:18573431
19. Nomori H, Watanabe K, Ohtsuka T, Naruke T, Suemasu K. Six-minute walking and pulmonary function test outcomes during the early period after lung cancer surgery with special reference to patients with chronic obstructive pulmonary disease. Jpn J Thorac Cardiovasc Surg. 2004;52(3):113-9. http://dx.doi.org/10.1007/s11748-004-0126-8 PMid:15077844
20. Win T, Jackson A, Groves AM, Sharples LD, Charman SC, Laroche CM. Comparison of shuttle walk with measured peak oxygen consumption in patients with operable lung cancer. Thorax. 2006;61(1):57-60. http://dx.doi.org/10.1136/thx.2005.043547 PMid:16244091 PMCid:PMC2080711
21. Ferguson MK, Vigneswaran WT. Changes in patient presentation and outcomes for major lung resection over three decades. Eur J Cardiothorac Surg. 2008;33(3):497-501. http://dx.doi.org/10.1016/j.ejcts.2007.12.023 PMid:18221882

22. Almanaseer Y, Mukherjee D, Kline-Rogers EM, Kesterson SK, Sonnad SS, Rogers B, et al. Implementation of the ACC/AHA guidelines for preoperative cardiac risk assessment in a general medicine preoperative clinic: improving efficiency and preserving outcomes. Cardiology. 2005;103(1):24-9. http://dx.doi.org/10.1159/000081848 PMid:15528897
23. Cagirici U, Nalbantgil S, Cakan A, Turhan K. A new algorithm for preoperative cardiac assessment in patients undergoing pulmonary resection. Tex Heart Inst J. 2005;32(2):159-62. PMid:16107106 PMCid:PMC1163462
24. Smetana GW, Lawrence VA, Cornell JE; American College of Physicians. Preoperative pulmonary risk stratification for noncardiothoracic surgery: systematic review for the American College of Physicians. Ann Intern Med. 2006;144(8):581-95. http://dx.doi.org/10.7326/0003-4819-144-8-200604180-00009
25. Dominguez-Ventura A, Cassivi SD, Allen MS, Wigle DA, Nichols FC, Pairolero PC, et al. Lung cancer in octogenarians: factors affecting long-term survival following resection. Eur J Cardiothorac Surg. 2007;32(2):370-4. http://dx.doi.org/10.1016/j.ejcts.2007.04.002 PMid:17555978
26. Algar FJ, Alvarez A, Salvatierra A, Baamonde C, Aranda JL, López-Pujol FJ. Predicting pulmonary complications after pneumonectomy for lung cancer. Eur J Cardiothorac Surg. 2003;23(2):201-8. http://dx.doi.org/10.1016/S1010-7940(02)00719-4
27. Birim O, Zuydendorp HM, Maat AP, Kappetein AP, Eijkemans MJ, Bogers AJ. Lung resection for non-small-cell lung cancer in patients older than 70: mortality, morbidity, and late survival compared with the general population. Ann Thorac Surg. 2003;76(6):1796-801. http://dx.doi.org/10.1016/S0003-4975(03)01064-6
28. Brunelli A, Monteverde M, Al Refai M, Fianchini A. Stair climbing test as a predictor of cardiopulmonary complications after pulmonary lobectomy in the elderly. Ann Thorac Surg. 2004;77(1):266-70. http://dx.doi.org/10.1016/S0003-4975(03)01327-4
29. Ferguson MK, Vigneswaran WT. Changes in patient presentation and outcomes for major lung resection over three decades. Eur J Cardiothorac Surg. 2008;33(3):497-501. http://dx.doi.org/10.1016/j.ejcts.2007.12.023 PMid:18221882

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PLATINO, a nine-year follow-up study of COPD in the city of São Paulo, Brazil: the problem of underdiagnosis*

PLATINO, estudo de seguimento de nove anos sobre DPOC na cidade de São Paulo: o problema do subdiagnóstico

Graciane Laender Moreira, Beatriz Martins Manzano, Mariana Rodrigues Gazzotti, Oliver Augusto Nascimento, Rogelio Perez-Padilla, Ana Maria Baptista Menezes, José Roberto Jardim

Abstract

Objective: To determine the underdiagnosis rate in new COPD cases at the end of a nine-year follow-up period—in the study designated "*Projeto Latino-Americano de Investigação em Obstrução Pulmonar*" (PLATINO, Latin-American Pulmonary Obstruction Investigation Project)—and compare that with the underdiagnosis rate during the initial phase of the study, as well as to identify the clinical features exhibited by the subjects who were not diagnosed until the end of the follow-up phase. **Methods:** The study population comprised the 1,000 residents of the city of São Paulo, Brazil, who took part in the PLATINO study. Of those, 613 participated in the follow-up phase, during which the subjects were assessed with the same instruments and equipment employed in the initial phase of the study. We used the chi-square test or the independent sample t-test to analyze the underdiagnosis rate and to identify the characteristics of the subjects who were not diagnosed until the end of the follow-up phase. **Results:** The underdiagnosis rate for new COPD cases at the end of the nine-year follow-up period was 70.0%. The underdiagnosis rate during the follow-up phase was 17.5% lower than that reported for the initial phase of the study. The subjects who were not diagnosed until the end of the follow-up phase presented with fewer respiratory symptoms, better pulmonary function, and less severe disease than did those previously diagnosed with COPD. **Conclusions:** The underdiagnosis rate for new COPD cases was lower in the follow-up phase of the study than in the initial phase. The subjects who were not diagnosed until the end of the follow-up phase of the PLATINO study presented with the same clinical profile as did those who were not diagnosed in the initial phase. These findings underscore the need for spirometry in order to confirm the diagnosis of COPD and provide early intervention.

Keywords: Pulmonary disease, chronic obstructive/diagnosis; Pulmonary disease, chronic obstructive/epidemiology; Spirometry.

Resumo

Objetivo: Determinar a taxa de subdiagnóstico em novos casos de DPOC em uma amostra de pacientes após nove anos de seguimento do estudo "Projeto Latino-Americano de Investigação em Obstrução Pulmonar" (PLATINO) e compará-la à taxa de subdiagnóstico obtida na fase inicial do estudo, assim como identificar as características clínicas dos indivíduos subdiagnosticados na fase de seguimento. **Métodos:** A população desse estudo foi composta por 1.000 residentes na cidade de São Paulo que fizeram parte do estudo PLATINO. Desses, 613 indivíduos participaram da fase de seguimento. Os indivíduos foram avaliados utilizando-se os mesmos instrumentos e equipamentos na fase inicial do estudo. O teste do qui-quadrado ou o teste t para amostras independentes foi utilizado para analisar a taxa de subdiagnóstico e identificar as características dos indivíduos subdiagnosticados durante a fase de seguimento. **Resultados:** A taxa de subdiagnóstico para novos casos da DPOC após nove anos de acompanhamento foi de 70,0%. A taxa de subdiagnóstico na fase de seguimento foi 17,5% menor que a da fase inicial do estudo. Os indivíduos subdiagnosticados na fase de seguimento apresentavam poucos sintomas respiratórios, função pulmonar mais preservada e menor gravidade da doença do que aqueles previamente diagnosticados com DPOC. **Conclusões:** A taxa de subdiagnóstico na fase de seguimento foi menor que a da fase inicial do estudo. Os indivíduos subdiagnosticados na fase de seguimento do estudo PLATINO apresentavam o mesmo perfil clínico daqueles subdiagnosticados na fase inicial. Esses achados reforçam a necessidade da utilização da espirometria para o diagnóstico de DPOC e possibilitar a intervenção precoce.

Descritores: Doença pulmonar obstrutiva crônica/diagnóstico; Doença pulmonar obstrutiva crônica/epidemiologia; Espirometria.

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*Study carried out at the Federal University of São Paulo, São Paulo, Brazil.

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Introduction

The study designated *Projeto Latino-Americano de Investigação em Obstrução Pulmonar* (PLATINO, Latin-American Pulmonary Obstruction Investigation Project) is a population-based epidemiological study in which the main objective was to investigate the prevalence of COPD in five major cities in Latin America.[1]

In the city of São Paulo, Brazil, the prevalence of COPD was 15.8%.[2] Despite such high prevalence, a small proportion of subjects had actually been diagnosed with the disease. Only 12.5% of the patients with spirometry-diagnosed COPD already had an established clinical diagnosis of COPD, although a significant number of patients had well-defined symptoms of the disease.[3] The main factor related to underdiagnosis is the infrequent use of spirometry as a diagnostic tool.[4]

Misdiagnosis or undiagnosis makes it unlikely that effective interventions will occur. This becomes evident when one examines again the findings from the PLATINO study, in which 83.3% of the subjects diagnosed with COPD in the city of São Paulo were found not to receive any pharmacological treatment. In addition, 47.3% were not advised to stop smoking, and 72.4% did not receive the flu vaccine.[5]

These findings show that COPD is an underdiagnosed and undertreated disease, which can have serious consequences for patients, such as higher morbidity and mortality, and can result in substantial economic impact on the health care system. Therefore, accurate, up-to-date information on COPD underdiagnosis is important in order to assist authorities and health professionals in implementing strategies for identifying and helping subjects with COPD, regardless of their degree of disease severity.[6]

The objective of the present study was to determine the underdiagnosis rate in new COPD cases at the end of a nine-year follow-up period and compare that with the underdiagnosis rate in prevalent COPD cases during the initial phase of the PLATINO study, as well as to determine the anthropometric characteristics, clinical features, and history of exposure to COPD risk factors of the subjects who went undiagnosed until the end of the follow-up phase of the PLATINO study, conducted in the city of São Paulo, Brazil, and compare them with those of the subjects previously diagnosed with COPD.

Methods

The present study population comprised the same subjects who originally took part in the initial phase of the PLATINO study in the city of São Paulo, Brazil (n = 1,000). Of those, a total of 613 subjects participated in this follow-up phase. The present study was approved by the Research Ethics Committee of the *Universidade Federal de São Paulo* (UNIFESP, Federal University of São Paulo) *Hospital São Paulo* (Ruling no. 04234/10), and, after being informed of the study and procedures, all subjects who agreed to participate gave written informed consent.

The information on the sampling process for the initial phase of the PLATINO study has been described in a previous study.[3]

All houses in which the subjects were interviewed in the initial phase of the PLATINO study were visited. The initial contact was made by one of four screeners, who confirmed whether the subjects still lived at those addresses, checked their telephone number, and informed them of the interviewers' visit.

With regard to the subjects who did not live in the same house (as that of the initial phase of the PLATINO study) anymore, the screeners sought to determine their whereabouts through information from neighbors or through inquiries in the neighborhood businesses. The names of those whose whereabouts was unknown were looked up in the registry of deaths within the state of São Paulo and other Brazilian states. All data obtained by the screeners were sent to the coordinating body responsible for organizing the files for the subsequent scheduling of interviews.

Before performing the field evaluation, all interviewers (14 physiotherapy undergraduates and physiotherapists) attended a training course, which included administering the questionnaire and performing spirometry, taught by the São Paulo team. Once the coordinating body was assured that the interviewers were qualified to perform the evaluations, a pilot study was conducted to clarify issues that could arise during the fieldwork, thereby ending the training phase for the interviewers. Once the pilot study was completed, the scheduling of visits (which was performed by the supervisors) actually began, and the respondents were subsequently visited by two interviewers.

At the respondent's house, the researchers first required written informed consent from the subject

and, if the subject agreed to participate in the study, they proceeded to data collection, according to the following sequence: anthropometric assessment; completion of the questionnaire with exclusion criteria for participation in spirometry[1]; pre-bronchodilator spirometry; administration of a portion of the main questionnaire (in the first 15 minutes after bronchodilator administration); post-bronchodilator spirometry; administration of the remainder of the main questionnaire.

The main questionnaire administered in this follow-up phase was the same as that used in the initial phase of the PLATINO study[1] (a combined version of the American Thoracic Society-Division of Lung Disease questionnaire,[7] the European Community Respiratory Health Survey II questionnaire,[8] and the Lung Health Study questionnaire) added with new questions on smoking, diagnosis, asthma, physical activity, sleep, and depression.

The diagnosis of COPD was confirmed by spirometry, which was performed before and after bronchodilator use, in accordance with the American Thoracic Society/European Respiratory Society guidelines.[9] Spirometric measurements were taken with a portable battery-powered spirometer and an ultrasound system (EasyOne™; Medical Technologies, Chelmsparad, MA, USA and NDD Medizintechnik AG, Zurich, Switzerland), identical to those used in the initial phase of the PLATINO study. Participants performed up to 15 forced expiratory maneuvers in order to achieve quality-A level, i.e., three acceptable maneuvers yielding the highest FEV_1 and FVC values, without exceeding a difference of 150 L. Subsequently, an inhaled bronchodilator (albuterol, 200 μg) was administered, with the use of a 500-mL spacer, and, after 15 minutes, the test was repeated. All spirometric tests were performed with the subjects seated and wearing a nose clip and a disposable mouthpiece. Only the expiratory phase was recorded.

Disease severity, on the basis of pulmonary function data, was classified in accordance with the Global Initiative for Chronic Obstructive Lung Disease criteria.[10]

In order to identify diagnoses of COPD, the same three questions used in the initial phase of the PLATINO study were used: "Has your doctor ever told you that you have emphysema in the lungs?"; "Has your doctor ever told you that you have chronic bronchitis?", "Has your doctor ever told you that you have chronic obstructive pulmonary disease (COPD)?"

A case of underdiagnosis was defined as that in which the subject answered "no" to the first three questions and had a post-bronchodilator FEV_1/FVC ratio < 0.7.

The data collected during the follow-up phase of the PLATINO study were added to the original database of the initial phase of the study, which was conducted in 2003, in the city of São Paulo, Brazil. Data analysis was performed with the Statistical Package for the Social Sciences, version 17.0 (SPSS Inc., Chicago, IL, USA), and the level of statistical significance was set at $p < 0.05$.

The underdiagnosis rate in new cases at the end of the nine-year follow-up period was assessed with the chi-square test, which was also used to compare the characteristics of the subjects who went undiagnosed until the end of the follow-up phase of the PLATINO study with those of the subjects with a prior diagnosis of COPD, when variables were categorical. For numerical variables, we used the t-test for independent samples. The characteristics investigated were as follows: gender; age; level of education; nutritional status; pulmonary function; disease severity; symptoms; quality of life; exposure to COPD risk factors (burning wood/dung or charcoal; smoking; and history of respiratory infections in childhood).

For continuous variables, the results are expressed as mean and standard deviation. Categorical variables are expressed as absolute values and as percentages, representing the number of cases in each category.

Results

The data regarding the follow-up phase of the PLATINO study in the city of São Paulo, Brazil, are shown in Figure 1.

Table 1 shows the rates of underdiagnosis and prior diagnosis of COPD in new (incident) COPD cases and in all COPD cases during the follow-up phase of the PLATINO study in the city of São Paulo, Brazil. It can be seen that 70.0% of the incident COPD cases and 62.3% of all COPD cases during this follow-up phase had airflow obstruction but had no physician-diagnosed COPD.

The underdiagnosis rates found for incident COPD cases (follow-up phase of the PLATINO study) and for prevalent COPD cases (initial phase of the PLATINO study), all of which were classified

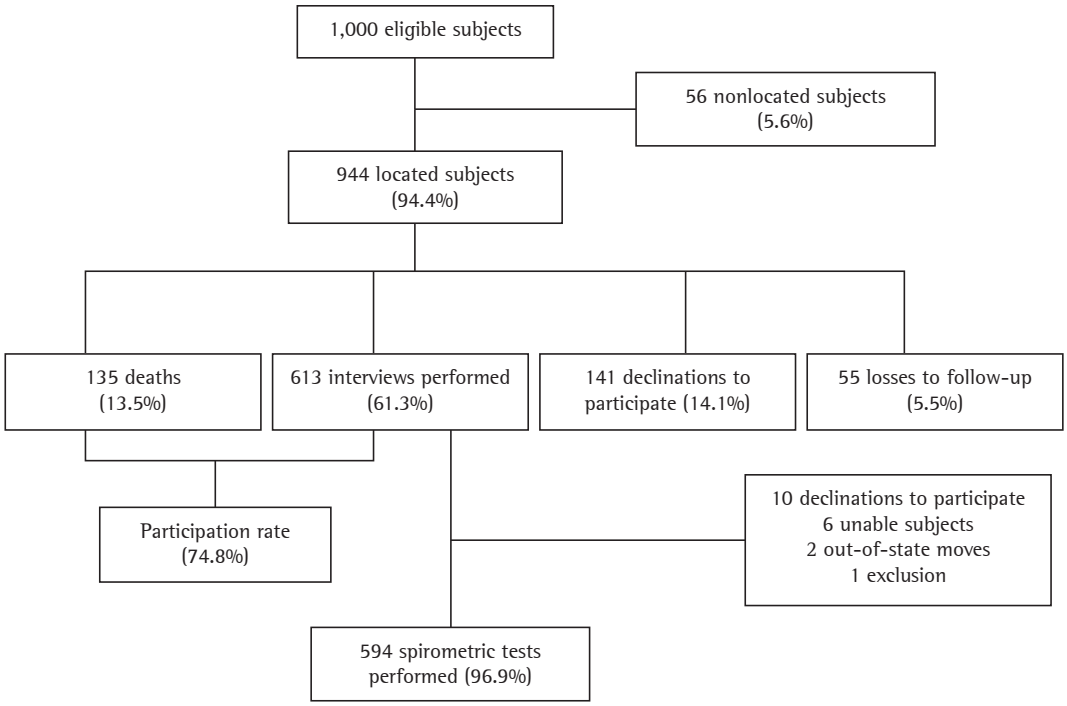

Figure 1 - Flowchart of the follow-up phase of the study designated Latin-American Pulmonary Obstruction Investigation Project in the city of São Paulo, Brazil.

Table 1 - Rates of underdiagnosis and prior diagnosis of COPD in new (incident) COPD cases and in all COPD cases during the follow-up phase of the study designated Latin-American Pulmonary Obstruction Investigation Project in the city of São Paulo, Brazil.[a]

Rate	New cases (n = 20)	All cases (n = 53)
Underdiagnosis	14 (70.0)	33(62.3)
Prior diagnosis	6 (30.0)	20 (37.7)

[a]Values expressed as n (%).

by using an FEV_1/FVC ratio < 0.7 as the diagnostic criterion, are shown in Table 2. There was a 17.5% reduction in the underdiagnosis rate, with a consequent increase in the proportion of subjects with a prior diagnosis of COPD for incident cases as compared with prevalent cases.

The characteristics of the subjects who went undiagnosed until the end of the follow-up phase of the study were also evaluated. We describe the anthropometric and clinical characteristics of the subjects who went undiagnosed and of those with a prior diagnosis of COPD during the follow-up phase of the PLATINO study (Table 3), as well as their history of exposure to COPD risk factors (Table 4). It can be seen that there were no statistically significant differences between these groups in terms of anthropometric characteristics or exposure to COPD risk factors (Tables 2 and 4); however, the subjects who went undiagnosed had better pulmonary function, less severe disease, and fewer symptoms of phlegm and wheeze, as well as a higher proportion of one or none self-reported symptom.

Discussion

The findings of the follow-up phase of the PLATINO study in the city of São Paulo, Brazil, show that approximately two thirds of the new COPD cases and of all COPD cases diagnosed until the end of the nine-year follow-up period had not received a prior diagnosis of COPD, and that these subjects have a clinical profile with fewer respiratory symptoms, better pulmonary function, and less severe disease as compared with those previously diagnosed with COPD.

It has been predicted that COPD will be the third leading cause of death in the world by 2020,[11] and, despite the significant socioeconomic impact of this disease, the underdiagnosis rates remain high. In the present study, the underdiagnosis rate was 70.0% for new COPD cases diagnosed until the end of the nine-year follow-up period and

62.3% for all of the participants in the follow-up phase of the PLATINO study. Similar rates have been reported in a study involving primary health care clinics in the city of Aparecida de Goiânia, Brazil,[12] and in cross-sectional epidemiological studies conducted in other countries, such as Spain[13] and the USA,[14]–71.4%, 78.2%, and 74.9%, respectively—which shows that underdiagnosing COPD is not a problem observed only in developing countries. This means that spirometry is underused, a finding that has also been reported in a study conducted in Spain.[15] Such a finding underscores the need for raising awareness of the importance of spirometry and for expanding its use in primary health care clinics, since spirometry is the best way to increase the detection of COPD,[16] which prevents underdiagnosis of this disease. In addition, the adoption of simple and reasonable measures for use in interpreting spirometry can assist the health professional to use it to diagnose subjects, so that they can be properly treated.

Table 2 - Rates of underdiagnosis and prior diagnosis of COPD in prevalent COPD cases during the initial phase of the study designated *Projeto Latino-Americano de Investigação em Obstrução Pulmonar* (PLATINO, Latin-American Pulmonary Obstruction Investigation Project) and in incident COPD cases during the follow-up phase of the PLATINO study, on the basis of the use of a post-bronchodilator FEV_1/FVC ratio < 0.7 as the diagnostic criterion.[a]

Rate	(Prevalent) COPD cases	New (incident) COPD cases
Underdiagnosis	126 (87.5)	14 (70.0)
Prior diagnosis	18 (12.5)	6 (30.0)

[a]Values expressed as n (%).

Table 3 - Anthropometric and clinical characteristics of the subjects who went undiagnosed and of those with a prior diagnosis of COPD during the follow-up phase of the study designated Latin-American Pulmonary Obstruction Investigation Project in the city of São Paulo, Brazil.[a]

Characteristic	Undiagnosed (n = 33)	With a prior diagnosis (n = 20)	p
Male gender	17 (53.1)	13 (65.0)	0.39
Age, years[b]	67.2 ± 10.3	67.7± 10.3	0.87
Level of education, years[b]	3.9± 4.4	4.2 ± 3.6	0.76
BMI,[b] kg/m^2	26.5 ± 6.4	26.7 ± 7.9	0.95
Pulmonary function[b]			
Post-BD FEV_1, L	1.84 ± 0.6	1.45 ± 0.7	0.04
Post-BD FEV_1, % predicted	75.7 ± 20.7	58.5 ± 20.6	0.005
Post-BD FVC, L	2.82 ± 0.83	2.46 ± 1.1	0.18
Post BD FVC, % predicted	87.0 ± 21.6	73.1 ± 20.4	0.026
Post-BD FEV_1/FVC	0.64 ± 0.05	0.58 ± 0.10	0.02
GOLD classification			
1 (mild; $FEV_1 \geq 80\%$ predicted)	12 (37.5)	4 (5.0)	0.028
2 (moderate; $50 \leq FEV_1 < 80\%$ predicted)	17 (53.1)	8 (40.0)	
3/4 (severe/very severe; $FEV_1 < 50\%$ predicted)	3 (9.4)	8 (40.0)	
Quality of life questionnaire[b]			
Physical domain	46.3 ± 10.5	40.2 ± 13.0	0.07
Mental domain	51.4 ± 11.0	48.0 ± 10.9	0.27
Presence of symptoms			
Cough	11 (33.3)	11 (55.0)	0.12
Phlegm	9 (27.3)	13 (65.0)	0.007
Wheeze	13 (39.4)	15 (75.0)	0.01
Dyspnea	17 (53.1)	14 (73.7)	0.14
Grouped symptoms			
None	7 (21.8)	1 (5.3)	0.021
1	10 (31.3)	2 (10.5)	
2	9 (28.1)	5 (26.3)	
> 2	6 (18.8)	11 (57.9)	

BMI: body mass index; post-BD: post-bronchodilator; and GOLD: Global Initiative for Chronic Obstructive Lung Disease. [a]Values expressed as n (%). [b]Values expressed as mean ± SD

Table 4 - Characteristics of the subjects who went undiagnosed and of those with a prior diagnosis of COPD during the follow-up phase of the study designated Latin-American Pulmonary Obstruction Investigation Project in the city of São Paulo, Brazil, by exposure to COPD risk factors.[a]

Characteristic	Undiagnosed (n = 33)	With a prior diagnosis (n = 20)	p
Exposure to burning wood			
Yes	24 (72.7)	15 (75.0)	0.94
No	9 (27.3)	5 (25.0)	
Exposure to burning charcoal			
Yes	8 (24.2)	5 (25.0)	0.86
No	25 (75.8)	15 (75.0)	
Exposure to dust			
Yes	22 (66.7)	17 (89.5)	0.07
No	11 (33.3)	2 (10.5)	
History of respiratory infections in childhood			
Yes	1 (3.0)	0 (0.0)	0.44
No	32 (97.0)	20 (100.0)	
Smoking			
Never smokers	11 (33.3)	6 (30.0)	0.89
Former smoker	14 (42.4)	8 (40.0)	
Smoker	8 (24.2)	6 (30.0)	

[a]Values expressed as n (%).

However, a comparison of the underdiagnosis rate in new COPD cases during the follow-up phase of the PLATINO study with the underdiagnosis rate in prevalent COPD cases during the initial phase of the PLATINO study showed that there was a 17.5% reduction (70% in incident cases vs. 87.5% in prevalent cases), with the proportion of diagnoses doubling (30.0% in incident cases vs. 12.5% in prevalent cases). It is very likely that the larger number of current diagnoses is due to the increased dissemination of information on the disease by the media, as a result of the efforts of the medical society. In addition, since we made our facility available to the subjects who had abnormal pulmonary function test results in the initial phase of the PLATINO study for consultation with a pulmonologist, this might also have contributed to the reduction in the underdiagnosis rate. However, special efforts should be made so that subjects with COPD can be diagnosed, and, therefore, the costs and impact of this disease on patients can be minimized.

The subjects who went undiagnosed until the end of the follow-up phase of the PLATINO study in the city of São Paulo, Brazil, had fewer respiratory symptoms, better pulmonary function, and less severe disease than did those previously diagnosed with COPD.

Previous epidemiological studies[5,6,17] and studies conducted in primary health care clinics[18,19] have reported these same characteristics in subjects who went undiagnosed. This shows that, even at the end of the nine-year follow-up period, the subjects who went undiagnosed had the same clinical profile, and the fact that they had few symptoms draws attention to the need for health professionals to use spirometry for diagnosis. It is of note that approximately 90% of the cases that went undiagnosed in the present study, considering the new COPD cases, had mild to moderate disease, showing that most of the subjects who went undiagnosed are in the initial stages of the disease, which makes early intervention possible.

One of the limitations of the present study is the rate of loss to follow-up, which exceeded 20%. However, a European multicenter longitudinal study over a similar follow-up period reported a participation rate of 63.3%.[20] In addition, the group consisting of losses to follow-up and declinations to participate had the same clinical and pulmonary function characteristics as those of the participants in the follow-up phase of the PLATINO study. Another limitation might be due to the fact that the diagnosis of COPD was based on the Global Initiative for Chronic Obstructive Lung Disease criterion ($FEV_1/FVC < 0.7$), because

the use of this criterion can increase the rates of false-positive results in older subjects and might not detect the disease in younger subjects (false-positive results)[21]; therefore, the use of the lower limit of normality is recommended by some authors.[22,23] It has recently been suggested that in disputed cases of airflow obstruction; i.e., cases with an FEV_1/FVC ratio < 0.7 and an $FEV_1/FVC \geq$ the lower limit of normality, subjects would not have clinically significant obstruction but would have a clinical profile characterized by important comorbidities, indicating that they could be at risk of developing COPD and should, therefore, be carefully followed.[24] However, the best criterion for the diagnosis of airflow obstruction remains in dispute in the literature,[25,26] and will continue so, since a recent longitudinal epidemiological study[27] has suggested the use of FEV_1/FEV_6 as a criterion, because FVC varies with expiratory time during forced maneuvers required for spirometry.

We conclude that the underdiagnosis rate in new COPD cases identified during the follow-up phase of the PLATINO study in the city of São Paulo, Brazil, was 70.0%. There was a 17.5% reduction in the underdiagnosis rate when we compared incident cases (follow-up phase of the PLATINO study) with prevalent cases (initial phase of the PLATINO study), and, even at the end of the nine-year follow-up period, the subjects who went undiagnosed continued to have the same clinical profile (better pulmonary function, less severe disease, and fewer symptoms).

The underdiagnosis rate of COPD identified in this population-based longitudinal epidemiological study was high, underscoring the need for raising awareness and expanding the use of spirometry in primary health care clinics.

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References

1. 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. http://dx.doi.org/10.1186/1471-2288-4-15 PMid:15202950 PMCid:PMC442126
2. Menezes AM, Jardim JR, Pérez-Padilla R, Camelier A, Rosa F, Nascimento O, Hallal PC. Prevalence of chronic obstructive pulmonary disease and associated factors: the PLATINO Study in São Paulo, Brazil. Cad Saude Publica. 2005;21(5):1565-73. http://dx.doi.org/10.1590/S0102-311X2005000500030 PMid:16158163
3. Menezes AM, Perez-Padilla R, Jardim JR, Mui-o 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. http://dx.doi.org/10.1016/S0140-6736(05)67632-5
4. Montes de Oca M, Tálamo C, Halbert RJ, Perez-Padilla R, Lopez MV, Mui-o A, et al. Health status perception and airflow obstruction in five Latin American cities: the PLATINO study. Respir Med. 2009;103(9):1376-82. http://dx.doi.org/10.1016/j.rmed.2009.03.005 PMid:19364640
5. Nascimento OA, Camelier A, Rosa FW, Menezes AM, Pérez-Padilla R, Jardim JR, et al. Chronic obstructive pulmonary disease is underdiagnosed and undertreated in São Paulo (Brazil): results of the PLATINO study. Braz J Med Biol Res. 2007;40(7):887-95. http://dx.doi.org/10.1590/S0100-879X2006005000133 PMid:17653440
6. Tálamo C, de Oca MM, Halbert R, Perez-Padilla R, Jardim JR, Mui-o A, et al. Diagnostic labeling of COPD in five Latin American cities. Chest. 2007;131(1):60-7. http://dx.doi.org/10.1378/chest.06-1149 PMid:17218557
7. Ferris BG. Epidemiology Standardization Project (American Thoracic Society). Am Rev Respir Dis. 1978;118(6 Pt 2):1-120. PMid:742764
8. European Community Respiratory Health Survey II Steering Committee. The European Community Respiratory Health Survey II. Eur Respir J. 2002;20(5):1071-9. http://dx.doi.org/10.1183/09031936.02.00046802 PMid:12449157
9. 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. http://dx.doi.org/10.1183/09031936.05.00034805 PMid:16055882
10. Global Initiative for Chronic Obstructive Lung Disease [homepage on the Internet]. Bethesda: Global Initiative for Chronic Obstructive Lung Disease. [cited 2013 Aug 20]. Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease. Updated 2013. [Adobe Acrobat document, 99p.]. Available from: http://www.goldcopd.org/uploads/users/files/GOLD_Report_2013_Feb20.pdf
11. Murray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990-2020: Global Burden of Disease Study. Lancet. 1997;349(9064):1498-504. http://dx.doi.org/10.1016/S0140-6736(96)07492-2
12. Queiroz MC, Moreira MA, Rabahi MF. Underdiagnosis of COPD at primary health care clinics in the city of Aparecida de Goiânia, Brazil. J Bras Pneumol. 2012;38(6):692-9. http://dx.doi.org/10.1590/S1806-37132012000600003 PMid:23288113
13. Pe-a VS, Miravitlles M, Gabriel R, Jiménez-Ruiz CA, Villasante C, Masa JF, et al. Geographic variations in prevalence and underdiagnosis of COPD: results of the IBERPOC multicentre epidemiological study. Chest. 2000;118(4):981-9. http://dx.doi.org/10.1378/chest.118.4.981
14. Coultas DB, Mapel D, Gagnon R, Lydick E. The health impact of undiagnosed airflow obstruction in a national sample of United States adults. Am J Respir Crit Care Med. 2001;164(3):372-7. http://dx.doi.org/10.1164/ajrccm.164.3.2004029 PMid:11500335
15. Miravitlles M, de la Roza C, Morera J, Montemayor T, Gobartt E, Martín A, et al. Chronic respiratory symptoms,

spirometry and knowledge of COPD among general population. Respir Med. 2006;100(11):1973-80. http://dx.doi.org/10.1016/j.rmed.2006.02.024 PMid:16626950
16. Mannino DM. Defining chronic obstructive pulmonary disease... and the elephant in the room. Eur Respir J. 2007;30(2):189-90. http://dx.doi.org/10.1183/09031936.00058707 PMid:17666553
17. Schirnhofer L, Lamprecht B, Firlei N, Kaiser B, Buist AS, Halbert RJ, et al. Using targeted spirometry to reduce non-diagnosed chronic obstructive pulmonary disease. Respiration. 2011;81(6):476-82. http://dx.doi.org/10.1159/000320251 PMid:20720402
18. Minas M, Hatzoglou C, Karetsi E, Papaioannou AI, Tanou K, Tsaroucha R, et al. COPD prevalence and the differences between newly and previously diagnosed COPD patients in a spirometry program. Prim Care Respir J. 2010;19(4):363-70. http://dx.doi.org/10.4104/pcrj.2010.00034 PMid:20532466
19. Hill K, Goldstein RS, Guyatt GH, Blouin M, Tan WC, Davis LL, et al. Prevalence and underdiagnosis of chronic obstructive pulmonary disease among patients at risk in primary care. CMAJ. 2010;182(7):673-8. http://dx.doi.org/10.1503/cmaj.091784 PMid:20371646 PMCid:PMC2855915
20. de Marco R, Accordini S, Marcon A, Cerveri I, Antó JM, Gislason T, et al. Risk factors for chronic obstructive pulmonary disease in a European cohort of young adults. Am J Respir Crit Care Med. 2011;183(7):891-7. http://dx.doi.org/10.1164/rccm.201007-1125OC PMid:20935112
21. Celli BR, Halbert RJ, Isonaka S, Schau B. Population impact of different definitions of airway obstruction. Eur Respir J. 2003;22(2):268-73. http://dx.doi.org/10.1183/09031936.03.00075102 PMid:12952259
22. Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, et al. Interpretative strategies for lung function tests. Eur Respir J. 2005;26(5):948-68. http://dx.doi.org/10.1183/09031936.05.00035205 PMid:16264058
23. Lung function testing: selection of reference values and interpretative strategies. American Thoracic Society. Am Rev Respir Dis. 1991;144(5):1202-18. http://dx.doi.org/10.1164/ajrccm/144.5.1202 PMid:1952453
24. Lamprecht B, Schirnhofer L, Kaiser B, Buist SA, Mannino DM, Studnicka M. Subjects with Discordant Airways Obstruction: Lost between Spirometric Definitions of COPD. Pulm Med. 2011;2011:780215. doi: 10.1155/2011/780215
25. Celli BR, Halbert RJ. Point: should we abandon FEV_1/FVC <0.70 to detect airway obstruction? No. Chest. 2010;138(5):1037-40. http://dx.doi.org/10.1378/chest.10-2049 PMid:21051393
26. Enright P, Brusasco V. Counterpoint: should we abandon FEV_1/FVC < 0.70 to detect airway obstruction? Yes. Chest. 2010;138(5):1040-2; discussion 1042-4. http://dx.doi.org/10.1378/chest.10-2052 PMid:21051394
27. Perez-Padilla R, Wehrmeister FC, Celli BR, Lopez-Varela MV, Montes de Oca M, Mui-o A, et al. Reliability of FEV1/FEV6 to diagnose airflow obstruction compared with FEV1/FVC: the PLATINO longitudinal study. PLoS One. 2013;8(8):e67960. http://dx.doi.org/10.1371/journal.pone.0067960 PMid:23936297 PMCid:PMC3731337

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Incidence of pulmonary embolism during COPD exacerbation*,**

Incidência de embolia pulmonar durante exacerbação da DPOC

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Abstract

Objective: Because pulmonary embolism (PE) and COPD exacerbation have similar presentations and symptoms, PE can be overlooked in COPD patients. Our objective was to determine the prevalence of PE during COPD exacerbation and to describe the clinical aspects in COPD patients diagnosed with PE. **Methods:** This was a prospective study conducted at a university hospital in the city of Ankara, Turkey. We included all COPD patients who were hospitalized due to acute exacerbation of COPD between May of 2011 and May of 2013. All patients underwent clinical risk assessment, arterial blood gas analysis, chest CT angiography, and Doppler ultrasonography of the lower extremities. In addition, we measured D-dimer levels and N-terminal pro-brain natriuretic peptide (NT-pro-BNP) levels. **Results:** We included 172 patients with COPD. The prevalence of PE was 29.1%. The patients with pleuritic chest pain, lower limb asymmetry, and high NT-pro-BNP levels were more likely to develop PE, as were those who were obese or immobile. Obesity and lower limb asymmetry were independent predictors of PE during COPD exacerbation (OR = 4.97; 95% CI, 1.775-13.931 and OR = 2.329; 95% CI, 1.127-7.105, respectively). **Conclusions:** The prevalence of PE in patients with COPD exacerbation was higher than expected. The association between PE and COPD exacerbation should be considered, especially in patients who are immobile or obese.

Keywords: Pulmonary disease, chronic obstructive; Pulmonary embolism; Risk factors.

Resumo

Objetivo: Visto que a embolia pulmonar (EP) e a exacerbação da DPOC têm apresentação e sintomas comuns, o diagnóstico de EP pode ser negligenciado nesses pacientes. Nosso objetivo foi determinar a prevalência de EP durante a exacerbação da DPOC e descrever os aspectos clínicos em portadores de DPOC diagnosticados com EP. **Métodos:** Estudo prospectivo conduzido em um hospital universitário na cidade de Ancara, Turquia. Entre maio de 2011 e maio de 2013, todos os pacientes hospitalizados por exacerbação aguda da DPOC foram incluídos no estudo. Todos os pacientes foram submetidos a avaliação de risco clínico, gasometria arterial, angiotomografia de tórax e ultrassonografia Doppler de membros inferiores. Além disso, foram medidos os níveis de dímero-D e de *N-terminal pro-brain natriuretic peptide* (NT-pro-BNP). **Resultados:** Foram incluídos 172 pacientes com DPOC. A prevalência de EP foi de 29,1 %. Os pacientes com DPOC e dor torácica pleurítica, assimetria de membros inferiores e altos níveis de NT-pro-BNP, assim como aqueles que estavam obesos ou imobilizados, apresentavam maior probabilidade de desenvolver EP. Obesidade e assimetria de membros inferiores foram preditores independentes de EP nos pacientes com exacerbação da DPOC (OR = 4,97; IC95%, 1,775-13,931 e OR = 2,329; IC95% CI, 1,127-7,105, respectivamente). **Conclusões:** A prevalência de EP em pacientes com exacerbação da DPOC foi maior que a esperada. A associação entre EP e exacerbação da DPOC deve ser considerada nesses pacientes, especialmente naqueles imobilizados ou obesos.

Descritores: Doença pulmonar obstrutiva crônica; Embolia pulmonar; Fatores de risco.

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Introduction

Not only is COPD a significant cause of morbidity worldwide, but it is also the fourth-leading cause of mortality today and is estimated to be the third-leading cause of death by 2020. Exacerbations of COPD are the episodic periods of the disease, characterized by deterioration of respiratory function. Most deaths caused by COPD appear to occur during exacerbations. Respiratory infections are responsible for 50-70% of COPD exacerbations, and environmental pollution causes another 10%. Nearly 30% of all COPD exacerbations have unknown etiology.[1,2] Although a meta-analysis found that the prevalence of pulmonary embolism (PE) was 20% among patients who were in a period of exacerbation of COPD,[3] that prevalence was found to be 13.7% in a recent study.[4] The prevalence of PE in post-mortem studies ranges from 28% to 51%.[5,6]

The presentation of common symptoms of COPD exacerbations, such as dyspnea and cough, might cause the diagnosis of acute PE to be overlooked. Patients with COPD are at risk of developing PE due to various reasons, such as immobility, systemic inflammation, and polycythemia. In addition, COPD has been recently defined as an independent risk factor for PE.[7] Mortality and delay in diagnosis of PE are higher in patients with COPD.[8] The prevalence of PE in a highly specific group of patients who were hospitalized for severe exacerbation with unknown origin was reported to be 25%.[9] Gunen et al. reported that venous thromboembolism (VTE) was three times more prevalent in patients with an exacerbation of unknown origin than in patients with an exacerbation of known origin.[4] The exact prevalence of PE in patients who are in a period of an acute exacerbation of COPD and the clinical features of those patients are as yet unclear. The objective of the present study was to determine the prevalence of PE in patients during COPD exacerbation and to describe the clinical aspects in those patients diagnosed with PE.

Methods

This was a prospective study conducted in a university hospital in the city of Ankara, Turkey. All COPD patients who were hospitalized due to acute exacerbation of COPD between May of 2011 and May of 2013 were included in the study. The study protocol was approved by the Research Ethics Committee of Ufuk University, located in Ankara, Turkey. All participating patients gave written informed consent. Exclusion criteria were having a history of hypersensitivity after the injection of contrast material; having chronic renal disease, pneumonia, or congestive heart failure; having been under anticoagulant treatment; and being unable to give written informed consent because of confusion or dementia. Patients with an inconclusive diagnosis of COPD were also excluded. As a result, a total of 172 patients were included in the study. Figure 1 shows the design of the study.

The diagnosis of COPD was confirmed by medical history and previous medical records (chest X-rays and pulmonary function testing). The severity of COPD was determined by using the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria. Acute exacerbation was diagnosed when the patient with COPD had a worsening in respiratory symptoms beyond the normal day-to-day variations that led to a change in medication.[10]

Detailed clinical evaluations were performed for all participants by medical history, physical examination, and chest X-rays. Blood samples were taken immediately for the evaluation of D-dimer, blood workup, arterial blood gas analysis, and N-terminal pro-brain natriuretic peptide (NT-pro-BNP) levels. D-dimer levels were measured with the Tina-quant® D-dimer assay system (Boehringer, Mannheim, Germany), which is a particle-enhanced immunoturbidimetric assay. We used Roche Elecsys ProBNP assay (Roche Diagnostics, Mannheim, Germany) in order to determine NT-pro-BNP levels.

Risk factors for developing VTE, such as surgery, malignancy, immobility (bed rest > 48 h), and previous VTE, were noted while recording the history of the patient. We used the simplified version of the revised Geneva score,[11] Well's score,[12] and the clinical classification proposed by Miniati et al.[13] in all patients who were included in the study.

Chest CT angiography (CTA) was performed with a 16-section multidetector CT scanner (GE Light Speed 16; GE Healthcare, Milwaukee, Wisconsin, USA) within 24 h of admission. The patients were injected 100 mL of non-ionic contrast media (Iohexol Omnipaque 300/100; GE Healthcare, Milwaukee, WI, USA) via an 18G

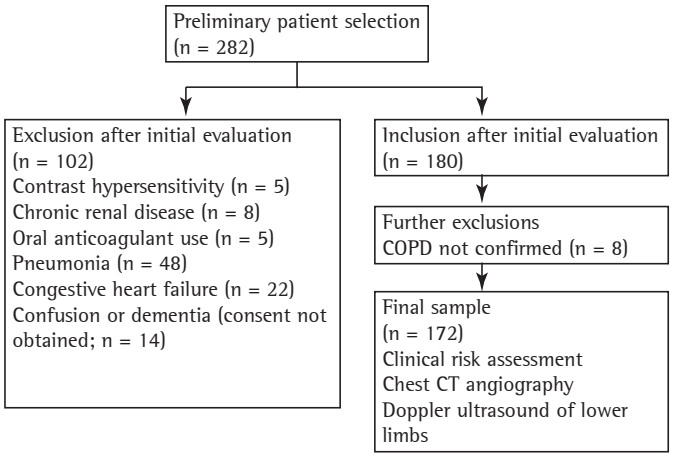

Figure 1 - Study design.

needle into the antecubital vein at a rate of 4 mL/s using a power injector (Medrad Stellant Dual; Medrad, Indianola, PA, USA). Chest CTA was carried out using a dedicated workstation (Advanced Workstation 4.0; GE Healthcare). The diagnosis of PE was reached when an intraluminal filling defect surrounded by intravascular contrast or total occlusion of the pulmonary arterial lumen was detected at any level of the pulmonary arteries. The localization of the thrombi was noted.

Doppler ultrasonography of the deep veins of the lower extremities was performed by an experienced radiologist who was blinded about the angiographic results. A standard method was used with a dedicated ultrasound unit (Logiq 7®; GE Healthcare) and a 10L linear array transducer (bandwidth, 6-10 MHz) in order to investigate the presence/absence of intravenous thrombi.

Arterial blood gas analyses were performed with a GEM Premier™ 3000 blood gas/electrolyte analyzer (model 570; Instrumentation Laboratory, Lexington, MA, USA). Interpretation of the results was as follows: acidosis, pH < 7.35; alkalosis, pH > 7.45; hypercapnia, $PaCO_2$ > 45 mmHg; hypocapnia, $PaCO_2$ < 35 mmHg; and hypoxemia, PaO_2 < 80 mmHg. Hypoxemia was further graded as mild (60-80 mmHg); moderate (40-59 mmHg); or severe (< 40 mmHg).[14]

Patients were considered obese with a body mass index (BMI) ≥ 30 kg/m²,[15] whereas a diagnosis of cachexia was given to male patients with a BMI < 16 kg/m² and to female patients with a BMI < 15 kg/m².[16]

A diagnosis of hypertension was confirmed when blood pressure was ≥ 140/90 mmHg on three separate occasions after hospital admission.[17] A diagnosis of diabetes mellitus was based on the American Diabetes Association criteria.[18] The participants on antihypertensive or antidiabetic treatment were considered to have hypertension or diabetes mellitus. A diagnosis of coronary artery disease was based on previous medical records (echocardiogram and CTA) of the patients. Anemia was diagnosed based on hemoglobin levels (≤ 13.5 g/dL in males ≥ 18 years of age and ≤ 12.0 g/dL in females ≥ 18 years of age).[19]

The data was analyzed using the Statistical Package for the Social Sciences 11.5 pocket program (SPSS Inc., Chicago, IL, USA). Categorical variables were expressed as absolute and relative frequencies, whereas continuous variables were expressed as means, standard deviations, medians, minimum values, and maximum values. The chi-square test was used in order to compare two independent groups of categorical variables. The Mann-Whitney U test was used in order to compare two independent groups of continuous variables. Statistical significance was set at a value of $p < 0.05$. Variables with $p < 0.1$ in the univariate analysis were evaluated by multiple logistic regression analysis in order to define independent risk factors of outcome variables.

Results

A total of 172 patients were enrolled in the study. The mean age was 71.31 ± 9.62 years; 142 patients (82.6%) were male, and 30 patients (17.4%) were female. The distribution of patients according to GOLD stages (GOLD I-IV) were

as follows: 7.0%, 37.2%, 28.5%, and 27.3%, respectively. Most of the patients (73.8%) had comorbidities accompanying COPD. Demographic properties and basic clinical characteristics of the COPD patients who were included in the study are shown in Table 1.

The prevalence of PE was 29.1%, and all of the patients who had PE based on CTA results also had deep vein thrombosis. The prevalence of PE did not differ between GOLD stages ($p > 0.05$). The localization of thrombi in patients who had PE and the results of the Doppler ultrasonography are shown in Table 2.

The ratios of low probability according to the revised Geneva score,[11] Well's score,[12] and the clinical classification by Miniati et al.[13] in patients who had a confirmed diagnosis of PE was 18%, 24%, and 44%, respectively. The clinical probabilities of the patients who were diagnosed with PE (positive results on CTA) according to the three abovementioned scores are shown in Table 3.

There was no statistically significant difference between the groups of patients with PE and without PE in terms of age, gender distribution, and presence/number of accompanying comorbidities ($p > 0.05$ for all). The prevalence of obesity was significantly higher among the patients with PE ($p = 0.033$). The prevalence of other comorbidities (cachexia, hypertension, diabetes mellitus, coronary artery disease, and anemia) was not different between the groups with or without PE ($p > 0.05$). However, the prevalence of immobility was significantly higher among those with PE ($p = 0.024$). Risk factors for VTE (trauma, malignancy, surgery, congestive heart failure, or previous history of VTE) did not significantly differ between the two groups ($p > 0.05$). In addition, the presence of symptoms, such as cough, sputum, hemoptysis, dyspnea, tachycardia, fever, etc., did not significantly differ between the two groups ($p > 0.05$). Pleuritic chest pain and lower limb asymmetry were significantly more prevalent among those diagnosed with PE ($p = 0.038$, and $p = 0.002$, respectively).

Levels of D-dimers and NT-pro-BNP were significantly higher among the patients with PE than among those without ($p < 0.001$ vs. $p = 0.006$). Arterial blood gas analyses revealed that the patients with PE had higher pH values and

Table 1 - Demographic properties and general clinical characteristics of the study population.[a]

Variable	Result
Age, years[b]	71.31 ± 9.62
Gender	
Male	142 (82.6)
Female	30 (17.4)
FEV_1, mL[b]	1,502.82 ± 359.86
FEV_1, % of predicted[b]	55.8 ± 19.4
mMRC[b]	1.39 ± 1.02
Exacerbations/year[b]	1.26 ± 0.71
GOLD stage	
I	12 (7.0)
II	64 (37.2)
III	49 (28.5)
IV	47 (27.3)
Comorbidities	
Obesity	24 (13.9)
Cachexia	6 (3.5)
Hypertension	35 (20.3)
Diabetes mellitus	26 (15.1)
Coronary artery disease	30 (17.4)
Anemia	17 (9.9)

mMRC: modified Medical Research Council scale; and GOLD: Global Initiative for Chronic Obstructive Lung Disease. [a]Values expressed as n (%), except where otherwise indicated. [b]Values expressed as mean ± SD.

Table 2 - Localization of the thrombi on chest CT angiography and Doppler ultrasonography of the lower limbs in the 172 patients studied.[a]

Localization	Patients
Chest CT angiography[b]	
Main pulmonary artery	10 (5.8)
Segmental	8 (4.7)
Subsegmental	32 (18.6)
Unilateral	45 (26.2)
Bilateral	5 (2.9)
Doppler ultrasonography[b]	
Proximal deep vein	10 (5.8)
Distal deep vein	18 (10.5)
Distal superficial vein	22 (12.8)

[a]Values expressed as n (%). [b]Thrombi detected in 50 patients (29.1%).

Table 3 - Clinical probabilities of the 50 patients diagnosed with pulmonary embolism according to the scoring systems used in the study.[a]

Scoring system	Probability		
	Low	Moderate	High
Revised Geneva[11]	9 (18)	32 (64)	9 (18)
Well's[12]	12 (24)	34 (68)	4 (8)
Miniati et al.[13]	22 (44)	6 (12)	22 (44)

[a]Values expressed as n (%).

lower $PaCO_2$ levels than did those without ($p < 0.01$ and $p < 0.05$, respectively). The length of hospitalization was longer in the patients with PE than in those without ($p = 0.001$). However, the three-month mortality rate and the need for intensive care did not differ between the groups ($p > 0.05$). The clinical and laboratory findings in the patients with and without PE are compared in Table 4.

Multiple logistic regression analysis revealed that obesity and lower limb asymmetry were the independent variables that predicted the presence of PE in the patients with COPD (OR = 4.97; 95% CI, 1.775-13.931 and OR = 2.329; 95% CI, 1.127-7.105, respectively).

Discussion

The present study showed that PE was present in 29.1% of the patients who were hospitalized due to an exacerbation of COPD. Patients with pleuritic chest pain, lower limb asymmetry, and high NT-pro-BNP levels were more likely to develop PE, as were those who were obese or immobile. Obesity and lower limb asymmetry were independent predictors of PE in the patients with COPD exacerbation.

Most deaths caused by COPD occur during the periods of exacerbation. The course of the disease can be worsened by PE. Because clinical features of PE are nonspecific (e.g., dyspnea and pleuritic chest pain), it might be underdiagnosed in patients with COPD during periods of exacerbation. Visual confirmation of the clot with an imaging technique is required in order to warrant anticoagulation therapy in appropriate dose and duration. The prevalence of PE in COPD exacerbations is not precisely known, but a recent meta-analysis reported that the prevalence of PE in COPD exacerbation with an unknown cause was 20%. The prevalence was higher (24.7%) in four studies that included hospitalized COPD patients.[3] However, Tillie-Leblond et al. found the prevalence of PE to be 25% in COPD patients with severe exacerbation of

Table 4 - Clinical and laboratory characteristics of the patients with and without pulmonary embolism.[a]

Characteristic	Pulmonary embolism		p
	Yes	No	
Age, years[b]	72.08 ± 10.89	71.00 ± 9.08	> 0.05
Gender			
Male	38 (76.0)	104 (85.2)	> 0.05
Female	12 (24.0)	18 (14.8)	
Comorbidities			
Cachexia	11 (22.0)	12 (9.8)	> 0.05
Obesity	5 (4.1)	1 (2.0)	0.033
Hypertension	18 (36.0)	42 (34.4)	> 0.05
Diabetes mellitus	13 (26.0)	21 (17.2)	> 0.05
Coronary artery disease	20 (40.0)	46 (37.7)	> 0.05
Anemia	8 (16.0)	19 (15.6)	> 0.05
D-dimer, µg/mL[b]	2.38 ± 2.80	1.06 ± 1.51	< 0.001
Hematocrit, %[b]	40.20 ± 6.77	41.70 ± 6.15	> 0.05
Pleuritic chest pain	12 (24.0)	14 (11.5)	0.038
Lower limb asymmetry	11 (22.0)	7 (5.7)	0.002
Hemoptysis	1 (2.0)	1 (0.8)	> 0.05
NT-pro-BNP, pg/L[b]	1,664 ± 3,247	1,188 ± 3,233	0.006
Arterial blood gas[b]			
pH	7.470 ± 0.072	7.400 ± 0.039	< 0.01
$PaCO_2$, mmHg	34.0 ± 20.0	37.5 ± 10.1	< 0.05
PaO_2, mmHg	57.0 ± 14.9	60.0 ± 13.3	> 0.05
Length of hospital stay, days	11.42 ± 5.69	8.89 ± 4.05	0.001
ICU need	5 (10.0)	5 (4.1)	> 0.05
Three-month mortality rate, %	12.0	6.6	> 0.05

NT-pro-BNP: N-terminal pro-brain natriuretic peptide. [a]Values expressed as n (%), except where otherwise indicated. [b]Values expressed as mean ± SD.

unknown origin.[9] In our study, we also evaluated the prevalence of PE among hospitalized patients with COPD exacerbation, and it was even higher (29.1%).

Gunen et al. found the prevalence of PE among patients who were hospitalized due to COPD exacerbation to be 13.7%,[4] which was lower than that in our study. They found that being female, having chest pain, having hypotension, and having syncope to be predictors of PE in patients with COPD exacerbation. Our study did not reveal a significant relationship between the genders. Similarly, we found positive relationships of pleuritic chest pain and lower limb asymmetry with the occurrence of PE. Gunen et al. found that none of the patients with low-risk determination and 20.7% of those with moderate-risk determination had PE. In contrast, our study showed that, among the patients with PE, 24% had a low clinical probability, and 68% had a moderate clinical probability according to the Well's score. Fernández et al. reported that patients with PE and COPD had a lower pre-test probability for PE than the patients with PE but without COPD.[8] In the present study, a low probability according to all three scoring systems (revised Geneva, Well's and Miniati et al.)[11-13] could not rule out PE in the patients with COPD exacerbation. These results showed that the clinical risk assessment of patients with COPD exacerbation for PE can mislead clinicians. The presence of common symptoms in COPD exacerbation and PE might be the reason that causes a high incidence of low-risk probability in these patients. COPD has been recently defined as an independent risk factor for PE.[7] Further studies are necessary to evaluate the inclusion of COPD to the criteria for the clinical risk assessment for PE in order to overcome this problem.

The variation in the prevalence of PE is thought to be the result of differences in study populations and study design. The prevalence of PE in COPD patients who were admitted to the emergency department was reported to be 3.3% in a study.[20] The low prevalence in that study might result from the evaluation of patients admitted to the emergency department. Additionally, the authors did not further evaluate the COPD patients who did not have a clinical suspicion of PE and had low D-dimer levels (< 0.5 μg/mL). We evaluated all hospitalized patients with COPD exacerbation using imaging methods without considering their clinical probabilities for PE and D-dimer levels. In a recent study by Choi et al., the prevalence of PE among hospitalized patients with COPD exacerbation was distinctly lower than that in our study (5% vs. 29.1%), despite the similarities in the selected population and the design of the two studies.[21] In contrast to their study, however, the location of PE in most of our patients was peripheral. In both studies, NT-pro-BNP levels were significantly higher in COPD patients with PE. Although the length of hospital stay was longer in the COPD patients with PE in our study, that study did not reveal a difference between the two groups in terms of length of hospital stay.

In contrast to the study by Gunen et al., which reported no difference in $PaCO_2$ levels in COPD patients with or without PE,[4] the present study showed that respiratory alkalosis and hypocapnia were more common in patients with COPD exacerbation accompanying PE. Tillie-Leblond et al. found lower $PaCO_2$ levels in patients with COPD exacerbation and PE.[9] Similarly, previous reports showed that a decrease in $PaCO_2$ during COPD exacerbation might indicate PE.[22,23]

It is known that BNP is released from the heart into the circulation. Levels of BNP increase in patients with congestive heart failure and acute myocardial infarction; BNP is also a marker of right ventricular dysfunction in acute PE[24] and correlates with pulmonary arterial pressure.[25] Gunen et al. showed that indicators of acute right heart failure on echocardiogram were more prevalent in COPD patients with PE.[4] In our study, we excluded the patients with congestive heart failure on their initial evaluation. NT-pro-BNP levels were significantly higher in COPD patients with PE than in those without PE. Echocardiograms require expertise and cannot be performed at all medical centers. However, NT-pro-BNP measurements might be more accessible for the evaluation of right heart failure and pulmonary arterial pressure in COPD patients without congestive heart failure who are being investigated for PE.

A few symptoms are closely related to the localization of the thrombus in patients with PE. Hypotension and syncope were more common symptoms in the study by Gunen et al., which can be explained based on the location of the thrombi (half of the patients with PE had a centrally located thrombus).[4] In the present study, the thrombi in patients with COPD exacerbation and

PE were most commonly peripheral (segmental and subsegmental) in 80% of the patients, and pleuritic chest pain was the most common symptom. In our study population, the peripheral location of most of the thrombi might be the reason of the similar mortality rates in the COPD patients with and without PE. However, it is important to detect and properly treat a peripherally located thrombus in order to prevent recurrence, which might cause death.

Our study had some limitations. Although this was the largest study to evaluate the prevalence and the characteristics of patients with COPD exacerbation associated with PE, it was a single center study. In addition, the present study only investigated the prevalence of PE and the clinical conditions in which PE was suspected in the patients with COPD exacerbation.

In conclusion, the prevalence of PE in the patients with COPD exacerbation was higher than expected in our study. Exacerbation of COPD and PE can be associated. Because of that, PE should be considered in patients with COPD exacerbation, especially in those who are immobile, have pleuritic chest pain, and present high D-dimer, NT-pro-BNP, and pH levels, as well as presenting low $PaCO_2$ levels. Obesity and lower limb asymmetry were independent predictors of the presence of PE in our patients. Larger studies are necessary in order to evaluate the prevalence of PE in patients with COPD exacerbation in a more precise fashion and to provide understanding about the factors and mechanisms that influence the development of PE in this population.

References

1. Sapey E, Stockley RA. COPD exacerbations . 2: Aetiology. Thorax. 2006;61(3):250-8. http://dx.doi.org/10.1136/thx.2005.041822
2. Seneff MG, Wagner DP, Wagner RP, Zimmerman JE, Knaus WA. Hospital and 1-year survival of patients admitted to intensive care units with acute exacerbation of chronic obstructive pulmonary disease. JAMA. 1995;274(23):1852-7. http://dx.doi.org/10.1001/jama.1995.03530230038027
3. Rizkallah J, Man SF, Sin DD. Prevalence of pulmonary embolism in acute exacerbations of COPD: A systematic review and metanalysis. Chest. 2009;135(3):786-93. http://dx.doi.org/10.1378/chest.08-1516
4. Gunen H, Gulbas G, In E, Yetkin O, Hacievliyagil SS. Venous thromboemboli and exacerbations of COPD. Eur Respir J. 2010;35(6):1243-8. http://dx.doi.org/10.1183/09031936.00120909
5. Baum GL, Fisher FD. The relationship of fatal pulmonary insufficiency with cor pulmonale, rightsided mural thrombi and pulmonary emboli: a preliminary report. Am J Med Sci. 1960;240:609-12.
6. Mitchell RS, Silvers GW, Dart GA, Petty TL, Vincent TN, Ryan SF, et al. Clinical and morphologic correlations in chronic airway obstruction. Aspen Emphysema Conf. 1968;9:109-23.
7. Poulsen SH, Noer I, Møller JE, Knudsen TE, Frandsen JL. Clinical outcome of patients with suspected pulmonary embolism. A follow-up study of 588 consecutive patients. J Intern Med. 2001;250(2):137-43. http://dx.doi.org/10.1046/j.1365-2796.2001.00866.x
8. Fernández C, Jiménez D, De Miguel J, Martí D, Díaz G, Sueiro A. Chronic obstructive pulmonary disease in patients with acute symptomatic pulmonary embolism [Article in Spanish]. Arch Bronconeumol. 2009;45(6):286-90. http://dx.doi.org/10.1016/j.arbres.2008.10.008
9. Tillie-Leblond I, Marquette CH, Perez T, Scherpereel A, Zanetti C, Tonnel AB, et al. Pulmonary embolism in patients with unexplained exacerbation of chronic obstructive pulmonary disease: prevalence and risk factors. Ann Intern Med. 2006;144(6):390-6. http://dx.doi.org/10.7326/0003-4819-144-6-200603210-00005
10. Global Initiative for Chronic Obstructive Lung Disease - GOLD [homepage on the Internet]. Bethesda: Global Initiative for Chronic Obstructive Lung Disease [cited 2013 Aug 26]. Global Strategy for the Diagnosis, Management, and Prevention of COPD - Revised 2011. [Adobe Acrobat document, 90p.]. Available from: http://www.goldcopd.org/.
11. Klok FA, Mos IC, Nijkeuter M, Righini M, Perrier A, Le Gal G, et al. Simplification of the revised Geneva score for assessing clinical probability of pulmonary embolism. Arch Intern Med. 2008;168(19):2131-6. http://dx.doi.org/10.1001/archinte.168.19.2131
12. Wells PS, Owen C, Doucette S, Ferguson D, Tran H. Does this patient have deep vein thrombosis? JAMA. 2006;295(2):199-207. http://dx.doi.org/10.1001/jama.295.2.199
13. Miniati M, Prediletto R, Formichi B, Marini C, Di Ricco G, Tonelli L, et al. Accuracy of clinical assessment in the diagnosis of pulmonary embolism. Am J Respir Crit Care Med. 1999;159(3):864-71. http://dx.doi.org/10.1164/ajrccm.159.3.9806130
14. Rose BD, TW Post. Clinical physiology of acid-base and electrolyte disorders. 5th ed. New York: McGraw Hill; 2001.
15. NHLBI Obesity Education Initiative Expert Panel on the Identification, Evaluation, and Treatment of Obesity in Adults. Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults: The Evidence Report. Bethesda: National Heart, Lung, and Blood Institute; 1998.
16. Schols AM, Broekhuizen R, Weling-Scheepers CA, Wouters EF. Body composition and mortality in chronic obstructive pulmonary disease. Am J Clin Nutr. 2005;82(1):53-9.
17. Carretero OA, Oparil S. Essential hypertension. Part I: definition and etiology. Circulation. 2000; 101(3):329-35. http://dx.doi.org/10.1161/01.CIR.101.3.329
18. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2010;33 Suppl 1:S62-9. http://dx.doi.org/10.2337/dc10-S062
19. White CT, Barrett BJ, Madore F, Moist LM, Klarenbach SW, Foley RN, et al. Clinical practice guidelines for evaluation of anemia. Kidney Int Suppl. 2008;(110):S4-6. http://dx.doi.org/10.1038/ki.2008.268

20. Rutschmann OT, Cornuz J, Poletti PA, Bridevaux PO, Hugli OW, Qanadli SD, et al. Should pulmonary embolism be suspected in exacerbation of chronic obstructive pulmonary disease? Thorax. 2007;62(2):121-5. http://dx.doi.org/10.1136/thx.2006.065557
21. Choi KJ, Cha SI, Shin KM, Lee J, Hwangbo Y, Yoo SS, et al. Prevalence and predictors of pulmonary embolism in Korean patients with exacerbation of chronic obstructive pulmonary disease. Respiration. 2013;85(3):203-9. http://dx.doi.org/10.1159/000335904
22. Lippmann M, Fein A. Pulmonary embolism in the patient with chronic obstructive pulmonary disease. A diagnostic dilemma. Chest. 1981;79(1):39-42. http://dx.doi.org/10.1378/chest.79.1.39
23. Rodger MA, Jones G, Rasuli P, Raymond F, Djunaedi H, Bredeson CN, et al. Steady-state end-tidal alveolar dead space fraction and D-dimer: bedside tests to exclude pulmonary embolism. Chest. 2001;120(1):115-9. http://dx.doi.org/10.1378/chest.120.1.115
24. Klok FA, Mos IC, Huisman MV. Brain-type natriuretic peptide levels in the prediction of adverse outcome in patients with pulmonary embolism: a systematic review and meta-analysis. Am J Respir Crit Care Med. 2008;178(4):425-30. http://dx.doi.org/10.1164/rccm.200803-459OC
25. Yetkin Ö, In E, Aksoy Y, Hacıevliyagil SS, Günen H. Brain natriuretic peptide in acute pulmonary embolism: its association with pulmonary artery pressure and oxygen saturations. Turkish Resp J. 2006;7(3):105-8.

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A new experimental model of cigarette smoke-induced emphysema in Wistar rats*,**

Um novo modelo experimental de enfisema induzido por fumaça de cigarro em ratos Wistar

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Abstract

Objective: To describe a new murine model of cigarette smoke-induced emphysema. **Methods:** Twenty-four male Wistar rats were divided into two groups: the cigarette smoke group, comprising 12 rats exposed to smoke from 12 commercial filter cigarettes three times a day (a total of 36 cigarettes per day) every day for 30 weeks; and the control group, comprising 12 rats exposed to room air three times a day every day for 30 weeks. Lung function was assessed by mechanical ventilation, and emphysema was morphometrically assessed by measurement of the mean linear intercept (Lm). **Results:** The mean weight gain was significantly (approximately ten times) lower in the cigarette smoke group than in the control group. The Lm was 25.0% higher in the cigarette smoke group. There was a trend toward worsening of lung function parameters in the cigarette smoke group. **Conclusions:** The new murine model of cigarette smoke-induced emphysema and the methodology employed in the present study are effective and reproducible, representing a promising and economically viable option for use in studies investigating the pathophysiology of and therapeutic approaches to COPD.

Keywords: Tobacco smoke pollution; Emphysema; Disease models, animal; Equipment and supplies.

Resumo

Objetivo: Descrever um novo modelo murino de enfisema induzido pela fumaça de cigarro. **Métodos:** Vinte e quatro ratos Wistar foram divididos em dois grupos: o grupo fumaça de cigarro, com 12 ratos expostos à fumaça de 12 cigarros comerciais com filtro três vezes ao dia (um total de 36 cigarros por dia), sete dias por semana, durante 30 semanas e o grupo controle, com 12 animais expostos ao ar ambiente três vezes ao dia, sete dias por semana, durante 30 semanas. A função pulmonar foi avaliada por meio de ventilação mecânica, e o enfisema foi morfometricamente avaliado por meio do diâmetro alveolar médio (Lm). **Resultados:** A média de ganho de peso foi significativamente menor (aproximadamente dez vezes menor) no grupo fumaça de cigarro do que no grupo controle. O Lm foi 25.0% maior no grupo fumaça de cigarro. Os parâmetros de função pulmonar tenderam a ser piores no grupo fumaça de cigarro. **Conclusões:** O novo modelo murino de enfisema induzido pela fumaça de cigarro e a metodologia empregada neste estudo são eficazes e reproduzíveis; são, portanto, uma opção promissora e economicamente viável para estudos sobre a fisiopatologia e o tratamento da DPOC.

Descritores: Poluição por fumaça de tabaco; Enfisema; Modelos animais de doenças; Equipamentos e provisões.

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Introduction

Worldwide, COPD is an important public health problem, having a high prevalence and carrying high socioeconomic costs. It is currently the fourth leading cause of death worldwide, and estimates indicate that it will be the third by 2020.[1,2]

Within the COPD spectrum, emphysema is defined as airspace enlargement distal to terminal bronchioles, accompanied by alveolar wall destruction, without significant fibrosis. Oxidative lung injury and inflammation in response to irritants (such as air pollution and cigarette smoke) speed up functional and morphological changes, gradually limiting gas exchange.[2-4]

Given that treatment is limited to palliative care, animal models are central to studies investigating the pathophysiology of COPD and new therapeutic approaches to the disease. Emphysema can be experimentally induced by the use of proteases, by exposure to cigarette smoke, and by genetic manipulation.[3-9]

Although animal models of enzyme-induced emphysema constitute an interesting methodological approach, they do not accurately reproduce the mechanisms of alveolar destruction resulting from smoke inhalation in human patients. Proteolytic activity leads to a significant increase in airspace size, not reproducing the sequence of pathological events characteristic of emphysema in humans.[6,10] Animal models of cigarette smoke-induced emphysema are used in an attempt to reproduce human disease, especially the pathophysiological mechanisms involved in the natural history of emphysema.[6,11] However, the duration of smoke exposure and the number of cigarettes used vary widely across models. In general, the most effective results are obtained with chronic exposure periods (> 6 months).[6,12]

The objective of the present study was to describe a new experimental model of cigarette smoke-induced emphysema. The model involves Wistar rats and an apparatus developed in the Laboratory of Genetics and Cell Therapy of the Júlio de Mesquita Filho São Paulo State University at Assis School of Sciences and Languages, located in the city of Assis, Brazil. The model can contribute to a better understanding of the pathophysiological processes in COPD, as well as to the development of new treatment strategies.

Methods

A total of 24 male Wistar rats (age, 12 weeks; weight, 400-450 g) were divided into two groups: the cigarette smoke group, comprising 12 rats exposed to smoke from 12 commercial filter cigarettes (Derby Vibrante; Souza Cruz SA, Rio de Janeiro, Brazil)—containing 0.8 mg of nicotine, 10 mg of tar, and 10 mg of carbon monoxide (CO)—for three 1-h exposure periods (from 8:00 a.m. to 9:00 a.m., from 12:00 p.m. to 1:00 p.m., and from 6:00 p.m. to 7:00 p.m.) every day for 30 weeks; and the control group, comprising 12 rats exposed to room air for three 1-h exposure periods every day for 30 weeks. During each exposure period, the rats in the cigarette smoke group were exposed to smoke from 4 cigarettes for 15 min, followed by a 5-min rest period (during which room air was delivered to prevent hypoxia). During each 15-min period of exposure, the smoking apparatus was set to cycle with cigarette-suction periods of 10 s and rest periods of 15 s.

The apparatus consists of an animal containment system and a cigarette smoking device (Figure 1). The animal containment system comprises four metal cages (24 cm × 17 cm × 15 cm) closed at the top. The four cages are placed equidistant from each other inside a hermetically sealed acrylic box (70 cm × 70 cm × 20 cm). Four large rats or 16 mice can be placed in each cage. Two apparatuses were used in the present study: one for the animals in the cigarette smoke group and one for the animals in the control group. Each apparatus was placed in a separate room. The cigarette smoke delivery system consists of an external cigarette holder connected to a dynamic suction pump by a flexible hose. The pump can be programmed to alternate between periods of cigarette suction and periods of clean air suction, to prevent asphyxia. The pump generates negative pressure, which forces the air through a lit-up cigarette, generating cigarette smoke and pushing it toward the hose and into the acrylic box. The concentration of CO in the containment system was assessed by means of a CO meter (ToxiPro® Single Gas Detector; Honeywell Analytics Distribution Inc., Lincolnshire, IL, USA) and was found to be 350-400 ppm during the exposure periods.

All animals were weighed weekly on an analytical scale. For standardization purposes,

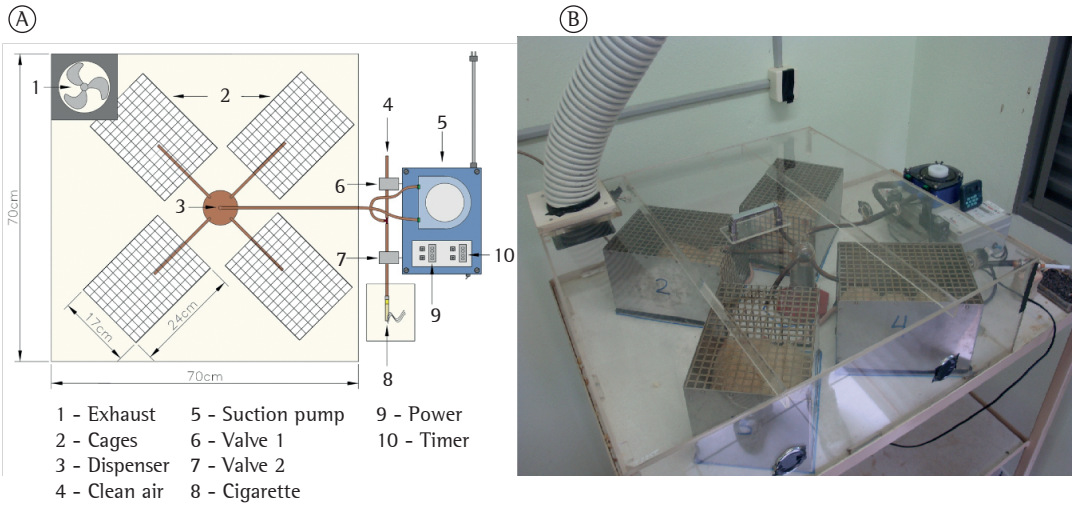

Figure 1 - In A, schematic illustration of the smoking apparatus. In B, upper view of the smoking apparatus.

all animals were weighed on the same day of the week and at the same time of day.

Lung function was assessed by means of a ventilator for small animals (flexiVent™; SCIREQ, Montreal, QC, Canada). After 30 weeks of daily exposure to mainstream cigarette smoke or room air, the animals were anesthetized by intraperitoneal injection of 250 mg/kg of Thiopentax® (Cristália - Produtos Químicos Farmacêuticos Ltda., Itapira, Brazil) and tracheostomized with a 20-G catheter connected to the ventilator, which was set to a tidal volume of 10 mL/kg, an RR of 120 breaths/min, and a positive end-expiratory pressure of 3 cmH_2O. Muscle paralysis was induced by intraperitoneal injection of pancuronium bromide (1 mg/kg). Lung function was expressed as airway resistance (Raw), respiratory system resistance, respiratory system compliance (Crs), tissue damping, and tissue elastance.

After mechanical evaluation of the respiratory system, the animals were euthanized and the lungs were removed. The trachea was cannulated and attached to the perfusion apparatus, the lungs being incubated in 4% paraformaldehyde solution for 24 h and kept inflated with sustained positive pressure (20 cmH_2O). The lung tissue was cut into 5-µm sections and stained with H&E for histological evaluation.

Emphysema was assessed by measurement of the mean linear intercept (Lm), in µm, as proposed by Weibel.[13] After fixation, each lung was cut into four sagittal sections. The sections were embedded in a single paraffin block, and each block was cut into three 5-µm sections, three slides being therefore prepared for each block. For each slide, ten randomly selected nonoverlapping fields were examined under light microscopy (magnification, ×400).

The results were analyzed by means of the Student's t-test and one-way ANOVA. In order to test the assumptions of normal distribution and homogeneity of variance, we performed the Shapiro-Wilk test and Levene's test. When the assumptions were not met, we used the Mann-Whitney test and Kruskal-Wallis ANOVA. For all tests, values of $p < 0.05$ were considered significant. The study project was approved by the Animal Research Ethics Committee of the Julio de Mesquita Filho São Paulo State University at Assis School of Sciences and Languages (Protocol no. 001/2011).

Results

As can be seen in Figure 2, there were no significant differences between the rats in the cigarette smoke group and those in the control group in terms of their initial weight. From the second week of exposure onward, the mean weight gain was lower in the cigarette smoke group than in the control group. There was a significant difference ($p < 0.05$) between the two groups regarding weight gain after the third week of exposure. After 30 weeks of exposure, the mean weight gain was 212.00 ± 83.40 g in the control group and 44.92 ± 43.40 g in the cigarette smoke group, the mean weight gain

in the cigarette smoke group corresponding to 21.2% of that in the control group.

As can be seen in Table 1, the values of Raw, tissue damping, respiratory system resistance, Crs, and tissue elastance were higher in the cigarette smoke group than in the control group. However, there was no significant difference between the two groups in terms of the respiratory parameters analyzed, which is probably due to the high variation among subjects in the same group (as evidenced by the high SD values).

Figure 3A shows the Lm for the right and left lungs in combination (for each group), and Figure 3B shows the Lm for the right and left lungs in isolation (for each group). As can be seen in Figure 3, there was a statistically significant difference in the Lm between the cigarette smoke group and the control group. When we analyzed the right and left lungs in combination, we found that the Lm was 25.0% higher in the cigarette smoke group than in the control group (Figure 3A). When the right and left lungs were analyzed separately, the Lm for the left lung was found to be 15.8% higher in the cigarette smoke group than in the control group (Figure 3B). Similarly, the Lm for the right lung was found to be 32.3% higher in the cigarette smoke group than in the control group (Figure 3B). These results suggest a difference in the degree of airspace enlargement between the right and left lungs in the cigarette smoke group. Alveolar septal destruction was significantly greater in the cigarette smoke group than in the control group, showing airspace enlargement resulting from increased lung parenchymal destruction in the cigarette smoke group, as assessed qualitatively by H&E staining of histological sections (Figure 4).

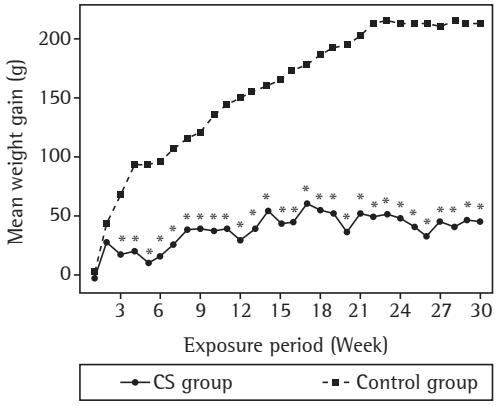

Figure 2 - Mean weight gain in the Wistar rats in the cigarette smoke (CS) group and in those in the control group. *p < 0.05.

Discussion

Cigarette smoke-induced emphysema has been studied under various experimental conditions.[5,6,11,12,14,15] Although some questions remain regarding the duration of exposure and the number of cigarettes used, animal models of cigarette smoke-induced emphysema are the experimental models that best mimic the clinical features of pulmonary emphysema in human patients and constitute an important tool in the study of the pathophysiological aspects of the disease.[6]

Although animal models of cigarette smoke-induced emphysema have been used in several studies, only a few smoke exposure systems are commercially available, including the Cigarette Smoke Generator® (TSE Systems, Inc., Chesterfield, MO, USA), the TE-2 Smoking Machine® (Teague Enterprises, Woodland, CA, USA), and the inExpose™ (SCIREQ). All have similar characteristics, consisting of a cigarette smoke generator and an animal exposure chamber, where animals are confined and exposed to cigarette smoke (via whole-body or nose-only exposure).[11,12,15,16] They all cost approximately US$ 75,000.00), which is approximately twenty times the final cost of our apparatus (i.e., US$ 3,000.00).

Table 1 - Airway resistance, respiratory system resistance, tissue damping, tissue elastance, and respiratory system compliance in Wistar rats exposed to cigarette smoke (the cigarette smoke group) and in those exposed to room air (the control group).

Groups	Raw[a]	Rrs[a]	G[b]	H[b]	Crs[b]
CS	0.09 ± 0.07	0.15 ± 0.07	0.35 ± 0.10	1.21 ± 0.24	1.37 ± 0.24
Control	0.04 ± 0.02	0.12 ± 0.07	0.22 ± 0.18	0.96 ± 0.89	1.14 ± 0.25

Raw: airway resistance; Rrs: respiratory system resistance; G: tissue damping; H: tissue elastance; Crs: respiratory system compliance; and CS: cigarette smoke. [a]Values expressed in mean ± SD ($cmH_2O \bullet mL^{-1} \bullet s^{-1}$). [b]Values expressed in mean ± SD ($cmH_2O \bullet mL^{-1} \bullet s^{-(1-a)}$).

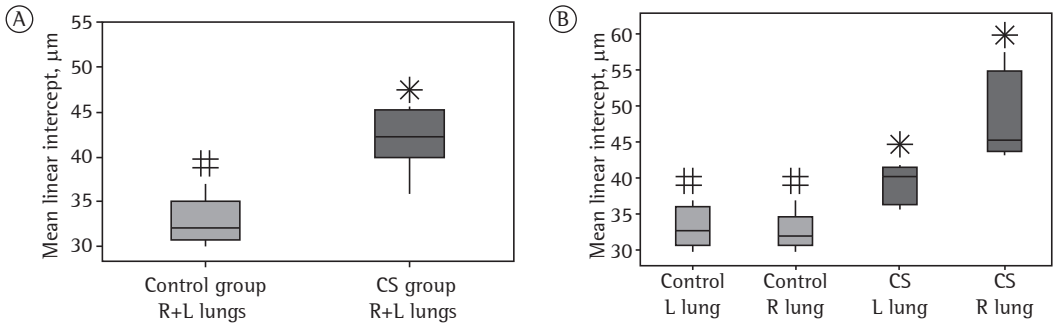

Figure 3 - In A, mean linear intercept values (in µm) for the right (R) and left (L) lungs in combination in the control and cigarette smoke (CS) groups. In B, mean linear intercept values (in µm) for the R and L lungs in isolation in the control and CS groups. Different symbols indicate a statistically significant difference ($p < 0.05$) between medians.

Several features of our apparatus are similar to those of commercially available systems used in previous studies.[11,12,15,16] One interesting feature is that animals are exposed to cigarette smoke via whole-body exposure. Another feature is that the smoke that is pumped into the exposure chamber is generated by the puffing of a cigarette, as occurs during actual smoking. Like other systems on the market, our apparatus allows us to regulate the suction power and the time of cigarette suction, alternating with periods of air suction, by means of a timer. The main advantages of our apparatus over commercially available devices include its low cost, simple design, and ease of installation, as well as the fact that it can be assembled from commercially available parts, such as a suction pump and a timer (to regulate the cigarette-suction and air-suction times, as described in the Methods section). In addition, the cost of our apparatus is 20 times lower than is that of commercially available devices.

The 30-week period of exposure employed in our study was based on a search for a model that offers greater reproducibility with respect to time. Previous studies of cigarette smoke-induced emphysema (employing different apparatuses) have reported exposure periods of 8-36 weeks. Although exposure periods of 6 months are common in animal model studies,[12,15-18] exposure periods of up to 9 months have also been used.[12,19]

In some protocols, animals are exposed to cigarette smoke 3-5 days a week, which is not enough to simulate daily smoking.[10,15,18-20] The duration of daily exposure varies widely across studies.[12,21,22] Li et al. adopted a two-step exposure protocol whereby animals were initially exposed to smoke from 8 cigarettes twice a day for 2 weeks (weeks 1 and 2) and subsequently exposed to smoke from 15 cigarettes three times a day for another 10 weeks (weeks 3-12).[23] The animal model used in the present study simulates the pathophysiological conditions of active smoking, animals having been exposed to mainstream cigarette smoke daily (7 days a week) for 30 weeks.

There are no studies involving a comparative morphometric analysis of alveolar damage in the right and left lungs. Comparative morphometric analysis is relevant because it allows the demonstration of the heterogeneity of parenchymal destruction in experimentally induced emphysema. Anatomical differences between the right and left lungs of rats provide a possible explanation for the results obtained. According to Cataneo and Reibscheid,[24] the rat trachea shows a deviation to the right, and the rat bronchi are similar to the human bronchi (i.e., short and large). The right bronchus appears to be a continuation of the trachea, whereas the left bronchus looks like a branch.[24] Therefore, it is possible that the right lung was more consistently exposed to cigarette smoke, which resulted in intense neutrophil and macrophage activation and increased secretion of proteases responsible for lung parenchymal destruction. These anatomical differences can explain why the Lm was higher in the right lung than in the left lung in the group of rats exposed to cigarette smoke.

Although functional testing is a valuable tool for assessing the development of emphysema in experimental models, it is less sensitive than morphometric analysis, which is more accurate in the assessment of parenchymal damage. Animals with moderate emphysema usually have normal functional values when compared with healthy

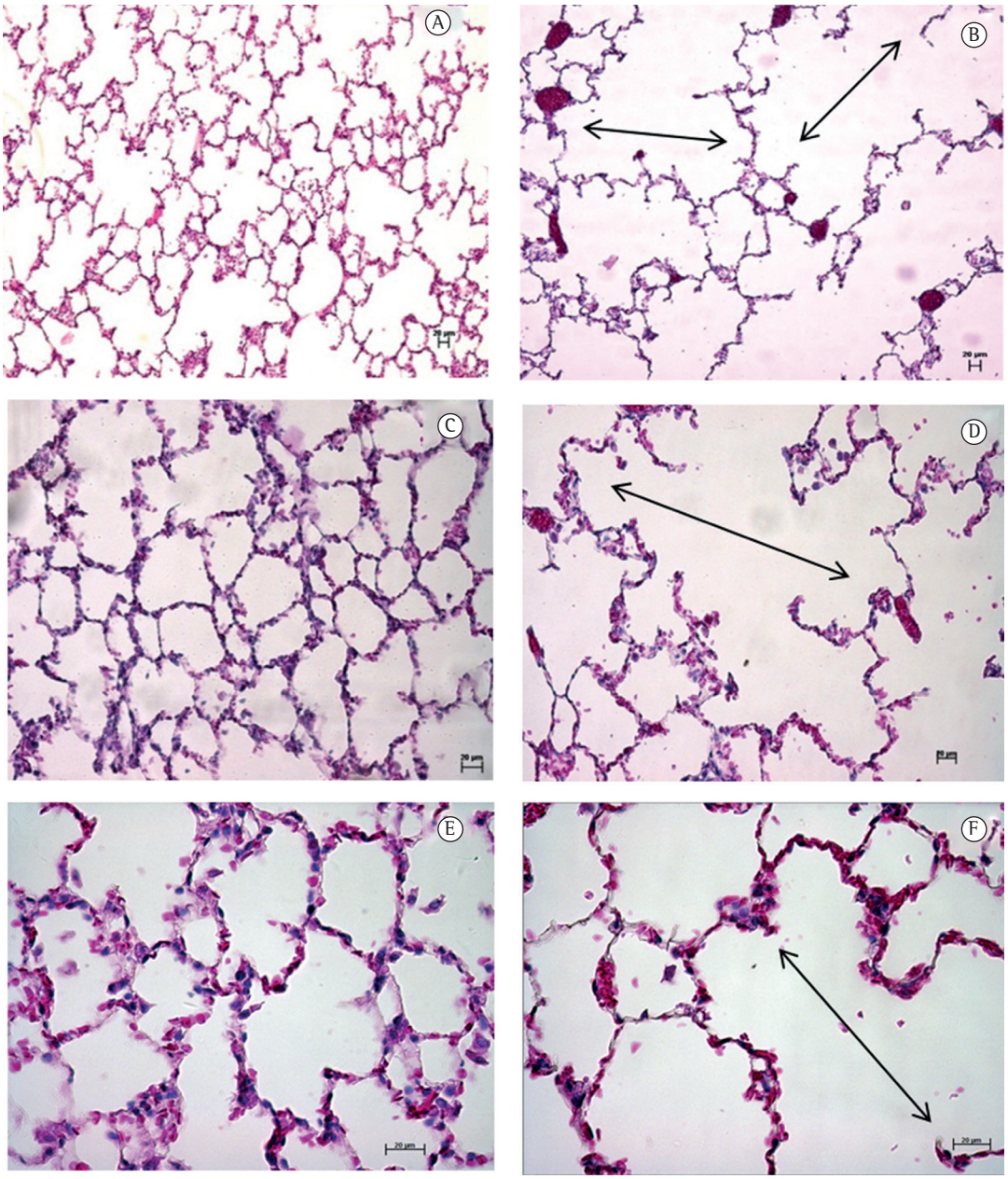

Figure 4 - Photomicrographs of rat lung tissue stained with H&E (magnification: ×100 [A and B]; ×200 [C and D]; and ×400 [E and F]). In A, C, and E, lung tissue from rats exposed to room air (control group). In B, D, and F, lung tissue from rats exposed to mainstream cigarette smoke. Double arrows indicate merged alveoli resulting in airspace enlargement. Scale bars: 20 µm.

animals, whereas animals with severe disease show significant changes in respiratory parameters.[6] This has been reported by other research groups. Foronjy et al.[25] exposed two strains of C57 mice to cigarette smoke for 6 months or 12 months and observed a significant increase in the Lm in comparison with the respective control groups. Nevertheless, there were no significant differences between the exposed animals and the respective control groups regarding the respiratory parameters. According to Wright et al.,[6] animals with moderate emphysema usually show borderline or normal functional values when compared with healthy animals; animals with advanced disease are the only ones that show significant changes in the respiratory parameters.

The results of the present study showed no significant differences in Raw or Crs between the animals in the cigarette smoke group and those in the control group. However, there was a trend toward increased Raw in the cigarette smoke group. The species under study plays a relevant role in the results of mechanical ventilation. Although Wistar rats allow researchers to perform a series of functional analyses, they are more resistant to the development of emphysema than are other rodent species.[6] From a pathophysiological standpoint, the disease can be milder in rats; this can complicate the comparison of functional parameters between animals that were exposed and unexposed to cigarette smoke.[6] This empirical finding can explain the results of the present study, which showed no statistically significant differences between the two groups of rats regarding the functional parameters assessed (Table 1), despite the morphometric evidence of emphysema (i.e., the Lm), as shown in Figure 3.

COPD can be considered a systemic disease, being characterized by skeletal changes, weakness, muscle dysfunction, and weight loss, which is due to oxidative stress and reduced caloric intake.[21,26,27] In smokers with COPD, nicotine increases satiety and reduces food intake,[28] smoking therefore contributing to weight loss, worsening emphysema, and generating a feedback circuit. Previous studies have shown that cigarette smoke can change hypothalamic appetite regulation in the central nervous system.[12,28,29] Mineur et al.[28] demonstrated that nicotine decreases food intake and body weight.

The inflammatory process is a fundamental component of the pathophysiology of COPD. Inflammation and other systemic effects of emphysema were not assessed in the present study, given that our main objective was to evaluate the feasibility of a new murine model of cigarette smoke-induced pulmonary emphysema. Other studies are currently under way in our laboratory, involving analysis of the lung for the presence of metalloproteinases 9 and 12, which play an important role in the inflammatory process,[3] and assessment of inflammatory cells in BAL fluid from animals exposed and unexposed to cigarette smoke.

The sharp weight loss observed in the present study was not due to the exposure period, given the statistically significant difference between the cigarette smoke group and the control group as of the third week of exposure (Figure 2). The animals in the control group showed a mean weight gain of 212.0 ± 83.40 g, whereas those in the cigarette smoke group showed a mean weight gain of 44.92 ± 43.40 g, which corresponded to 21.2% of that in the control group. Our results also showed a large standard deviation regarding the mean weight gain of the exposed animals after 30 weeks (44.92 ± 43.40 g). These results might be due to the intensity of exposure to cigarette smoke in the present study, which resulted in pulmonary changes and widespread pathophysiological changes. As noted above, COPD should be considered a systemic disease, as in a feedback circuit in which the side effects of smoke exposure determine morphological and functional changes in the lung. These changes reflect and are aggravated by the systemic effects of nicotine and the large number of toxic substances in cigarette smoke and other air pollutants.

The results of the present study indicate that mainstream cigarette smoke leads to decreased weight gain and development of emphysema in exposed animals, as assessed by morphometric analysis (i.e., the Lm). The methodology employed in the present study is feasible, and the new apparatus is effective for use in animal models of cigarette smoke-induced emphysema. This new murine model of cigarette smoke-induced emphysema is a promising and economically viable option for use in studies investigating the pathophysiology of and therapeutic approaches to COPD.

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References

1. World Health Organization. Global Alliance against Chronic Respiratory Diseases (GARD). General Meeting Report; 2008 May 30-31; Istanbul, Turkey. Geneva: WHO; 2008.
2. Global Initiative for Chronic Obstructive Lung Disease [homepage on the Internet. Bethesda: GOLD [cited 2012 Dec 10]. Global Strategy for the Diagnosis, Management and Prevention of COPD---Revised, 2011. Available from: http://www.goldcopd.org/
3. de Faria CA, de las Heras Kozma R, Stessuk T, Ribeiro-Paes JT. Experimental basis and new insights for cell therapy in Chronic Obstructive Pulmonary Disease. Stem Cell Rev. 2012;8(4):1236-44. http://dx.doi.org/10.1007/s12015-012-9410-7 PMid:23054962

4. Ribeiro-Paes JT, Stessuk T, de las Heras Kozma R. Cell Therapy in Chronic Obstructive Pulmonary Disease: State of the Art and Perspectives. In: Ong KC, editor. Chronic Obstructive Pulmonary Disease - Current Concepts and Practice. Rijeka: InTech; 2012. p. 455-74.
5. Churg A, Cosio M, Wright JL. Mechanisms of cigarette smoke-induced COPD: insights from animal models. Am J Physiol Lung Cell Mol Physiol. 2008;294(4): L612-31. http://dx.doi.org/10.1152/ajplung.00390.2007 PMid:18223159
6. Wright JL, Cosio M, Churg A. Animal models of chronic obstructive pulmonary disease. Am J Physiol Lung Cell Mol Physiol. 2008;295(1):L1-15. http://dx.doi.org/10.1152/ajplung.90200.2008 PMid:18456796 PMCid:PMC2494776
7. Fusco L, Pêgo-Fernandes P, Xavier A, Pazetti R, Rivero D, Capelozzi V, Janete F Modelo experimental de enfisema pulmonar em ratos induzido por papaína. J Pneumol. 2002; 28:1-7. http://dx.doi.org/10.1590/S0102-35862002000100003
8. Antunes MA, Rocco PR. Elastase-induced pulmonary emphysema: insights from experimental models. An Acad Bras Cienc. 2011;83(4):1385-96. http://dx.doi.org/10.1590/S0001-37652011005000039
9. Churg A, Sin DD, Wright JL. Everything prevents emphysema: are animal models of cigarette smoke-induced chronic obstructive pulmonary disease any use? Am J Respir Cell Mol Biol. 2011;45(6):1111-5. http://dx.doi.org/10.1165/rcmb.2011-0087PS PMid:21685155
10. Cendon SP, Battlehner C, Lorenzi Filho G, Dohlnikoff M, Pereira PM, Conceição GM, et al. Pulmonary emphysema induced by passive smoking: an experimental study in rats. Braz J Med Biol Res. 1997;30(10):1241-7. http://dx.doi.org/10.1590/S0100-879X1997001000017 PMid:9496445
11. Huh JW, Kim SY, Lee JH, Lee JS, Van Ta Q, Kim M, et al. Bone marrow cells repair cigarette smoke-induced emphysema in rats. Am J Physiol Lung Cell Mol Physiol. 2011;301(3):L255-66. http://dx.doi.org/10.1152/ajplung.00253.2010 PMid:21622846
12. Zheng H, Liu Y, Huang T, Fang Z, Li G, He S. Development and characterization of a rat model of chronic obstructive pulmonary disease (COPD) induced by sidestream cigarette smoke. Toxicology Lett. 2009;189(3):225-34. http://dx.doi.org/10.1016/j.toxlet.2009.06.850 PMid:19524650
13. Weibel E. Principles and methods for the morphometric study of the lung and other organs. Lab Invest. 1963;12:131-55. PMid:13999512
14. Valença SS, Porto LC. Immunohistochemical study of lung remodeling in mice exposed to cigarette smoke. J Bras Pneumol. 2008;34(10):787-95. http://dx.doi.org/10.1590/S1806-37132008001000006 PMid:19009211
15. Toledo AC, Magalhaes RM, Hizume DC, Vieira RP, Biselli PJ, Moriya HT, et al. Aerobic exercise attenuates pulmonary injury induced by exposure to cigarette smoke. Eur Respir J. 2012;39(2):254-64. http://dx.doi.org/10.1183/09031936.00003411 PMid:21700603
16. D'Agostino B, Sullo N, Siniscalco D, De Angelis A, Rossi F. Mesenchymal stem cell therapy for the treatment of chronic obstructive pulmonary disease. Expert Opin Biol Ther. 2010;10(5):681-7. http://dx.doi.org/10.1517/14712591003610614 PMid:20384521
17. Zhang XY, Zhang C, Sun QY, Li D, Luo RR, Wan ZF, et al. Infliximab protects against pulmonary emphysema in smoking rats. Chin Med J (Engl). 2011;124(16):2502-6.
18. Guerassimov A, Hoshino Y, Takubo Y, Turcotte A, Yamamoto M, Ghezzo H, et al. The development of emphysema in cigarette smoke-exposed mice is strain dependent. Am J Respir Crit Care Med. 2004;170(9):974-80. http://dx.doi.org/10.1164/rccm.200309-1270OC PMid:15282203
19. Marumo CK, Otsuki DA, Fantoni DT, Margarido CB, Ambrósio AM, Pelosi P, et al. Hemodynamic effects of PEEP in a porcine model of HCl-induced mild acute lung injury. Acta Anaesthesiol Scand. 2009;53(2):190-202. http://dx.doi.org/10.1111/j.1399-6576.2008.01842.x PMid:19094174
20. Churg A, Wang R, Wang X, Onnervik PO, Thim K, Wright JL. Effect of an MP-9/MMP-12 inhibitor on smoke-induced emphysema and airway remodelling in guinea pigs. Thorax. 2007;62(8):706-13. http://dx.doi.org/10.1136/thx.2006.068353 PMid:17311841 PMCid:PMC2117295
21. Rinaldi M, Maes K, De Vleeschauwer S, Thomas D, Verbeken EK, Decramer M, et al. Long-term nose-only cigarette smoke exposure induces emphysema and mild skeletal muscle dysfunction in mice. Dis Model Mech. 2012;5(3):333-41. http://dx.doi.org/10.1242/dmm.008508 PMid:22279084 PMCid:PMC3339827
22. Jardim JR, Bizeto L, Fleig Mayer A, Camelier A, Rosa FW, Oliveira D, et al. An inhalation chamber model for controlled studies of tobacco smoke toxicity in rodents [Article in Spanish]. Arch Bronconeumol. 2010;46(9):455-8. http://dx.doi.org/10.1016/j.arbres.2010.05.012 PMid:20624668
23. Li Y, Li SY, Li JS, Deng L, Tian YG, Jiang SL, et al. A rat model for stable chronic obstructive pulmonary disease induced by cigarette smoke inhalation and repetitive bacterial infection. Biol Pharm Bull. 2012;35(10):1752-60. http://dx.doi.org/10.1248/bpb.b12-00407 PMid:22863994
24. Cataneo AJM, Reibscheid SM. Broncografia e planimetria torácicos -- estudo experimental no rato. J Pneumol. 1988;14(2):66-9.
25. Foronjy RF, Mercer BA, Maxfield MW, Powell CA, D'Armiento J, Okada Y. Structural emphysema does not correlate with lung compliance: lessons from the mouse smoking model. Exp Lung Res. 2005;31(6):547-62. http://dx.doi.org/10.1080/019021490951522 PMid:16019987
26. Decramer M, De Benedetto F, Del Ponte A, Marinari S. Systemic effects of COPD. Respir Med. 2005;99 Suppl B:S3-10.
27. Gea J, Barreiro E. Update on the mechanisms of muscle dysfunction in COPD [Article in Spanish]. Arch Bronconeumol. 2008;44(6):328-37. http://dx.doi.org/10.1016/S1579-2129(08)60054-3
28. Mineur YS, Abizaid A, Rao Y, Salas R, DiLeone RJ, Gündisch D, et al. Nicotine decreases food intake through activation of POMC neurons. Science. 2011;332(6035):1330-2. http://dx.doi.org/10.1126/science.1201889 PMid:21659607 PMCid:PMC3113664
29. Chen BR, Hansen MJ, Jones JE, Vlahos R; Bozinovski S, Anderson GP, et al. Cigarette smoke exposure reprograms the hypothalamic neuropeptide Y axis to promote weight loss. Am J Respir Crit Care Med. 2006;173(11):1248-54. http://dx.doi.org/10.1164/rccm.200506-977OC PMid:16531608

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Chest compression with a higher level of pressure support ventilation: effects on secretion removal, hemodynamics, and respiratory mechanics in patients on mechanical ventilation*

Compressão torácica com incremento da pressão em ventilação com pressão de suporte: efeitos na remoção de secreções, hemodinâmica e mecânica pulmonar em pacientes em ventilação mecânica

Wagner da Silva Naue, Luiz Alberto Forgiarini Junior, Alexandre Simões Dias, Silvia Regina Rios Vieira

Abstract

Objective: To determine the efficacy of chest compression accompanied by a 10-cmH_2O increase in baseline inspiratory pressure on pressure support ventilation, in comparison with that of aspiration alone, in removing secretions, normalizing hemodynamics, and improving respiratory mechanics in patients on mechanical ventilation. **Methods:** This was a randomized crossover clinical trial involving patients on mechanical ventilation for more than 48 h in the ICU of the Porto Alegre *Hospital de Clínicas*, in the city of Porto Alegre, Brazil. Patients were randomized to receive aspiration alone (control group) or compression accompanied by a 10-cmH_2O increase in baseline inspiratory pressure on pressure support ventilation (intervention group). We measured hemodynamic parameters, respiratory mechanics parameters, and the amount of secretions collected. **Results:** We included 34 patients. The mean age was 64.2 ± 14.6 years. In comparison with the control group, the intervention group showed a higher median amount of secretions collected (1.9 g vs. 2.3 g; p = 0.004), a greater increase in mean expiratory tidal volume (16 ± 69 mL vs. 56 ± 69 mL; p = 0.018), and a greater increase in mean dynamic compliance (0.1 ± 4.9 cmH_2O vs. 2.8 ± 4.5 cmH_2O; p = 0.005). **Conclusions:** In this sample, chest compression accompanied by an increase in pressure support significantly increased the amount of secretions removed, the expiratory tidal volume, and dynamic compliance.
(ClinicalTrials.gov Identifier:NCT01155648 [http://www.clinicaltrials.gov/])
Keywords: Physical therapy modalities; Respiration, Artificial; Intensive care units; Respiratory therapy.

Resumo

Objetivo: Determinar a eficácia da manobra de compressão torácica, associada ao acréscimo de 10 cmH_2O na pressão inspiratória basal em modo ventilatório com pressão de suporte, em comparação com a da aspiração isolada, em relação a remoção de secreções, normalização da hemodinâmica e melhora da mecânica pulmonar em pacientes em ventilação mecânica. **Métodos:** Ensaio clínico randomizado cruzado incluindo pacientes em ventilação mecânica por mais de 48 h internados no CTI do Hospital de Clínicas de Porto Alegre, em Porto Alegre, RS. Os pacientes foram randomizados para receber aspiração isolada (grupo controle) ou compressão torácica associada ao acréscimo de 10 cmH_2O na pressão inspiratória basal em modo ventilatório com pressão de suporte (grupo intervenção). Foram mensurados parâmetros hemodinâmicos e de mecânica respiratória, assim como a quantidade de secreção aspirada. **Resultados:** Foram incluídos 34 pacientes. A idade média foi de 64,2 ± 14,6 anos. Na comparação com o grupo controle, o grupo intervenção apresentou uma maior mediana da quantidade de secreção aspirada (1,9 g vs. 2,3 g; p = 0,004), maior aumento da variação da média do volume corrente expirado (16 ± 69 mL vs. 56 ± 69 mL; p = 0,018) e maior aumento da variação da média da complacência dinâmica (0,1 ± 4,9 cmH_2O vs. 2,8 ± 4,5 cmH_2O; p = 0,005). **Conclusões:** Na amostra estudada, a compressão torácica associada ao aumento da pressão de suporte aumentou significativamente a quantidade de secreção aspirada, o volume corrente expirado e a complacência dinâmica.
(ClinicalTrials.gov Identifier:NCT01155648 [http://www.clinicaltrials.gov/])

Descritores: Modalidades de fisioterapia; Respiração artificial; Unidades de terapia intensiva; Terapia respiratória.

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Introduction

Most ICU patients require invasive ventilatory support and are therefore subject not only to the benefits gained from the institution of that support, such as maintenance of gas exchange and decreased work of breathing, but also to the deleterious effects associated with it, such as the impairment of the mucociliary transport and mucociliary clearance mechanisms.[1,2] This impairment, in turn, can lead to stasis of secretions in the airways and consequently result in bronchial obstruction,[3] which, in the long term, can cause atelectasis and episodes of hypoxemia. In addition, accumulation of bronchial secretions favors the multiplication of microorganisms in unventilated areas, leading to the establishment of respiratory infections, such as ventilator-associated pneumonia.[4-6]

Some physiotherapy techniques aim to enhance mucociliary clearance and thus prevent bronchial obstruction caused by accumulation of secretions. Chief among these techniques is manual expiratory passive therapy, which is defined as compression of the patient's chest during the expiratory phase with the aim of accelerating expiratory flow and moving secretions from peripheral to central airways, thereby facilitating their expectoration.[7,8]

The technique of chest compression alone is not always efficient. This is because patients on mechanical ventilation (MV) have impaired mucociliary clearance, which, combined with reduced expiratory flow, results in accumulation of secretions. The combination of techniques that are routinely used by physiotherapists in the ICU, together with adjustment of ventilator settings, can result in greater effectiveness in removing secretions. Therefore, MV can be combined with techniques that increase inspiratory flow, such as ventilator hyperinflation. This technique aims to increase alveolar ventilation and thus facilitate the cough mechanism, assisting in mucus transport.[9,10] One way to perform ventilator hyperinflation is to increase pressure support (PS) progressively until a peak airway pressure of 40 cmH_2O is reached. The application of this technique has resulted in a trend toward an increase in static compliance and in the amount of secretions collected.[11,12]

The objective of the present study was to compare the efficacy of chest compression combined with a 10-cmH_2O increase in baseline inspiratory pressure on PS ventilation with that of aspiration alone in terms of the amount of secretions removed, hemodynamic effects, and respiratory mechanics.

Methods

This was a randomized crossover clinical trial conducted in the ICU of the *Hospital de Clínicas de Porto Alegre* (HCPA, Porto Alegre *Hospital de Clínicas*), in the city of Porto Alegre, Brazil, between May of 2008 and May of 2010. The research project was approved by the HCPA Research Ethics Committee (Protocol no. 07504/2007). Written informed consent was completed by and obtained from the legal guardian of each study participant. Randomization was performed with an online Research Randomizer, version 4.0 (Social Psychology Network, http://www.randomizer.org/), through which patients were allocated to undergo one of two techniques, and then, in the subsequent period, patients underwent the other technique.

We included patients who had been on MV for more than 48 h, had not been diagnosed with ventilator-associated pneumonia, had a positive end-expiratory pressure ≤ 10 cmH_2O, had an adequate respiratory drive, had undergone aspiration 2 h prior to the protocol being applied, and were hemodynamically stable (mean arterial pressure ≥ 60 cmH_2O). The exclusion criteria were having contraindications to increasing positive pressure (undrained pneumothorax and hemothorax or subcutaneous emphysema), having been diagnosed with osteoporosis, having a peak pressure > 40 cmH_2O, being a neurosurgical patient, or having declined to participate in the study.

Following inclusion, all participants were placed in the supine position, with the head of the bed elevated 30°, and underwent a single aspiration (number 12 tube; MarkMed Ind. e Com. Ltda, São Paulo, Brazil) with vacuum set at −40 cmH_2O of pressure. All participants underwent aspiration 2 h prior to the application of both techniques—this procedure was performed to equate the groups in terms of secretion volume. After that period, hemodynamic and pulmonary parameters were assessed, the results of which corresponded to the patient's baseline evaluation.

Patients randomized to the control group were ventilated with 100% FiO_2 for 1 min. Subsequently, each patient was disconnected from the ventilator and underwent aspiration for 15 s, three times. The secretion collected was stored in a collection

vial (Intermedical®; Intermedical-Setmed, São Paulo, Brazil). Hemodynamic and pulmonary parameters were reassessed for variations 1 min after the aspirations, characterizing the control group.

When patients were randomized to the intervention group, they equally underwent aspiration 2 h prior to the procedure, in accordance with the previously described sequence. They were placed in the supine position and received chest compression combined with a 10-cmH_2O increase in baseline inspiratory pressure on PS ventilation. Subsequently, they underwent aspiration, and secretion was collected in the same way as for the control group patients. Hemodynamic and pulmonary parameters were reassessed 1 min after the technique was applied, and the results were recorded on a data collection sheet. The secretions collected were then weighed in the same way as for the control group, and weight values were recorded on a data collection sheet.

The secretions collected were weighed on a Cubis® scale (Sartorius, Bohemia, NY, USA) in the HCPA Microbiology Laboratory. All measurements were performed by a blinded collaborator who was not part of the study team, and weight values were recorded on a data collection sheet.

We assessed hemodynamic parameters, such as HR, RR, mean arterial pressure, and SpO_2 (IntelliVue MP60 monitor; Philips Medizin Systeme Böblingen GmbH, Böblingen, Germany). Respiratory assessment involved measuring peak inspiratory pressure, expiratory tidal volume (V_{Texp}), and dynamic compliance (Cdyn), and these parameters were assessed prior to and after the techniques were applied. Delta values were defined as the difference between baseline and post-treatment values.

The sample size required to obtain a difference of 0.7 ± 1.0 g of secretion collected or more between the groups for a p value < 0.05 and a study power of 80% was calculated to be 32 patients. We used the Statistical Package for the Social Sciences, version 18.0 (SPSS Inc., Chicago, IL, USA). Quantitative data are expressed as mean and standard deviation, whereas categorical data are expressed as absolute and relative frequencies. The groups were compared with the t-test for paired and independent samples and by using the general linear model analysis of variance for variables with normal distribution (as confirmed by the Kolmogorov-Smirnov test). The Wilcoxon test was used for variables with nonparametric distribution, whereas the chi-square test and Fisher's exact test were used for categorical variables.

Results

Between May of 2008 and May of 2010, 34 individuals were included in the study. There was a predominance of male patients, the mean age of the patients was 64.2 ± 14.6 years, and the most common pathology was sepsis (in (41.2%). The other characteristics of the sample are shown in Table 1.

Assessment of variations in HR revealed that, in comparison with the control group, the intervention group showed an increase in HR after the intervention. However, this increase was not clinically relevant. Assessment of variations in RR revealed no significant differences between the groups. In contrast, assessment of variations in V_{Texp} revealed that the intervention group showed a significant increase in V_{Texp} after chest compression combined with hyperinflation, and the same was true for the assessment of variations in Cdyn, i.e., the intervention group showed a significant increase in Cdyn when compared with the control group. Assessment of the other parameters analyzed revealed no significant differences between the groups (Table 2).

When the mean amount of secretions collected was evaluated, we found that, in comparison with the control group, the intervention group showed a significant increase in the amount of secretions collected (p = 0.004; Figure 1).

Table 1 - Clinical characteristics of the sample of 34 study participants.[a]

Variable	Result
Age, years	64.2 ± 14.6
APACHE II, score	25.5 ± 6.6
Female gender	15 (44.1)
Duration of MV, days	8.2 ± 4.9
Pathology	
COPD	7 (20.6)
Bronchopneumonia	9 (25.6)
Congestive heart failure	6 (17.6)
Stroke	8 (23.5)
Sepsis	14 (41.2)
Others	18 (52.9)

APACHE II: Acute Physiology and Chronic Health Evaluation II; MV: mechanical ventilation; and Others: immunosuppression, AIDS, or neoplasms. n ± SD or n (%).

Discussion

In the present study, we found that the use of chest compression combined with an increase in PS caused an increase in the amount of secretions collected. In addition, it caused significant increases in V_{Texp} and Cdyn.

Some authors have shown that hyperinflation techniques can prevent lung collapse, reexpand areas of atelectasis, improve oxygenation and lung compliance, and increase the movement of secretions from small to central airways.[1,7,12-14] This is due to the increase in tidal volume caused by hyperinflation, which expands the normal alveoli and thus, through the mechanism of interdependence, ultimately reexpands the collapsed alveoli.[15]

We showed that chest compression combined with an increase in PS increases the amount of secretions collected, which was similarly reported by Lemes et al., who, in a randomized crossover study, found a trend toward an increase in the amount of secretions collected after hyperinflation, with increases in PS, in patients on MV.[8] In contrast, Unoki et al. showed that, in comparison with tracheal aspiration, chest compression alone resulted in no increases in the amount of secretions collected.[16] It is possible that chest compression has greater effectiveness when combined with strategies of increasing tidal volume in patients on MV.

The fact that there was a significant increase in V_{Texp} in the intervention group (i.e., those who received chest compression combined with an increase in PS) as compared with the control group is an expected finding, because it is known that increases in inspiratory pressures cause increases in lung volumes. In addition, the increase in peak inspiratory flow caused by hyperinflation can assist in moving secretions from smaller to larger airways, assisting the mucociliary mechanism, reducing airway resistance, and thus contributing to an increase in lung volumes.[17-19]

Likewise, there was a significant increase in Cdyn in the intervention group as compared with the control group. This result corroborates the findings of Berney et al., who reported a significant increase in lung compliance after ventilator hyperinflation.[9] Savian et al. presented similar findings, attributing the increase in lung compliance to the fact that hyperinflation leads to better airflow distribution, resulting in re-expansion of collapsed lung units.[7]

One alternative to ventilator hyperinflation accomplished by increasing PS is manual

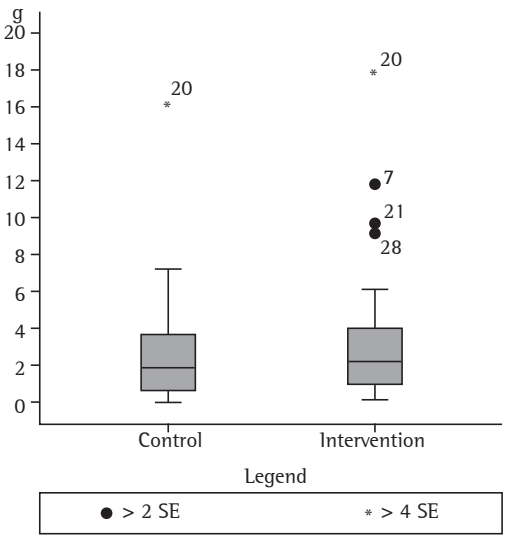

Figure 1 - Amount of secretion collected in the control and intervention groups, in median ± standard error (SE). p = 0.004.

Table 2 - Comparison of the variation in hemodynamic and pulmonary parameters in the groups studied.

Parameter	Control group			Intervention group			p
	Baseline	Post-treatment	Δ	Baseline	Post-treatment	Δ	
HR, bpm	97.4 ± 22.6	90.5 ± 23.0	−6.9 ± 7.8	91.6 ± 20.6	95.9 ± 19.7	4.3 ± 9.5	0.001
RR, breaths/min	20.8 ± 5.2	21.6 ± 5.1	0.7 ± 4.5	22.1± 6.2	22.2 ± 5.3	0.1 ± 5.6	0.592
MAP, mmHg	90.6 ± 20.1	86.8 ± 18.9	−3.8 ± 11.4	93.2 ± 18.8	91 ± 17.7	−2.2 ± 11.6	0.515
PIP, cmH_2O	20.7 ± 4.1	20.5 ± 3.6	−0.2 ± 1.2	20.9 ± 4.1	21.2 ± 4.5	0.3 ± 0.9	0.066
Cdyn, cmH_2O	34 ± 10.3	34.1 ± 10.7	0.1 ± 4.9	31.9 ± 9.2	34.8 ± 10.2	2.9 ± 4.5	0.018
V_{Texp}, mL	478 ± 147	496 ± 121	16 ± 69	465 ± 88	521 ± 120	56 ± 69	0.005
SpO_2, %	97.4 ± 2.3	96.8 ± 3.1	−0.5 ± 2.1	96.9 ± 2.5	96.9 ± 3.0	0.0 ± 2.0	0.170

MAP: mean arterial pressure; PIP: peak inspiratory pressure; V_{Texp}: expiratory tidal volume; Cdyn: dynamic compliance. [a]Values expressed as mean ± SD.

hyperinflation, which has the same therapeutic goals, with a manual resuscitation bag.[20] Comparison of the two techniques reveals similar results in terms of secretion volume, improvement in respiratory mechanics, and hemodynamic stability.[21,22] However, ventilator hyperinflation has a significant advantage in that it enables monitoring of the pressures, volumes, and flows used during its performance, thereby allowing fine tuning of the technique.[23] Another important factor is evident in the study by Ortiz et al., who evaluated the efficacy of manual hyperinflation in a lung model and showed that, although the technique yields safe values of alveolar pressure, it may not promote secretion removal because peak inspiratory flow exceeds peak expiratory flow.[24]

We conclude that, in comparison with aspiration alone, chest compression combined with an increase in PS significantly increased the amount of secretions collected. In addition, it significantly increased V_{Texp} and Cdyn.

References

1. Ciesla ND. Chest physical therapy for patients in the intensive care unit. Phys Ther. 1996;76(6):609-25. PMid:8650276
2. Jerre G, Silva Tde J, Beraldo MA, Gastaldi A, Kondo C, Leme F, et al. Physiotherapy on the mechanically ventilated patients. [Article in Portuguese] J Bras Pneumol. 2007;33 Suppl 2S S142-50. http://dx.doi.org/10.1590/S1806-37132007000800010 PMid:18026673
3. Amato MB, Carvalho CR, Isola A, Vieira S, Rotman V, Moock M, et al. Mechanical ventilation in Acute Lung Injury (ALI)/Acute Respiratory Discomfort Syndrome (ARDS). [Article in Portuguese] J Bras Pneumol. 2007;33 Suppl 2S S119-27. http://dx.doi.org/10.1590/S1806-37132007000800007 PMid:18026670
4. França EE, Ferrari F, Fernandes P, Cavalcanti R, Duarte A, Martinez BP, et al. Physical therapy in critically ill adult patients: recommendations from the Brazilian Association of Intensive Care Medicine Department of Physical Therapy. Rev Bras Ter Intensiva. 2012;24(1):6-22. http://dx.doi.org/10.1590/S0103-507X2012000100003 PMid:23917708
5. 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. http://dx.doi.org/10.1007/s00134-002-1342-2 PMid:12122521
6. McCarren B, Alison JA, Herbert RD. Manual vibration increases expiratory flow rate via increased intrapleural pressure in healthy adults: an experimental study. Aust J Physiother. 2006;52(4):267-71. http://dx.doi.org/10.1016/S0004-9514(06)70006-X
7. Savian C, Paratz J, Davies A. Comparison of the effectiveness of manual and ventilator hyperinflation at different levels of positive end-expiratory pressure in artificially ventilated and intubated intensive care patients. Heart Lung. 2006;35(5):334-41. http://dx.doi.org/10.1016/j.hrtlng.2006.02.003 PMid:16963365
8. Lemes DA, Zin WA, Guimaraes FS. Hyperinflation using pressure support ventilation improves secretion clearance and respiratory mechanics in ventilated patients with pulmonary infection: a randomised crossover trial. Aust J Physiother. 2009;55(4):249-54. http://dx.doi.org/10.1016/S0004-9514(09)70004-2
9. Berney S, Denehy L. A comparison of the effects of manual and ventilator hyperinflation on static lung compliance and sputum production in intubated and ventilated intensive care patients. Physiother Res Int. 2002;7(2):100-8. http://dx.doi.org/10.1002/pri.246
10. Lemes DA, Guimarães FS. The use of hyperinflation as a physical therapy resource in intensive care unit. [Article in Portuguese] Rev Bras Ter Intensiva. 2007;19(2):221-5. http://dx.doi.org/10.1590/S0103-507X2007000200014
11. Branson R. Secretion management in the mechanically ventilated patient. Respir Care. 2007;52(10):1328-42; discussion 1342-7. PMid:17894902
12. Singer M, Vermaat J, Hall G, Latter G, Patel M. Hemodynamic effects of manual hyperinflation in critically ill mechanically ventilated patients. Chest. 1994;106(4):1182-7. http://dx.doi.org/10.1378/chest.106.4.1182 PMid:7924493
13. Hodgson C, Carroll S, Denehy L. A survey of manual hyperinflation in Australian hospitals. Aust J Physiother. 1999;45(3):185-93. PMid:11676766
14. Denehy L. The use of manual hyperinflation in airway clearance. Eur Respir J. 1999;14(4):958-65. http://dx.doi.org/10.1034/j.1399-3003.1999.14d38.x PMid:10573249
15. Stiller K. Physiotherapy in intensive care: towards an evidence-based practice. Chest. 2000;118(6):1801-13. http://dx.doi.org/10.1378/chest.118.6.1801 PMid:11115476
16. Unoki T, Kawasaki Y, Mizutani T, Fujino Y, Yanagisawa Y, Ishimatsu S, et al. Effects of expiratory rib-cage compression on oxygenation, ventilation, and airway-secretion removal in patients receiving mechanical ventilation. Respir Care. 2005;50(11):1430-7. PMid:16253149
17. Choi JS, Jones AY. Effects of manual hyperinflation and suctioning in respiratory mechanics in mechanically ventilated patients with ventilator-associated pneumonia. Aust J Physiother. 2005;51(1):25-30. http://dx.doi.org/10.1016/S0004-9514(05)70050-7
18. Van der Schans CP. Bronchial mucus transport. Respir Care. 2007;52(9):1150-6; discussion 1156-8. PMid:17716383
19. Santos LJ, Blattner CN, Micol CA, Pinto FA, Renon A, Pletsch R. Effects of manual hyperinflation maneuver associated with positive end expiratory pressure in patients within coronary artery bypass grafting. [Article in Portuguese] Rev Bras Ter Intensiva. 2010;22(1):40-6.
20. Berti JS, Tonon E, Ronchi CF, Berti HW, Stefano LM, Gut AL, et al. Manual hyperinflation combined with expiratory rib cage compression for reduction of length of ICU stay in critically ill patients on mechanical ventilation. J Bras Pneumol. 2012;38(4):477-86. http://dx.doi.org/10.1590/S1806-37132012000400010 PMid:22964932
21. Dennis D, Jacob W, Budgeon C. Ventilator versus manual hyperinflation in clearing sputum in ventilated intensive care unit patients. Anaesth Intensive Care. 2012;40(1):142-9. PMid:22313075
22. Savian C, Paratz J, Davies A. Comparison of the effectiveness of manual and ventilator hyperinflation at different levels of positive end-expiratory pressure in artificially ventilated and intubated intensive care

patients. Heart Lung. 2006;35(5):334-41. http://dx.doi.org/10.1016/j.hrtlng.2006.02.003 PMid:16963365
23. Berney S, Denehy L, Pretto J. Head-down tilt and manual hyperinflation enhance sputum clearance in patients who are intubated and ventilated. Aust J Physiother. 2004;50(1):9-14. PMid:14987187
24. Ortiz Tde A, Forti G, Volpe MS, Carvalho CR, Amato MB, Tucci MR. Experimental study on the efficiency and safety of the manual hyperinflation maneuver as a secretion clearance technique. J Bras Pneumol. 2013;39(2):205-13. PMid:23670506

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The burden of disease due to tuberculosis in the state of Santa Catarina, Brazil*,**

A carga de doença por tuberculose no estado de Santa Catarina

Glênio César Nunes Ferrer, Rosemeri Maurici da Silva, Kelian Tenfen Ferrer, Jefferson Traebert

Abstract

Objective: To estimate the burden of disease due to tuberculosis in the state of Santa Catarina, Brazil, in 2009. **Methods:** This was an epidemiological study with an ecological design. Data on tuberculosis incidence and mortality were collected from specific Brazilian National Ministry of Health databases. The burden of disease due to tuberculosis was based on the calculation of disability-adjusted life years (DALYs). The DALYs were estimated by adding the years of life lost (YLLs) and years lived with disability (YLDs). Absolute values were transformed into rates per 100,000 population. The rates were calculated by gender, age group, and health care macroregion. **Results:** The burden of disease due to tuberculosis was 5,644.27 DALYs (92.25 DALYs/100,000 population), YLLs and YLDs respectively accounting for 78.77% and 21.23% of that total. The highest rates were found in males in the 30-44 and 45-59 year age brackets, although that was not true in every health care macroregion. Overall, the highest estimated burden was in the *Planalto Norte* macroregion (179.56 DALYs/100,000 population), followed by the *Nordeste* macroregion (167.07 DALYs/100,000 population). **Conclusions:** In the majority of the health care macroregions of Santa Catarina, the burden of disease due to tuberculosis was concentrated in adult males, the level of that concentration varying among the various macroregions.

Keywords: Tuberculosis/epidemiology; Life expectancy; Cost of illness.

Resumo

Objetivo: Estimar a carga de doença por tuberculose no estado de Santa Catarina em 2009. **Métodos:** Estudo epidemiológico de delineamento ecológico. Dados sobre a incidência e mortalidade de tuberculose foram coletados de bancos de dados específicos do Ministério da Saúde do Brasil. A carga de doença por tuberculose baseou-se no cálculo de *disability-adjusted life years* (DALYs, anos de vida perdidos ajustados por incapacidade). Os DALYs foram estimados pela soma de *years of life lost* (YLLs, anos de vida perdidos) e *years lived with disability* (YLDs, anos vividos com incapacidade). Os valores absolutos foram transformados em taxas por 100 mil habitantes. As taxas foram calculadas por sexo, faixa etária e macrorregião de saúde. **Resultados:** A carga de doença por tuberculose foi de 5.644,27 DALYs (92,25 DALYs/100 mil habitantes), dos quais 78,77% foram YLLs e 21,23% foram YLDs. As maiores taxas foram encontradas no sexo masculino nas faixas etárias de 30-44 e 45-59 anos, com distribuição desigual por macrorregião de saúde. A maior carga foi estimada na macrorregião do Planalto Norte (179,56 DALYs/100 mil habitantes), seguida pela do Nordeste (167,07 DALYs/100 mil habitantes). **Conclusões:** A carga de doença por tuberculose concentrou-se em homens adultos, com distribuição desigual nas macrorregiões de saúde de Santa Catarina.

Descritores: Tuberculose/epidemiologia; Expectativa de vida; Efeitos psicossociais da doença.

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Introduction

Although tuberculosis is an ancient, well-known infectious disease and is vulnerable to drug treatment for more than half a century, it remains one of the main global health concerns.[1] Tuberculosis is one of the most significant causes of mortality in the developing world, especially in males in the 45-59 year age bracket, which places *Mycobacterium tuberculosis* as the single most important etiologic factor in terms of mortality among infectious diseases.[2]

Brazil currently ranks 19th in number of cases of tuberculosis among the 22 countries prioritized by the World Health Organization (WHO) that collectively account for 80% of the global burden of the disease.[3] However, Brazil ranked 14th in 2004.[4]

Guimarães et al.,[5] in a recent study of a 20-year historical time series, reported a reduction in the incidence of tuberculosis of 11.4% worldwide, of 50% in the Americas, and of 48.8% in Brazil. That same study also highlighted a decrease in the mortality rates of 40.0%, 70.7%, and 70.8%, respectively.

The tuberculosis/HIV co-infection reflects mortality trends due to tuberculosis in Brazil.[6] The Brazilian Ministry of Health recommends strategies to actively search for new cases of tuberculosis, aiming at the early diagnosis, especially in high-risk groups, such as those who live with HIV and other immunosuppressive conditions. Individuals infected with *M. tuberculosis* have a 10% chance of developing tuberculosis in their lifetime, whereas individuals with HIV have an 8-10% chance per year.[2]

There are no studies in the state of Santa Catarina that include, in a single index, morbidity and mortality data regarding tuberculosis in order to estimate the burden of the disease. The proposed index to measure burden of disease is the disability-adjusted life years (DALYs).[7] One DALY is equivalent to one year of healthy life lost or lived with disability due to a disease. The 2002 Burden of Disease Project in Brazil[8] reported the burden of disease due to tuberculosis in the country. Tuberculosis was found to be the 19th cause of early death in both sexes, and the 17th among men.

Between 1992 and 2002, in a study performed in Serbia[9], a higher burden was observed among men than among women, with a progressive increase with advancing age. The rate found was 1.38 DALYs/100,000 population in the 55-64 year age group. In a recent publication, Murray et al.[10] showed that tuberculosis accounted for 2.0% of all DALYs worldwide in 2010. However, when comparing data from 1990 with those from 2010, the authors reported a decrease of 19.4% in the total number of DALYs due to tuberculosis.

The objective of the present study was to estimate the burden of disease due to tuberculosis in the state of Santa Catarina, Brazil, in 2009.

Methods

This was an epidemiological study with an ecological design using data on morbidity and mortality due to tuberculosis in the nine health macroregions in the state of Santa Catarina in 2009.

The mortality data were obtained from the Brazilian Mortality Database, whereas the incidence data were obtained from the National Case Registry Database as cases of tuberculosis (International Classification of Diseases, 10th revision: from A15 to A19). For the purpose of compensating for occasional underreporting of the tuberculosis/HIV co-infection and of tuberculosis alone, a rate of 17.7%[11] and of 60% was respectively added to the data.[12] These rates were added following the same parameters for the distribution of tuberculosis according to sex, age group, and health macroregions obtained from the National Case Registry Database in 2009.

The estimation of DALYs was carried out by adding the years of life lost (YLLs) and the years lived with disability (YLDs). The estimation of YLLs was based on the difference between the age at death and the life expectancy at birth. In the present study, the standardized values of 80 years of age for men and of 82.5 years of age for women[8] were used in order to allow for comparisons of the results with international studies. A 3% discount rate per year was applied in relation to the future years lost in order to estimate the YLLs in the present.[8] The YLD rate was calculated as the product of the tuberculosis weight by the mean duration of the disease. Studies of burden of disease define a measurement designated disease weight, which attributes a numerical value to the time lived with a specific nonfatal ailment designated disease weight. In 2004, according to a WHO report,[13] the attributed tuberculosis weight was 0.271. According to the

Global Burden of Disease Study,[7] the median survival period after diagnosis for Latin America is 18 months for HIV-negative tuberculosis patients and 12 months for HIV-positive individuals. These values were used in order to define the duration of the disease.

In summary, the equations used in order to calculate YLLs, YLDs, and DALYs were:

YLLs (males) = (80 years – age at death) × (–3% by year)

YLLs (females) = (82.5 years – age at death) × (–3% by year)

YLDs (HIV-negative patients) = 0.271 × 18 months

YLDs (HIV-positive patients) = 0.271 × 12 months

DALYs = YLLs + YLDs

The data were saved in electronic format (Microsoft Excel), and we used the Statistical Package for the Social Sciences, version 16.0 (SPSS Inc., Chicago, IL, USA) for descriptive analyses. The rates were calculated per 100,000 population, using the estimated population in July of 2009, distributed by sex and age groups, as a reference.

In the present study, anonymous secondary data from official public domain health information systems were used, and therefore there was neither risk of losses to individuals or institutions nor ethical principle violations.

Results

In 2009, 223 deaths were related to tuberculosis, and 2,138 patients were diagnosed with the disease in the state of Santa Catarina. Among the 2,138 patients, 563 were co-infected with HIV.

The total number of YLLs was 4,446.29, which generated a rate of 72.67 YLLs/100,000 population. For males, it was 2,947.97 YLLs (66.3%), with a rate of 96.98 YLLs/100,000 population. For females, it was 1,498.32 YLLs (33.7%), generating a rate of 48.66 YLLs/100,000 population.

Regarding the age groups, the highest YLL rate was found in the 30-44 year age bracket (153.74 YLLs/100,000 population), followed by the 45-59 year age bracket (112.43 YLLs/100,000 population) and the 60-69 year age bracket (103.4 YLLs/100,000 population). The health macroregions with the highest rates were *Nordeste*, *Planalto Norte* and *Planalto Serrano* (Figure 1).

The total number of YLDs was 1,197.98, which generated a rate of 19.58 YLDs/100,000 population. For males, it was 809.49 YLDs (67.6%), with a rate of 26.63 YLDs/100,000 population. For females, it was 388.49 YLDs (32.4%), generating a rate of 12.62 YLDs/100,000 population.

The highest YLD rates were encountered in the 45-59 year age bracket (30.20 YLDs/100,000 population), followed by the 30-44 year age bracket (28.71 YLDs/100,000 population) and the 15-29 year age bracket (21.03 YLDs/100,000 population). The health macroregions with the highest rates were *Planalto Norte*, *Nordeste* and *Grande Florianópolis* (Figure 1).

The total number of DALYs due to tuberculosis in Santa Catarina was 5,644.27, which generated a rate of 92.25 DALYs/100,000 population. The rates for males and females were, respectively, 123.62 DALYs/100,000 population (66.6%) and 61.28 DALYs/100,000 population (33.4%). The DALY rates according to the age groups are shown in Figure 2, whereas those by age groups and gender are shown in Figure 3.

The highest burden of disease was found in the macroregion *Planalto Norte* (179.56 DALYs/100,000 population), followed by *Nordeste* (167.07 DALYs/100,000 population), and *Grande Florianópolis* (133.14 DALYs/100,000 population), whereas the lowest rates were seen in *Foz do Rio Itajaí* (16.65 DALYs/100,000 population), *Extremo Oeste* (28.58 DALYs/100,000 population), and *Meio Oeste* (42.18 DALYs/100,000 population; Table 1 and Figure 4).

Overall, the male-to-female ratio was 2.02 in the state of Santa Catarina. The health macroregions with the highest and lowest male-to-female ratios were, respectively, *Foz do Rio Itajaí* (7.58) and *Extremo Oeste* (0.77; Table 1).

In terms of the ratio between the rates observed in the macroregions in relation to that found in the state, *Planalto Norte* showed the highest ratio (1.95) followed by *Nordeste* (1.81), whereas the lowest ratios were found in *Foz do Rio Itajaí* (0.18) and *Extremo Oeste* (0.31; Table 1).

Discussion

The decrease in tuberculosis mortality rates is a global trend. The WHO reports that the absolute

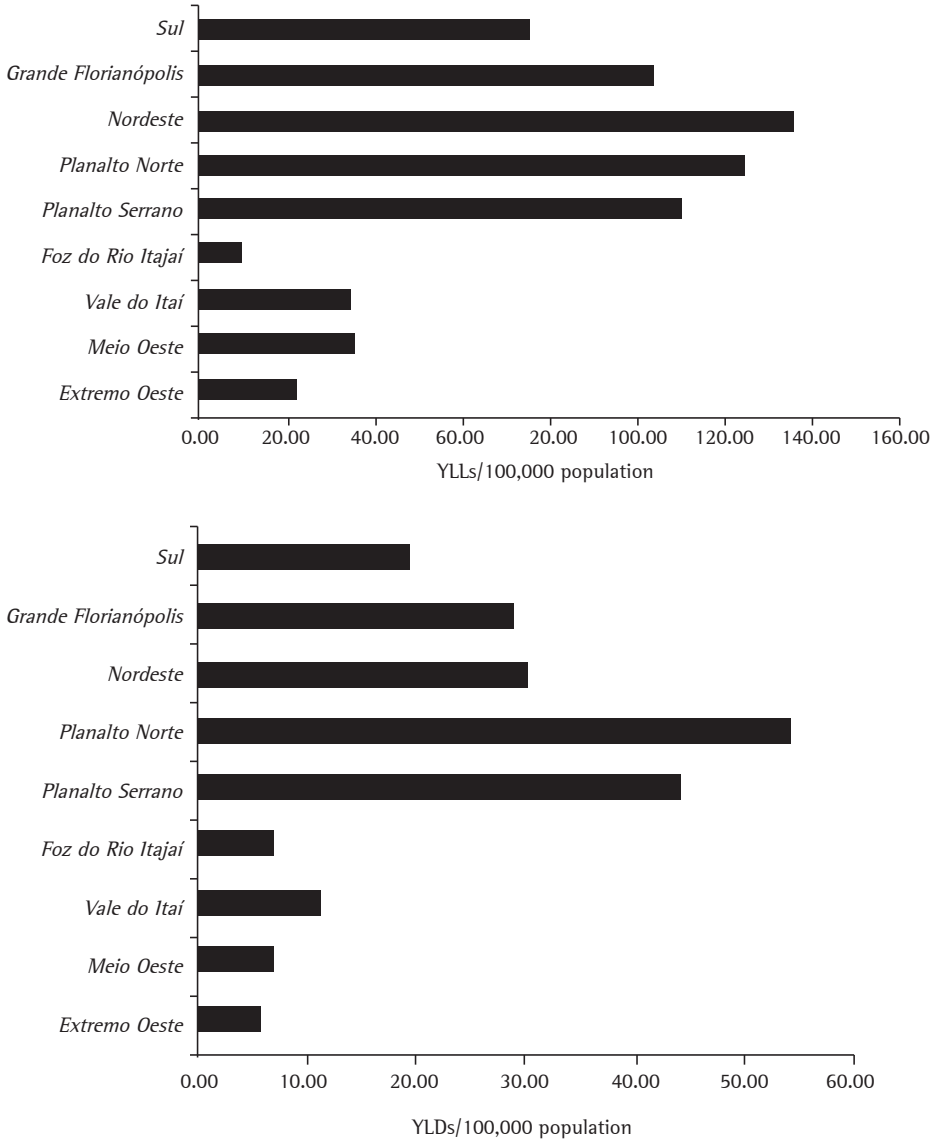

Figure 1 - Years of life lost (YLLs) and years lived with disability (YLDs) per 100,000 population according to the health macroregions in the state of Santa Catarina, Brazil, 2009.

number of cases has been falling since 2006, as has its incidence since 2002. Mortality fell by 8.6% *per annum* between 1990 and 2010.[14] This trend is also observed in various studies in Brazil.[15-17]

One aspect that might have positively influenced the mortality and incidence rates since 1999 was the implementation of the directly observed treatment, short-course (DOTS) in Brazil, which resulted in a 32% drop in mortality by 2007.[2,3] This strategy increases cure rates by 1% a year and drastically reduces noncompliance with the treatment, which is directly related to poor disease outcomes.[18] However, since the present study had an ecological design, the proportion of individuals in which the DOTS strategy was applied was unavailable. Nevertheless, with the implementation of this strategy as a government policy, being an integral part of the Brazilian National Tuberculosis Control Program, it could be inferred that the great majority of individuals have been offered DOTS. The decrease in morbidity and mortality could also be attributed to the free and universal access to treatment, as well as to improvements in primary health care.[3,14]

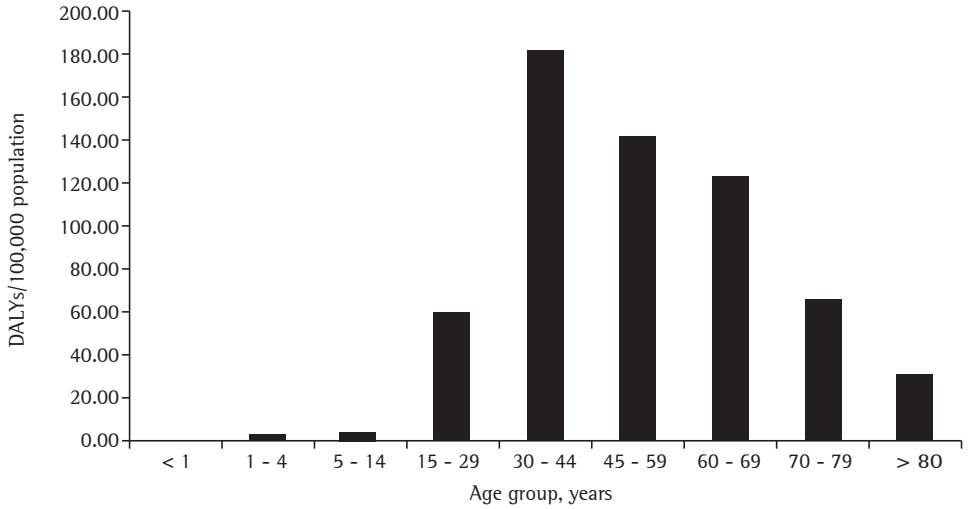

Figure 2 - Disability-adjusted life years (DALYs)/100,000 population rates according to age groups in the state of Santa Catarina, Brazil, 2009.

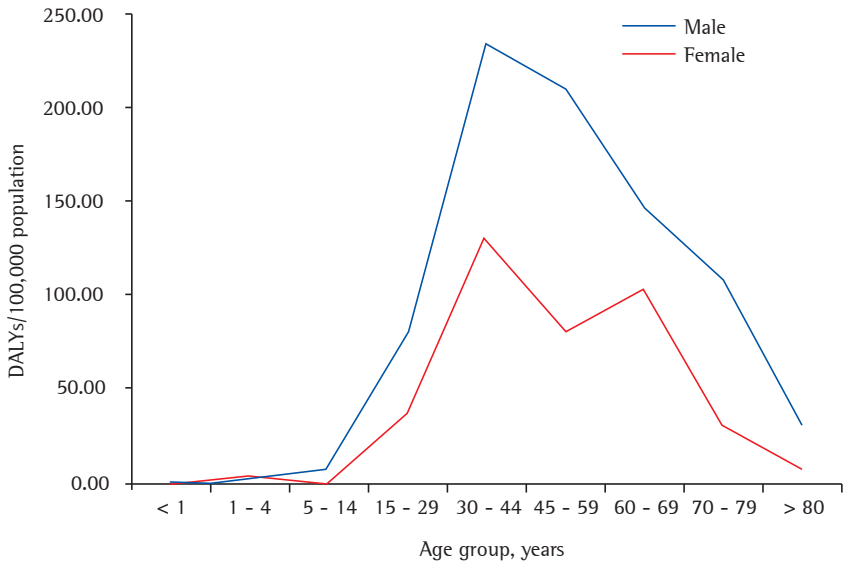

Figure 3 - Disability-adjusted life years (DALYs)/100,000 population rates according to sex and age groups in the state of Santa Catarina, Brazil, 2009.

As previously mentioned, the epidemiology of tuberculosis has been tirelessly investigated, using different methodologies, in order to provide a clearer understanding of its behavior in the country. The present study, however, sheds new light on the matter, since no previous studies have reported both morbidity and mortality by tuberculosis in the same index.

The 2002 Disease Burden Project in Brazil[8] revealed that tuberculosis ranked 19th among the major causes of premature deaths, which translated into 1.1% of the total number of deaths in the country. However, that study did not present YLL, YLD and DALY values specifically related to tuberculosis, which prevents any comparisons with the current study.

As expected, the burden of disease due to tuberculosis in Santa Catarina was higher in males. Classic epidemiological indices had already suggested that reality.[2,19-21] In the present study, the burden rate was estimated to be twice as high among males. A similar scenario was observed in a study carried out in Serbia.[9] According to the authors, those rates for men and women were,

Table 1 - Disability-adjusted life years/100,000 population rates by health macroregions in the state of Santa Catarina, Brazil, 2009.

Macroregion	DALYs/100,000 population	YLLs, %	YLDs, %	MS ratio	MF ratio	Most affected age brackets			
						Males		Females	
						1st	2nd	1st	2nd
Extremo Oeste	28.58	78.61	21.39	0.31	0.77	70-79	30-44	30-44	15-29
Meio Oeste	42.18	84.96	15.04	0.46	2.51	45-59	30-44	70-79	30-44
Vale do Itajaí	45.99	75.92	24.08	0.50	4.63	30-44	70-79	45-59	15-29
Foz do Rio Itajaí	16.65	60.78	39.22	0.18	7.58	30-44	15-29	60-69	45-59
Planalto Serrano	126.30	87.52	12.48	1.37	1.94	60-69	15-29	60-69	30-44
Planalto Norte	179.56	69.70	30.30	1.95	1.09	45-59	15-29	30-44	15-29
Nordeste	167.07	81.58	18.42	1.81	2.02	45-59	60-69	60-69	30-44
Grande Florianópolis	133.14	78.13	21.87	1.44	2.20	30-44	45-59	60-69	45-59
Sul	94.94	79.59	20.41	1.03	2.41	30-44	60-69	45-59	30-44
Santa Catarina state	92.25	78.78	21.22	-	2.02	30-44	45-59	30-44	60-69

DALYs: disability-adjusted life years; YLLs: years of life lost; YLDs: years lived with disability; MS: macroregion to state; and MF: male to female.

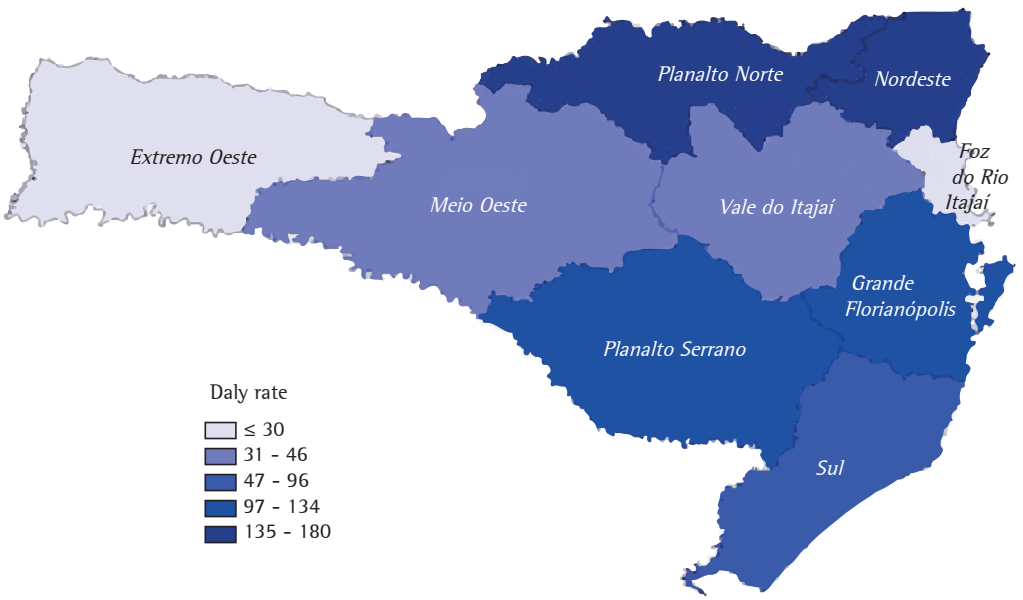

Figure 4 - Disability-adjusted life years (DALYs)/100,000 population rates according to the health macroregions in the state of Santa Catarina, Brazil, 2009.

respectively, 36.7 DALYs/100,000 population and 21.4 DALYs/100,000 population.

The YLL rate was found to be considerably high due to the fact that mortality by tuberculosis is associated with HIV infection, which is highly prevalent in the state of Santa Catarina. Even with antiretroviral therapy, individuals living with HIV have a high incidence of tuberculosis, showing low AFB counts in sputum and a high incidence of multidrug-resistant tuberculosis.[2]

The 30-44 year age bracket was the age group most affected for both sexes, whereas the 45-59 and the 60-69 year age brackets were more prevalent for males and females, respectively. Similar age brackets have also been reported in other studies. In developing countries, 80% of

the infected individuals are between 15 and 59 years of age—mostly men in the economically active age group—causing a negative impact on economic growth and, consequently, on social development, generating more poverty and social exclusion.[22]

The distribution of the burden of disease has unearthed heterogeneous realities throughout the health macroregions of the state. *Planalto Norte*, *Nordeste*, *Grande Florianopolis*, and *Planalto Serrano* showed rates higher than 100 DALYs/100,000 population, whereas *Extremo Oeste* and *Foz do Rio Itajaí* had rates lower than 30 DALYs/100,000 population. The heterogeneous distribution could be explained by the analysis of various aspects, including the quality of the health care facilities in each macroregion. The gap between the demand for medical services and the diagnosis, with the consequent notification of tuberculosis cases, might have contributed to the increased morbidity and mortality rates.

One should take into consideration the likely underreporting of tuberculosis cases when measuring the burden of disease. Another possible limitation of the present study was the use of parameters defined by the WHO that reflected the tuberculosis trends in Latin America in the 2000s. Such parameters might have had a limiting impact on the estimation of the current burden, despite being the best available parameters to date, permitting comparisons between both national and international studies.

In conclusion, despite the need for a degree of caution when interpreting the present results, the use of DALYs is recommended as a helpful tool to assess priorities in terms of specific profiles regarding tuberculosis in the state of Santa Catarina. Further studies regarding the burden of disease due to tuberculosis are necessary in order to generate parameters for comparisons in the state and in Brazil as a whole, as well as to identify impact trends.

References

1. Barreira D, Grangeiro A. Evaluation of tuberculosis control strategies in Brazil. Foreword [Article in Portuguese]. Rev Saude Publica. 2007;41 Suppl 1:4-8. http://dx.doi.org/10.1590/S0034-89102007000800002 PMid:18038085
2. Conde MB, Melo FA, Marques AM, Cardoso NC, Pinheiro VG, Dalcin Pde T, et al. III Brazilian Thoracic Association Guidelines on tuberculosis. J Bras Pneumol. 2009;35(10):1018-48. PMid:19918635
3. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de Vigilância Epidemiológica. Manual de recomendações para o controle da tuberculose no Brasil. Brasília: Ministério da Saúde; 2011.
4. World Health Organization. Global Tuberculosis Control WHO Report 2010. Geneva: World Health Organization; 2010.
5. Guimarães RM, Lobo Ade P, Siqueira EA, Borges TF, Melo SC. Tuberculosis, HIV, and poverty: temporal trends in Brazil, the Americas, and worldwide. J Bras Pneumol. 2012;38(4):511-7. http://dx.doi.org/10.1590/S1806-37132012000400014 PMid:22964936
6. Bierrenbach AL, Stevens AP, Gomes AB, Noronha EF, Glatt R, Carvalho CN, et al. Impact on tuberculosis incidence rates of removal of repeat notification records [Article in Portuguese]. Rev Saude Publica. 2007;41 Suppl 1:67-76. http://dx.doi.org/10.1590/S0034-89102007000800010 PMid:18038093
7. Murray CJ, Lopez AD. Estimating causes of death: new methods and global and regional applications for 1990. In: Murray CJ, Lopez AD, editors. The Global Burden of Disease: a comprehensive assessment of mortality and disability from diseases, injuries, and risk factors in 1990 and projected to 2020. Boston: Harvard School of Public Health; 1996. p. 117-200.
8. Escola Nacional de Saúde Pública. Fundação Oswaldo Cruz. Projeto Carga de Doença: relatório final do projeto estimativa da carga de doença do Brasil - 1998. Rio de Janeiro: FIOCRUZ; 2002.
9. Gledovic Z, Vlajinac H, Pekmezovic T, Grujicic-Sipetic S, Grgurevic A, Pesut D. Burden of tuberculosis in Serbia. Am J Infect Control. 2006;34(10):676-9. http://dx.doi.org/10.1016/j.ajic.2006.03.013 PMid:17161745
10. Murray CJ, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380(9859):2197-223. http://dx.doi.org/10.1016/S0140-6736(12)61689-4
11. Carvalho CN, Dourado I, Bierrenbach AL. Underreporting of the tuberculosis and AIDS comorbidity: an application of the linkage method. Rev Saude Publica. 2011;45(3):548-55. http://dx.doi.org/10.1590/S0034-89102011005000021 PMid:21503555
12. Galesi VM. Mortalidade por Tuberculose no Município de São Paulo: análise de uma década, 1986 a 1995 [dissertation]. São Paulo: Universidade de São Paulo; 1999.
13. World Health Organization. Global Burden of Disease 2004 update: disability weights for diseases and conditions. Geneva: WHO; 2004.
14. World Health Organization. Global Tuberculosis Control: WHO report 2011. Geneva: WHO; 2011.
15. Bierrenbach AL, Duarte EC, Gomes AB, Souza Mde F. Mortality trends due to tuberculosis in Brazil, 1980-2004 [Article in Portuguese]. Rev Saude Publica. 2007;41 Suppl 1:15-23. http://dx.doi.org/10.1590/S0034-89102007000800004 PMid:18038087
16. Hino P, da Costa-Júnior ML, Sassaki CM, Oliveira MF, Villa TC, dos Santos CB. Time series of tuberculosis mortality in Brazil (1980-2001). Rev Lat Am Enfermagem. 2007;15(5):936-41. http://dx.doi.org/10.1590/S0104-11692007000500009 PMid:18157445
17. Traebert J, Ferrer GC, Nazário NO, Schneider IJ, Silva RM. Temporal trends in tuberculosis-related morbidity and mortality in the state of Santa Catarina, Brazil, between 2002 and 2009. J Bras Pneumol. 2012;38(6):771-5.

http://dx.doi.org/10.1590/S1806-37132012000600014 PMid:23288124
18. Domingos MP, Caiaffa WT, Colosimo EA. Mortality, TB/HIV co-infection, and treatment dropout: predictors of tuberculosis prognosis in Recife, Pernambuco State, Brazil. Cad Saude Publica. 2008;24(4):887-96. http://dx.doi.org/10.1590/S0102-311X2008000400020 PMid:18392367
19. Cortezi MD, Silva MV. Abandono do tratamento da tuberculose em pacientes co-infectados com HIV em Itajaí, Santa Catarina, 1999 – 2004 Bol Pneumol Sanit. 2006;14(3):145-52.
20. Silveira MP, de Adorno RF, Fontana T. Profile of patients with tuberculosis: evaluation of the Brazilian national tuberculosis control program in Bagé, Brazil. J Bras Pneumol. 2007;33(2):199-205. http://dx.doi.org/10.1590/S1806-37132007000200015 PMid:17724540
21. Coelho AG, Zamarioli LA, Perandones CA, Cuntiere I, Waldman EA. Characteristics of pulmonary tuberculosis in a hyperendemic area: the city of Santos, Brasil. J Bras Pneumol. 2009;35(10):998-1007. PMid:19918633
22. Chirinos NEC, Meirelles BHS. Fatores associados ao abandono do tratamento da tuberculose: Uma revisão integrativa. Texto Contexto- Enferm. 2011;20(3):599-406.

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Empyema and bacteremic pneumococcal pneumonia in children under five years of age*,**

Empiema e pneumonia pneumocócica bacterêmica em menores de cinco anos de idade

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Abstract

We compared bacteremic pneumococcal pneumonia (BPP) and pneumococcal empyema (PE), in terms of clinical, radiological, and laboratory findings, in under-fives. A cross-sectional nested cohort study, involving under-fives (102 with PE and 128 with BPP), was conducted at 12 centers in Argentina, Brazil, and the Dominican Republic. Among those with PE, mean age was higher; disease duration was longer; and tachypnea, dyspnea, and high leukocyte counts were more common. Among those with BPP, fever and lethargy were more common. It seems that children with PE can be distinguished from those with BPP on the basis of clinical and laboratory findings. Because both conditions are associated with high rates of morbidity and mortality, prompt diagnosis is crucial.

Keywords: Empyema, pleural; Pneumonia, pneumococcal; Pneumococcal infections.

Resumo

Comparamos crianças menores de cinco anos com pneumonia pneumocócica bacterêmica (PPB) àquelas com empiema pneumocócico (EP) quanto aos achados clínicos, radiológicos e laboratoriais. Um estudo de coorte aninhado transversal, com 102 crianças com EP e 128 com PPB, foi realizado em 12 centros na Argentina, no Brasil e na República Dominicana. Nas crianças com EP, a média de idade e a duração da doença foram maiores. Taquipneia, dispneia e contagem de leucócitos alta foram mais comuns nas crianças com EP; febre e letargia foram mais comuns naquelas com PPB. Parece possível distinguir crianças com EP de crianças com PPB a partir de achados clínicos e laboratoriais. Como essas duas doenças estão associadas a altas taxas de morbidade e mortalidade, o diagnóstico rápido é crucial.

Descritores: Empiema pleural; Pneumonia pneumocócica; Infecções pneumocócicas.

Streptococcus pneumoniae is widely recognized as the leading cause of community-acquired pneumonia (CAP)-related mortality during hospitalization, as well as being the most common cause of empyema in children. The incidence of complicated pneumococcal CAP (CP-CAP) has been reported to be increasing worldwide.[1] In Scottish children in the 1-4 year age bracket, there was a tenfold increase in empyema admissions in the period between the 1980s and the year

*Study carried out at the University of São Paulo School of Public Health, São Paulo, Brazil; the Federal University of Bahia School of Medicine, Salvador, Brazil; the Pedro de Elizalde Children's Hospital, Buenos Aires, Argentina; the Santa Casa School of Medical Sciences in São Paulo, São Paulo, Brazil; the Durand Municipal Hospital, Buenos Aires, Argentina; the Martagão Gesteira Institute of Pediatrics and Child Care, Rio de Janeiro, Brazil; the Center for Meningitis, Pneumonia, and Pneumococcal Infections, Department of Bacteriology, Adolfo Lutz Institute, São Paulo, Brazil; the Pernambuco Mother and Child Institute, Recife, Brazil; the Dr. Robert Reid Cabral Children's Hospital, Santo Domingo, Dominican Republic; the Department of Child and Adolescent Health and Development, Pan American Health Organization, Washington, DC, USA; and the Department of Pediatric Pulmonology, Federal University of Minas Gerais *Hospital das Clínicas*, Belo Horizonte, Brazil.
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2005.[2] This increase might be related to host susceptibility, individual characteristics, and pathogen virulence.

Few studies have investigated the characteristics of CP-CAP, especially those of CP-CAP associated with pleural empyema or bacteremia—although few cases of pneumococcal pneumonia are bacteremic—in children under 5 years of age, who are at the highest risk of death from CAP. Bacteremic pneumococcal pneumonia (BPP) is considered an advanced stage of severe pneumococcal pneumonia, in which early recognition and appropriate management can have a favorable impact on the outcome.[3] Given that pleural empyema and BPP are potentially severe, it is important to recognize their clinical peculiarities in order to provide early and appropriate management.

In a recent study of hospitalized CAP patients, the prevalence rates of pleural effusion and empyema were reported to be 27% and 17%, respectively.[3] In another study, empyema was found in 83 (11%) of 767 children hospitalized with CAP; in comparison with the children with CAP without empyema, those with empyema were older, had longer symptomatic periods, and were more likely to receive nonsteroidal anti-inflammatory drugs.[4] The objective of the present study was to compare children under 5 years of age with BPP and those with pneumococcal empyema (PE) in terms of their clinical, radiological, and laboratory features.

A cross-sectional nested cohort study was conducted at 12 centers in Argentina, Brazil, and the Dominican Republic and included 2,536 children 3-59 months of age hospitalized with severe CAP, the results having been published elsewhere.[5] On admission, blood cultures and, when appropriate, pleural fluid cultures were performed. S. pneumoniae was isolated from 283 children by standard procedures used in local referral laboratories. Most (90%) of the children lived in urban settings, and none had received the conjugate pneumococcal vaccine or steroidal/nonsteroidal anti-inflammatory drugs. Cases of BPP were defined as those in which S. pneumoniae was isolated from blood culture. Cases of PE were defined as those in which S. pneumoniae was isolated from pleural fluid culture.

The exclusion criteria were as follows: showing signs of very severe pneumonia (including severe malnutrition, stridor in a calm child, unconsciousness, convulsions, nasal flaring, and central cyanosis); and presenting with concurrent infections. Patients with concomitant PE and BPP (n = 3) and those with pleural effusion of unknown cause (n = 50) were also excluded.

A favorable response to the initial treatment (i.e., conventional doses of intravenous ampicillin or penicillin G for BPP and PE patients alike) was defined as unequivocal clinical improvement within the first 48 h after hospital admission; conversely, treatment failure was defined as no improvement (persistent fever—body temperature being measured at least every 6 h—tachypnea, difficulty breathing, or hypoxemia) after at least 48 h of antibiotic therapy or deterioration during antimicrobial therapy.[5] Demographic, clinical, radiological, and laboratory data were obtained on admission. In addition, the length of hospital stay and the treatment outcome were recorded. Descriptive statistics were calculated, and two multiple logistic regression models were used, both of which were controlled for age. One of the models included variables obtained on admission and the other included variables obtained during hospitalization.

The present study included 230 children under 5 years of age (102 children with PE and 128 children with BPP). There was no significant difference between the two groups in terms of antibiotic use prior to hospital admission ($p = 0.23$). Table 1 displays the frequency distribution and the comparison (multivariate analysis) of the two groups of children on admission and during hospitalization.

In brief, our logistic regression analysis showed that, on hospital admission, children with PE were older and presented with a longer symptomatic period before hospitalization. In addition, tachypnea, difficulty breathing, and a leukocyte count > 15,000 cells/mm^3 were more common in those children. Persistent fever was one of the most common findings during the first days of hospitalization, requiring further investigation (chest X-ray, chest ultrasound, or both). Fever (axillary temperature > 37.5°C) and lethargy at diagnosis/baseline tended to be more common in the children with BPP. The hospital stay tended to be longer for the children with PE ($p < 0.001$; data not shown).

In the children with PE, the most common serotypes were 14, 1, 6B, 3, 9V, 19A, and 5,

Table 1 - Comparison (multivariate analysis) of children with pneumococcal empyema and those with bacteremic pneumococcal pneumonia on admission and during hospitalization.

Characteristic	PE (n = 102)	BPP (n = 128)	Adjusted OR (95% CI)	p
On admission				
Age (months)[a]	19 (12-33)	13 (9-22)	1.03 (1.00-1.05)	0.01
Duration of disease[b]				
≤ 3 days	17.7	34.4	1	0.013
4-6 days	39.2	35.1	2.84 (1.23-6.58)	
≥ 7 days	43.1	30.5	3.12 (1.35-7.20)	
Tachypnea[b,c]	91.2	75.6	4.16 (1.54-11.22)	0.005
Difficulty breathing[b]	87.9	70.9	3.61 (1.51-8.63)	0.004
Body temperature > 37.5°C on admission[b]	42.4	68.2	0.32 (0.17-0.63)	0.001
Lethargy[b]	53.5	67.7	0.35 (0.17-0.71)	0.004
Leukocyte count > 15,000 cells/mm^3[b]	48.5	29.8	2.13 (1.10-4.13)	0.02
During hospitalization				
Difficulty breathing on the 3rd day[b]	57.6	27.0	2.9 (1.52-5.56)	0.001
Body temperature (°C) on the 3rd day[a]	37.6 (37.0-38.8)	37.0 (36.6-38.0)	1.65 (1.05-2.59)	0.028
Treatment failure[b]	17.6	12.5	0.39 (0.14-1.07)	0.06
Length of hospitalization[a]	11 (7-15)	7 (5-10.5)	1.09 (1.02-1.17)	0.004

PE: pneumococcal empyema; and BPP: bacteremic pneumococcal pneumonia. [a]Values expressed as median (interquartile range). [b]Values expressed as %. [c]RR > 50 breaths/min in the children 3-11 months of age and > 40 breaths/min in those ≥ 12 months of age.

accounting for 92.4% of all serotypes in those children. In the children with BPP, the most common serotypes were 14, 6B, 5, 1, 6A, 9V, and 19F, accounting for 84.9% of all serotypes in those children. In other words, serotypes 1, 5, 6B, and 14 were found in both PE and BPP, whereas serotypes 6A, 9V, 19A, and 19F were found in either PE or BPP. It is of note that serotypes 6A and 19A are not included in the 10-valent pneumococcal conjugate vaccine currently used in Brazil.

To the best of our knowledge, the present study is the first to have focused specifically on BPP and PE in children under 5 years of age. Therefore, the results presented herein cannot be compared with those of other studies. In fact, our analyses showed that demographic characteristics, clinical features, and hematologic findings (i.e., leukocyte counts) are likely to be quite different between children with BPP and those with PE.

Although our objectives and methods were different from those of François et al.,[4] some of the results were similar between the two studies. François et al. studied 767 children with CAP and found that 83 (11%) had empyema.[4] The children with CAP and empyema were older and had a longer symptomatic period in comparison with those with CAP without empyema.[4] Interestingly, the length of hospital stay found in the present study was quite similar to that reported in a study involving 33 Brazilian children with empyema (i.e., 12 days).[6] In addition, serotype 1 was one of four serotypes found in both PE and BPP (i.e., 14, 1, 6B, and 5), a finding that is consistent with those of the study by François et al.,[4] which was conducted in a developed country.

In conclusion, our study investigated CAP patients under 5 years of age and showed clinical and laboratory findings at admission and during the first three days of hospitalization. Our findings can help clinicians and pediatricians to distinguish children with PE from those with BPP. Because these two critical conditions are associated with high rates of morbidity and mortality, prompt clinical, laboratory, and radiological diagnosis is crucial for appropriate management.

References

1. Grijalva CG, Nuorti JP, Zhu Y, Griffin MR Increasing incidence of empyema complicating childhood community-acquired pneumonia in the United States. Clin Infect Dis. 2010;50(6):805-13. http://dx.doi.org/10.1086/650573 PMid:20166818
2. Roxburgh CS, Youngson GG, Townend JA, Turner SW. Trends in pneumonia and empyema in Scottish children

in the past 25 years. Arch Dis Child. 2008;93(4):316-8. http://dx.doi.org/10.1136/adc.2007.126540 PMid:18006562
3. Calado C, Nunes P, Pereira L, Nunes T, Barreto C, Bandeira T. Are there any differences in the community acquired pneumonias admitted to hospital over the past decade? Rev Port Pneumol. 2010;16(2):287-305. PMid:20437005
4. François P, Desrumaux A, Cans C, Pin I, Pavese P, Labarère J Prevalence and risk factors of suppurative complications in children with pneumonia. Acta Paediatr. 2010;99(6):861-6. http://dx.doi.org/10.1111/j.1651-2227.2010.01734.x PMid:20178517
5. Cardoso MR, Nascimento-Carvalho CM, Ferrero F, Berezin EN, Ruvinsky R, Camargos PA, et al. Penicillin-resistant pneumococcus and risk of treatment failure in pneumonia. Arch Dis Child. 2008;93(3):221-5. http://dx.doi.org/10.1136/adc.2006.111625 PMid:17848490
6. Amorim PG, Morcillo AM, Tresoldi AT, Fraga Ade M, Pereira RM, Baracat EC. Factors associated with complications of community-acquired pneumonia in preschool children. J Bras Pneumol. 2012;38(5):614-21. http://dx.doi.org/10.1590/S1806-37132012000500011 PMid:23147054

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Assessment of ICU readmission risk with the Stability and Workload Index for Transfer score*

Avaliação de riscos de readmissão em UTI através do escore *Stability and Workload Index for Transfer*

Daiane Ferreira Oakes, Ingrid Nemitz Krás Borges, Luiz Alberto Forgiarini Junior, Marcelo de Mello Rieder

Abstract

Patient discharge from the ICU is indicated on the basis of clinical evidence and the result of strategies aimed at improving health care. Nevertheless, some patients might be discharged too early. We attempted to identify risk factors for unplanned ICU readmission, using a score for risk assessment, designated the Stability and Workload Index for Transfer (SWIFT) score. We evaluated 100 patients discharged from an ICU and found that the SWIFT score can be used as a tool for improving the assessment of ICU patients and the appropriateness of ICU discharge, thus preventing readmission.

Keywords: Intensive care units; Risk factors; Patient readmission.

Resumo

A alta da UTI é indicada com base em evidências clínicas e resultados de estratégias que objetivam melhorar o atendimento. No entanto, os pacientes podem ser submetidos a alta precoce. Objetivamos identificar fatores de risco para a readmissão não planejada na UTI, através de um escore de avaliação dos riscos denominado *Stability and Workload Index for Transfer* (SWIFT). Foram avaliados 100 pacientes com alta de uma UTI e verificamos que o escore SWIFT pode ser uma possível ferramenta para uma melhor avaliação do paciente e adequação da alta da UTI, evitando sua readmissão.

Descritores: Unidades de terapia intensiva; Fatores de risco; Readmissão do paciente.

Introduction

The best timing for ICU discharge is determined on the basis of clinical evidence that is usually subjective. The process of discharging a patient from the ICU involves careful evaluation of disease severity and patient clinical status. Therefore, there is a need to evaluate tools for assessing the risk of ICU readmission.[1,2]

In many critically ill patients, clinical status deterioration or death occurs shortly after ICU discharge.[3] Studies have shown that the decision regarding patient discharge from the ICU also depends on organizational factors, such as workload and the number of beds available.[4,5] In addition, early discharge accounts for 22-44% of all cases of ICU readmission, mortality being higher in such cases.[6]

The objective of the present study was to identify risk factors for unplanned ICU readmission by using a risk assessment scale designated the Stability and Workload Index for Transfer (SWIFT) score.

This was a prospective cohort study conducted in the Central ICU of the Santa Clara Hospital, which is part of the Santa Casa Hospital Complex, located in the city of Porto Alegre, Brazil. Between September of 2008 and January of 2009, we evaluated 156 patients who had been discharged from the ICU, who met the inclusion criteria, and who agreed to participate in the present study.

The inclusion criteria were as follows: being over 18 years of age; having stayed in the ICU for

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more than 24 h; and having been followed during the ICU stay, at discharge, and at readmission (when applicable). Clinical features, clinical diagnosis, length of ICU stay, and time to readmission were analyzed. Acute Physiology and Chronic Health Evaluation II (APACHE II) and SWIFT scores were calculated. The values of SWIFT score variables PaO_2, $PaCO_2$, FiO_2, and PaO_2/FiO_2 were those obtained in the most recent arterial blood gas analysis. Patients who died during their ICU stay and those who were transferred from the hospital in which the study was conducted were excluded.

The SWIFT score is a risk assessment score that measures the extent to which the conditions for ICU discharge are appropriate. It ranges from 0 to 64, a higher score translating to a higher risk of ICU readmission. The SWIFT score is practical and easy to use.[7] The ICU patients investigated in the present study were divided into two groups: the readmission group, comprising those who were readmitted to the ICU; and the non-readmission group, comprising those who were not.

The present study was approved by the Research Ethics Committees of the Santa Casa Hospital Complex and the Porto Alegre Institute Methodist University Center. All patients or their legal guardians gave written informed consent.

Quantitative variables were expressed as mean and standard deviation, whereas qualitative variables were expressed as absolute and relative frequencies. In order to compare the variables between the two groups, we used the Mann-Whitney U test. For all tests, the level of significance was set at 5%. In order to determine the risk of readmission, we calculated the area under the ROC curve for the SWIFT score. We used the Statistical Package for the Social Sciences, version 16.0 (SPSS Inc., Chicago, IL, USA).

During the data collection period, 156 patients were included in the initial sample. However, 56 patients were excluded because they died during their ICU stay. The final study sample consisted of 100 patients who stayed in the ICU for more than 24 h and then were discharged. Of those 100 patients, 9 were readmitted. The general characteristics of the sample are shown in Table 1.

The SWIFT score was significantly higher in the readmission group than in the non-readmission group (p = 0.001). With the objective of predicting ICU readmission, we calculated the area under the ROC curve for the SWIFT score and found an area of 0.76 (95% CI: 0.619-0.918). We also found a significant difference between the non-readmission and readmission groups in terms of the Glasgow Coma Scale score (p = 0.001; Table 2).

Nine patients (9%) were readmitted to the ICU. The mean time to readmission was 5.3 ± 5.5 days. Of the readmitted patients, 5 (55.6%) were readmitted in less than 48 h. Five patients died after having been readmitted to the ICU, 2 (22.2%) were transferred to other hospitals, and only 2 (22.2%) were discharged.

The hospital stay was longer in the readmission group (17 ± 24 days) than in the non-readmission group (13 ± 21 days), the difference being statistically significant (p = 0.007).

The main finding of the present study was that the SWIFT score was higher and the hospital stay was longer in the patients who were readmitted to the ICU than in those who were not.

We used the SWIFT score, previously validated by Gajic et al.[7] The SWIFT score assesses PaO_2, FiO_2, and $PaCO_2$, among other parameters. When

Table 1 - General characteristics of the patients included in the present study.[a]

Characteristics	Non-readmission group	Readmission group
Age, years[b]	59.36 ± 16.88	78.8 ± 9.79
Gender		
Male	48 (52.7)	3 (33.3)
Female	43 (47.3)	6 (66.7)
Type of health insurance		
Public	58 (64.4)	4 (44.4)
Private	33 (35.6)	5 (55.6)
Race		
White	77 (84.6)	9 (100)
Black	12 (13.2)	-
Mulatto	2 (2.2)	-
Physical therapy		
Yes	65 (71.4)	9 (100)
No	26 (28.6)	-
APACHE II score[b]	20.91 ± 6.81	20.77 ± 5.95
Reason for readmission		
Acute respiratory failure	-	4 (44.4)
Cardiopulmonary arrest	-	3 (33.3)
Sepsis	-	2 (22.2)
Length of ICU stay, days[b]	11 ± 21	7 ± 25

APACHE II: Acute Physiology and Chronic Health Evaluation II.
[a]Values expressed as n (%), except where otherwise indicated.
[b]Values expressed as mean ± SD.

Table 2 - Comparison of the study variables between the two groups of patients under study.[a]

Variable	Non-readmission group	Readmission group
Patient referral source		
Hospital ward	35 (38.5)	4 (44.4)
Emergency room	23 (25.3)	1 (11.1)
Surgical ward	21 (23.1)	2 (22.2)
Another hospital	12 (13.2)	2 (22.2)
Reason for hospitalization		
Acute respiratory failure	22 (24.4)	3 (33.3)
Immediate postoperative period	21 (23.3)	2 (22.2)
Sepsis	12 (13.3)	-
Stroke	8 (8.9)	-
Decompensated congestive heart failure	5 (5.6)	1 (11.1)
Hypovolemic shock	5 (5.6)	1 (11.1)
Renal failure	4 (4.4)	1 (11.1)
Bronchopneumonia	3 (3.3)	-
Other reasons	10 (11.1)	1 (11.1)
Glasgow Coma Scale score[b]	13.60 ± 1.03	11.66 ± 1.32*
FiO_2[b]	0.48 ± 0.29	0.23 ± 0.35
PaO_2, mmHg[b]	112.42 ± 41.43	86.28 ± 35.24
PaO_2/FiO_2[b]	489.44 ± 188.44	373.28 ± 118.72
$PaCO_2$, mmHg[b]	37.77 ± 10.16	36.82 ± 2.77
SWIFT score[b]	13.81 ± 7.85	23.50 ± 8.75*

SWIFT: Stability and Workload Index for Transfer. [a]Values expressed as n (%), except where otherwise indicated. [b]Values expressed as mean ± SD. *p = 0.001.

we analyzed those variables in isolation, we found no significant differences between the two groups of patients.

Several studies have shown that mortality is significantly higher and hospital stays are significantly longer in patients who are readmitted to the ICU.[8-10] In our study, the hospital stay was longer for the patients who were readmitted to the ICU than for those who were not.

Nishi et al. evaluated 10,840 ICU patients and found that 97 had been readmitted to the ICU; of those 97 patients, 5% had been readmitted because of early discharge. In our study, 5 patients were readmitted to the ICU for that reason.[11]

Kastrup et al. attempted to validate the use of the SWIFT score in heterogeneous ICU populations (a total of 7,175 patients) and found that the SWIFT score is poor at predicting ICU readmission, having found an area under the ROC curve of 0.581.[12] Unlike Kastrup et al., we found an area under the ROC curve of 0.76, showing that the SWIFT score was good at predicting ICU readmission in our study population.

Ounes et al. sought to evaluate independent predictors of ICU readmission and develop an analytical model of mortality and readmission after discharge. The authors evaluated 3,462 patients and found that independent risk factors for ICU readmission included disease severity and ICU discharge at night; the authors also found that the rate of ICU readmission within 7 days after discharge was 3%.[13] In the present study, there was no difference between the two groups of patients regarding disease severity as measured by APACHE II scores.

As shown in the present study, the SWIFT score can be used as a tool for improving the assessment of ICU patients and the appropriateness of ICU discharge, thus preventing readmission.

References

1. Skowronski GA. Bed rationing and allocation in the intensive care unit. Curr Opin Crit Care. 2001;7(6):480-4. http://dx.doi.org/10.1097/00075198-200112000-00020 PMid:11805556
2. Alban RF, Nisim AA, Ho J, Nishi GK, Shabot MM. Readmission to surgical intensive care increases severity-adjusted patient mortality. J Trauma. 2006;60(5):1027-31. http://dx.doi.org/10.1097/01.ta.0000218217.42861.b7 PMid:16688065
3. Campbell AJ, Cook JA, Adey G, Cuthbertson BH. Predicting death and readmission after intensive care discharge. Br J Anaesth. 2008;100(5):656-62. http://dx.doi.org/10.1093/bja/aen069 PMid:18385264

4. Metnitz PG, Fieux F, Jordan B, Lang T, Moreno R, Le Gall JR. Critically ill patients readmitted to intensive care units--lessons to learn? Intensive Care Med. 2003;29(2):241-8. PMid:12594586
5. Ho KM, Knuiman M. Bayesian approach to predict hospital mortality of intensive care readmissions during the same hospitalisation. Anaesth Intensive Care. 2008;36(1):38-45. PMid:18326130
6. Snow N, Bergin KT, Horrigan TP. Readmission of patients to the surgical intensive care unit: patient profiles and possibilities for prevention. Crit Care Med. 1985;13(11):961-4. http://dx.doi.org/10.1097/00003246-198511000-00037 PMid:4053645
7. Gajic O, Malinchoc M, Comfere TB, Harris MR, Achouiti A, Yilmaz M, et al. The Stability and Workload Index for Transfer score predicts unplanned intensive care unit patient readmission: initial development and validation. Crit Care Med. 2008;36(3):676-82. http://dx.doi.org/10.1097/CCM.0B013E318164E3B0 PMid:18431260
8. Franklin C, Jackson D. Discharge decision-making in a medical ICU: characteristics of unexpected readmissions. Crit Care Med. 1983;11(2):61-6. http://dx.doi.org/10.1097/00003246-198302000-00001
9. Kirby EG, Durbin CG. Establishment of a respiratory assessment team is associated with decreased mortality in patients re-admitted to the ICU. Respir Care. 1996;41:903-7.
10. Durbin CG Jr, Kopel RF. A case-control study of patients readmitted to the intensive care unit. Crit Care Med. 1993;21(10):1547-53. http://dx.doi.org/10.1097/00003246-199310000-00025
11. Nishi GK, Suh RH, Wilson MT, Cunneen SA, Margulies DR, Shabot MM. Analysis of causes and prevention of early readmission to surgical intensive care. Am Surg. 2003;69(10):913-7. PMid:14570374
12. Kastrup M, Powollik R, Balzer F, Röber S, Ahlborn R, von Dossow-Hanfstingl V, et al. Predictive ability of the stability and workload index for transfer score to predict unplanned readmissions after ICU discharge. Crit Care Med. 2013;41(7):1608-15. http://dx.doi.org/10.1097/CCM.0b013e31828a217b PMid:23660731
13. Ouanes I, Schwebel C, Français A, Bruel C, Philippart F, Vesin A, et al. A model to predict short-term death or readmission after intensive care unit discharge. J Crit Care. 2012;27(4):422.e1-9. doi: 10.1016/j.jcrc.2011.08.003.

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Adalimumab-induced acute interstitial lung disease in a patient with rheumatoid arthritis*

Doença pulmonar intersticial aguda induzida por adalimumabe em paciente com artrite reumatoide

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Abstract

The use of immunobiological agents for the treatment of autoimmune diseases is increasing in medical practice. Anti-TNF therapies have been increasingly used in refractory autoimmune diseases, especially rheumatoid arthritis, with promising results. However, the use of such therapies has been associated with an increased risk of developing other autoimmune diseases. In addition, the use of anti-TNF agents can cause pulmonary complications, such as reactivation of mycobacterial and fungal infections, as well as sarcoidosis and other interstitial lung diseases (ILDs). There is evidence of an association between ILD and the use of anti-TNF agents, etanercept and infliximab in particular. Adalimumab is the newest drug in this class, and some authors have suggested that its use might induce or exacerbate preexisting ILDs. In this study, we report the first case of acute ILD secondary to the use of adalimumab in Brazil, in a patient with rheumatoid arthritis and without a history of ILD.

Keywords: Lung diseases, interstitial; Arthritis, rheumatoid; Antirheumatic agents; Antibodies, monoclonal, humanized/adverse effects.

Resumo

O uso de imunobiológicos no tratamento das doenças autoimunes é cada vez mais frequente na prática médica. Terapias anti-TNF têm sido cada vez mais utilizadas nas doenças autoimunes refratárias, especialmente na artrite reumatoide, com resultados promissores. Entretanto, o uso dessas terapias está relacionado ao aumento do risco do desenvolvimento de outras doenças autoimunes. Adicionalmente, o uso de agentes anti-TNF pode determinar repercussões pulmonares, como a reativação de infecções por micobactérias e fungos e o desenvolvimento de sarcoidose e de outras doenças pulmonares intersticiais (DPIs). A associação de DPI e uso dos agentes anti-TNF, em especial infliximabe e etanercepte, já foi descrita. O adalimumabe é a mais nova droga dessa classe, e algumas publicações sugerem que seu uso pode determinar a indução ou mesmo a exacerbação de DPIs preexistentes. Neste estudo, relatamos o primeiro caso de DPI aguda secundária à utilização de adalimumabe, em uma paciente portadora de artrite reumatoide sem DPI prévia no Brasil.

Descritores: Doenças pulmonares intersticiais; Artrite reumatoide; Antirreumáticos; Anticorpos monoclonais humanizados/efeitos adversos.

Introduction

The use of immunobiological agents for the treatment of autoimmune diseases is increasing in medical practice. Anti-TNF therapies and therapies with B-cell-depleting agents (rituximab) have been increasingly used in refractory autoimmune diseases, especially rheumatoid arthritis (RA), systemic sclerosis, and systemic lupus erythematosus, with promising results. The TNF is an interleukin secreted by activated macrophages and T cells as a common pathway in a series of inflammatory, autoimmune, or neoplastic responses; its blockade, whether in the form of blockade of its receptors or in the form of soluble antibodies, decreases adhesion molecule expression on the endothelial surface, decreases leukocyte migration, and inhibits the production

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of other inflammatory cytokines. However, the use of such therapies has been associated with an increased risk of developing other autoimmune diseases, such as systemic lupus erythematosus, autoimmune hepatitis, thyroiditis, and cutaneous vasculitis. According to the literature, the use of anti-TNF agents particularly in the lung is little effective in controlling interstitial lung disease (ILD) secondary to collagenosis, and can lead to other complications, such as reactivation of mycobacterial and fungal infections, as well as sarcoidosis and other ILDs.[1]

There is evidence of an association between ILD and the use of anti-TNF agents, etanercept and infliximab in particular.[2] Adalimumab is the newest drug in this class, and, because it is a humanized monoclonal antibody, it would have the potential advantage of being less immunogenic than its precursors. However, although adalimumab is infrequently used, some authors have suggested that its use might induce or exacerbate preexisting ILDs.[3-9]

The objective of the present study was to report the first case of acute ILD secondary to the use of adalimumab in Brazil, in a patient with RA and without a history of ILD.

Case report

A 62-year-old female patient with a 20-year history of RA had been on methotrexate, leflunomide, and prednisone. Because the articular inflammatory process persisted, we decided to start the patient on adalimumab, continuing her on methotrexate. A chest X-ray showed no changes suggestive of previous tuberculosis or signs of incipient ILD; and the intradermal (PPD) test for tuberculosis was negative (0 mm). One week after receiving the second dose of adalimumab (40 mg weekly), the patient started experiencing dry cough, dyspnea on moderate exertion, and daily fever (38°C). At that point, the results of chest X-ray, physical examination, and laboratory tests, including blood workup, were normal—hemoglobin, 13.1 g/dL; hematocrit, 39.2%; 8,380 leukocytes (75% neutrophils, 0.4% eosinophil, 9.8% lymphocytes); and 355,000 platelets, except for an increase in inflammatory markers (C-reactive protein, 326 mg/dL; reference value < 3 mg/dL) and in ESR (67 mm, reference value < 20.2 mm). Sputum smears for AFB and blood cultures were negative. The patient was started on empiric treatment with levofloxacin; however, she continued to have fever and dyspnea. A HRCT scan of the chest, performed two weeks after symptom onset, revealed ground-glass opacities, predominantly in the upper and middle lung fields, associated with areas of smooth interlobular septal thickening (Figure 1). Therefore, a presumptive diagnosis of ILD secondary to the use of adalimumab was made. We decided to discontinue the patient from the anti-TNF agent and methotrexate and to continue her on low-dose prednisone (5 mg/day). The patient showed progressive reduction in dyspnea, remission of fever, and normalization of inflammatory markers, without reactivation of the articular inflammatory process. Three weeks

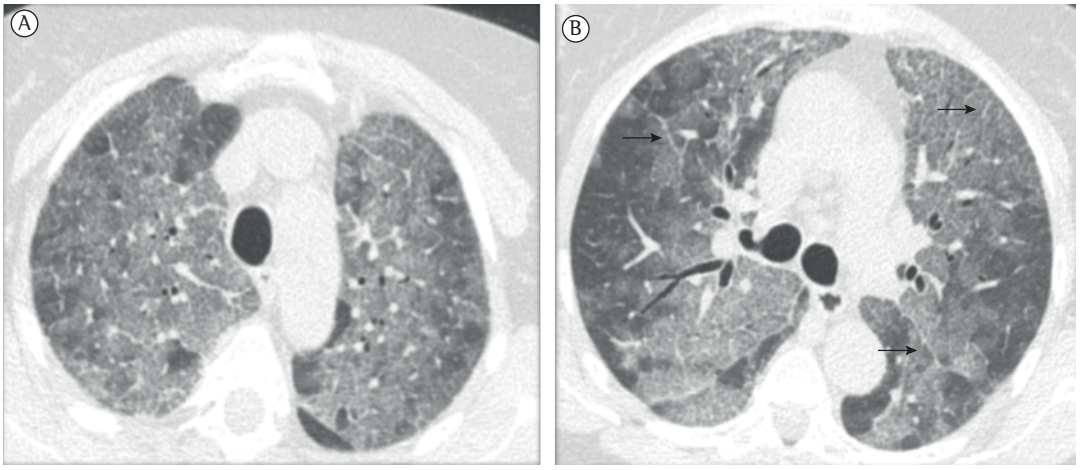

Figure 1 - HRCT scan of the chest showing pulmonary ground-glass opacities, predominantly in the upper lobes, in A, and in the central regions, in B, associated with areas of smooth interlobular septal thickening (arrows).

after the onset of the condition, the results of physical examination and spirometry were normal, with an SpO_2 of 98% on room air. A second HRCT, performed three weeks after symptom onset, showed near-complete resolution of the ground-glass areas (Figure 2).

Discussion

The pathogenesis of anti-TNF-agent-induced lung injury remains unknown; TNF is believed to exert a pro-fibrotic action by stimulating collagen synthesis by fibroblasts and myofibroblasts.[10] In addition, an increased Th2-type lymphocyte response,[7] the action of IFN-γ unopposed by TNF,[7] and the synergistic action of methotrexate are speculated to play a role in the development of lung injury.[8,9,11,12]

Clinical findings are nonspecific, and include dry cough, fever, and dyspnea,[2] which can be progressive or more intense after each administration of the medication.[6] Symptoms can appear from one month[9] to three and a half years after treatment initiation.[7] Findings on HRCT can include ground-glass opacities, foci of consolidation, reticulated patterns, and traction bronchiectasis.[6,8]

Attributing lung injury to drugs and, in the present case, to anti-TNF agents is a challenge. The diagnosis is usually presumptive, and the causal connection is determined by temporal association between drug initiation and symptom onset and by improvement after drug discontinuation, always after excluding other etiologies. In such patients, in the context of immunosuppression, infection should be considered as an important differential.[13] It should be borne in mind that the use of adalimumab has been associated with cases of pulmonary cryptococcosis[14] and disseminated mycobacteriosis.[15] In this clinical context, diffuse ground-glass opacities associated with intralobular septal thickening should also lead to the exclusion of other etiologies, such as viral infections or infections with *Pneumocystis jiroveci*,[16] alveolar hemorrhage, pulmonary congestion, and drug toxicity due to concomitant treatment with methotrexate. Bronchoscopy and bronchoalveolar lavage aid in the differential diagnosis.

In the largest sample of patients with lung injury secondary to anti-TNF therapy, 122 cases were reported (3 of which were secondary to adalimumab). The mean time to symptom onset was 26 weeks. The most common histological patterns were usual interstitial pneumonia, organizing pneumonia, diffuse alveolar damage, and even lymphocytic interstitial pneumonia. Of the cases that were followed up until the outcome was known, 40% experienced improvement in ILD, 25% had partial resolution of ILD, and 35% had no resolution of ILD, with death occurring in 29% of the patients. Predictors of poor prognosis were age > 65 years, late onset of symptoms, frequent use of other immunosuppressants (especially methotrexate), and a previous diagnosis of ILD.[2] Despite an isolated report of improvement in ILD with the use of this medication for RA,[9] it is currently recommended that adalimumab and

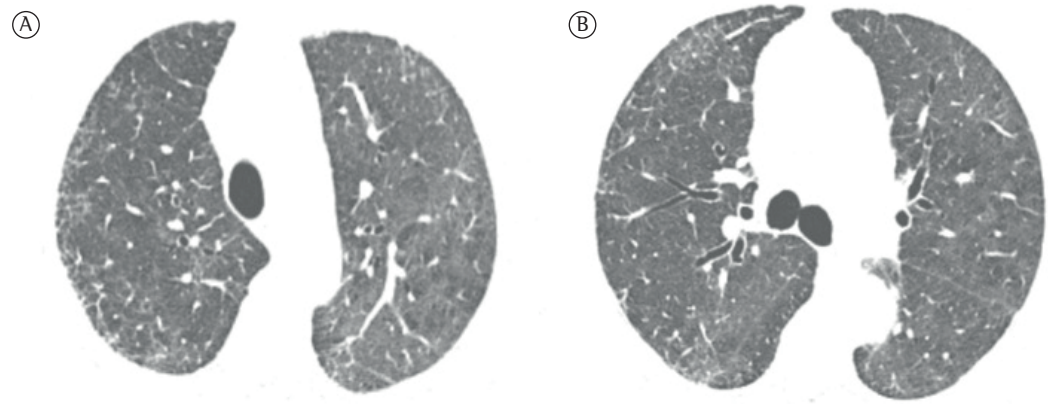

Figure 2 - HRCT scan of the chest performed three weeks after the onset of the condition. A comparative analysis of the slices shows significant spontaneous improvement in the ground-glass opacities, in relation to the first scan, in the upper lung fields, in A, and at the level of the main carina, in B. There remain faint ground-glass opacities together with slight reticular infiltrates in the subpleural regions, predominantly in the right hemithorax, especially in the middle lobe.

other anti-TNF drugs should not be contraindicated in patients with preexisting ILD or other lung diseases but that caution should be exerted.[1-3,10]

The course of cases of adalimumab-induced ILD can vary from complete remission after drug discontinuation alone to treatment refractoriness,[2,6] with rapid progression to death.[3] The use of corticosteroids or intravenous immunoglobulin, or both, should be considered in selected cases. Because of the potential severity of the patient's condition, we decided in favor of CT follow-up, with scans being performed within a short interval of each other despite the resulting radiation load.

Once it is confirmed that drug reaction has occurred, it is not recommended that the drug be reintroduced or even replaced with another drug belonging to the same class of anti-TNF agents.[2,10] Therefore, adalimumab, like other anti-TNF drugs, should always be considered in the list of drugs potentially causing lung injury.

References

1. Ramos-Casals M, Brito-Zerón P, Soto MJ, Cuadrado MJ, Khamashta MA. Autoimmune diseases induced by TNF-targeted therapies. Best Pract Res Clin Rheumatol. 2008;22(5):847-61. http://dx.doi.org/10.1016/j.berh.2008.09.008 PMid:19028367
2. Perez-Alvarez R, Perez-de-Lis M, Diaz-Lagares C, Pego-Reigosa JM, Retamozo S, Bove A, et al. Interstitial lung disease induced or exacerbated by TNF-targeted therapies: analysis of 122 cases. Semin Arthritis Rheum. 2011;41(2):256-64. http://dx.doi.org/10.1016/j.semarthrit.2010.11.002 PMid:21277618
3. Allanore Y, Devos-François G, Caramella C, Boumier P, Jounieaux V, Kahan A. Fatal exacerbation of fibrosing alveolitis associated with systemic sclerosis in a patient treated with adalimumab. Ann Rheum Dis. 2006;65(6):834-5. http://dx.doi.org/10.1136/ard.2005.044453 PMid:16699057 PMCid:PMC1798181
4. Huggett MT, Armstrong R. Adalimumab-associated pulmonary fibrosis. Rheumatology (Oxford). 2006;45(10):1312-3. http://dx.doi.org/10.1093/rheumatology/kel220 PMid:16935921
5. Schoe A, van der Laan-Baalbergen NE, Huizinga TW, Breedveld FC, van Laar JM. Pulmonary fibrosis in a patient with rheumatoid arthritis treated with adalimumab. Arthritis Rheum. 2006;55(1):157-9. http://dx.doi.org/10.1002/art.21716 PMid:16463430
6. Yamazaki H, Isogai S, Sakurai T, Nagasaka K. A case of adalimumab-associated interstitial pneumonia with rheumatoid arthritis. Mod Rheumatol. 2010;20(5):518-21. http://dx.doi.org/10.1007/s10165-010-0308-4 PMid:20467775
7. Dascalu C, Mrejen-Shakin K, Bandagi S. Adalimumab-induced acute pneumonitis in a patient with rheumatoid arthritis. J Clin Rheumatol. 2010;16(4):172-4. http://dx.doi.org/10.1097/RHU.0b013e3181df8361 PMid:20511978
8. Reid JD, Bressler B, English J. A case of adalimumab-induced pneumonitis in a 45-year-old man with Crohn's disease. Can Respir J. 2011;18(5):262-4. PMid:21969926 PMCid:PMC3267602
9. Komiya K, Ishii H, Fujita N, Oka H, Iwata A, Sonoda H, et al. Adalimumab-induced interstitial pneumonia with an improvement of pre-existing rheumatoid arthritis-associated lung involvement. Intern Med. 2011;50(7):749-51. http://dx.doi.org/10.2169/internalmedicine.50.4748 PMid:21467710
10. Panopoulos ST, Sfikakis PP. Biological treatments and connective tissue disease associated interstitial lung disease. Curr Opin Pulm Med. 2011;17(5):362-7. http://dx.doi.org/10.1097/MCP.0b013e3283483ea5 PMid:21597375
11. Thavarajah K, Wu P, Rhew EJ, Yeldandi AK, Kamp DW. Pulmonary complications of tumor necrosis factor-targeted therapy. Respir Med. 2009;103(5):661-9. http://dx.doi.org/10.1016/j.rmed.2009.01.002 PMid:19201589 PMCid:PMC2743303
12. Golden MR, Katz RS, Balk RA, Golden HE. The relationship of preexisting lung disease to the development of methotrexate pneumonitis in patients with rheumatoid arthritis. J Rheumatol. 1995;22(6):1043-7. PMid:7674228
13. 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. http://dx.doi.org/10.1590/S1806-37132012000300002 PMid:22782597
14. Iwata T, Nagano T, Tomita M, Suehiro Y, Nakatsuka S, Kimura H, et al. Adalimumab-associated pulmonary cryptococcosis. Ann Thorac Cardiovasc Surg. 2011;17(4):390-3. http://dx.doi.org/10.5761/atcs.cr.10.01561 PMid:21881327
15. Yoo WH. Multiple organ tuberculosis of lung, pleura, and peritoneum in ankylosing spondylitis during adalimumab therapy. Rheumatol Int. 2012;32(3):787-90. http://dx.doi.org/10.1007/s00296-009-1357-x PMid:20049444
16. Kameda H, Tokuda H, Sakai F, Johkoh T, Mori S, Yoshida Y, et al. Clinical and radiological features of acute-onset diffuse interstitial lung diseases in patients with rheumatoid arthritis receiving treatment with biological agents: importance of Pneumocystis pneumonia in Japan revealed by a multicenter study. Intern Med. 2011;50(4):305-13. http://dx.doi.org/10.2169/internalmedicine.50.4508 PMid:21325762

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Add-on treatment with nebulized hypertonic saline in a child with plastic bronchitis after the Glenn procedure*,**

Tratamento adjuvante com nebulização de salina hipertônica em uma criança com bronquite plástica após operação de Glenn

Grzegorz Lis, Ewa Cichocka-Jarosz, Urszula Jedynak-Wasowicz, Edyta Glowacka

Abstract

Plastic bronchitis (PB), although a rare cause of airway obstruction, has mortality rates up to 50% in children after Fontan-type cardiac surgery. We present the case of an 18-month-old female patient with PB following pneumonia. At 6 months of age, the patient underwent the Glenn procedure due to functionally univentricular heart. Fiberoptic bronchoscopy revealed complete blockage of the left bronchus by mucoid casts. Pharmacotherapy consisted of glucocorticosteroids, azithromycin, and enalapril maleate. The child also received nebulized 3% NaCl solution, which proved to be beneficial. In children submitted to Fontan-type procedures, physicians must be alert for PB, which can be triggered by respiratory tract infection.

Keywords: Bronchitis; Heart defects, congenital; Saline solution, hypertonic.

Resumo

A bronquite plástica (BP), embora uma causa rara de obstrução de vias aéreas, apresenta taxas de mortalidade de até 50% em crianças submetidas a cirurgia cardíaca do tipo Fontan. Apresentamos o caso de uma menina de 18 meses de idade com BP secundária a pneumonia. Aos 6 meses de idade, a paciente havia sido submetida à operação de Glenn devido a coração funcionalmente univentricular. A fibrobroncoscopia revelou obstrução completa do bronco esquerdo por moldes mucoides. A farmacoterapia consistiu em glicocorticosteroides, azitromicina e maleate de enalapril. Adicionalmente, a criança recebeu nebulização de solução de NaCl a 3%, que provou ser benéfica. Em crianças submetidas a operações do tipo Fontan, devemos nos manter alerta quanto à BP, que pode ser desencadeada por infecção do trato respiratório.

Descritores: Bronquite; Cardiopatias congênitas; Solução salina hipertônica.

Introduction

Plastic bronchitis (PB), despite being a rare cause of airway obstruction, has a high mortality rate (up to 50%). Therefore, physicians should maintain a high level of clinical suspicion of PB, which is most often seen in children with congenital heart disease (CHD) after Fontan-type procedures. However, PB can also affect adults.[1] In addition, PB can occur due to pulmonary lymphatic abnormalities, respiratory tract allergies, infectious diseases, or acute chest syndrome in sickle cell disease.[2] Anecdotally, PB has been reported in cystic fibrosis patients and postoperatively in heart transplant patients.[3,4]

In the pathophysiology of PB due to CHD, Fontan circulation predisposes to dysfunction of membranes, leading to leakage of proteinaceous material into the airways. This can cause significant obstruction by the formation of branching gelatinous casts in the tracheobronchial tree. The casts might be either spontaneously expectorated or require bronchoscopy for their removal as a life-saving procedure. Death due to airway obstruction from a cast is not uncommon.[2] Clinical symptoms and X-ray findings are nonspecific and might mimic foreign body aspiration or severe asthma exacerbation. There are two known types of casts, differing histologically and in their composition[5]: type 1—inflammatory, associated with underlying inflammatory disease of the lung—consisting of fibrin with eosinophilic, neutrophilic, and lymphocytic infiltration; and type 2—acellular, associated with pulmonary hypertension and heart

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insufficiency due to CHD—consisting of mucin, with no infiltration. Because PB is rare, there are no specific recommendations for treatment, and therapeutic options are mainly based on individual experience.

Case report

We present the case of an 18-month-old female patient with PB following pneumonia. At 2 months of age, the patient was hospitalized due to pneumonia. At 6 months of age, she underwent a palliative bidirectional Glenn procedure (Fontan-type) due to CHD (double-inlet and double-outlet ventricle with common atrioventricular canal). The perioperative period was uneventful. Echocardiography at 12 and 18 months of age showed proper heart function (ejection fraction, 67%). At 18 months of age, she was again hospitalized due to pneumonia that remained unresolved after three courses of antibiotics in the home setting. Infiltration and atelectasis of the left upper lobe had been clinically suspected (because of dullness and diminished breath sounds over that region) and was confirmed by a chest X-ray. Blood pressure was normal. However, SpO_2 was approximately 50% (having previously been at 70-80%). In addition, hypogammaglobulinemia was detected. In the differential diagnosis, we excluded atopy, cystic fibrosis, immunodeficiency disorders, viral infections (with cytomegalovirus, Epstein-Barr virus, and pneumotropic viruses), and fungal infections (*Aspergillus* sp. and *Candida* sp.). Within a few days, her coughs were more productive and there was expectoration of small mucoid casts. Despite antibiotic treatment, gamma-globulin replacement therapy, oxygen therapy, and intensive chest physiotherapy, as well as the use of nebulized bronchodilators and mucolytics, there was no clinical improvement. On post-admission day 17, fiberoptic bronchoscopy (FB) revealed complete obliteration of the left bronchus. Application of suction allowed to remove bronchial casts, followed by bronchial lavage of that region (Figure 1). Cultures of the bronchial lavage fluid were negative for fungi and bacteria. Microscopic analysis of the material collected revealed type-1 bronchial casts. After the bronchoscopy, the inflammation of the left lobes was resolved. Treatment with azithromycin, systemic and inhaled steroids, [6] and enalapril maleate was initiated, as was the use of nebulized 3% NaCl solution plus a bronchodilator. One week after treatment initiation, a control FB revealed only small fragments of casts, which were removed easily and completely. On post-admission day 33, the patient was discharged.

Discussion

In children, PB is uncommon. In one study, Madsen et al. reviewed 56 well-documented cases of PB after cardiac surgery conducted prior to 2005.[2] Thereafter, two groups of authors described the cases of 32 adults and 22 children, respectively, in China.[7,8] In addition, two studies on PB were carried out in Poland.[9,10] To our knowledge, this is the first reported case of PB in a child with CHD in Poland. Our patient was 18 months old at admission, with moderately severe symptoms of PB, which differs from the two fatal cases of PB after a Glenn procedure cited by Madsen et al.[2] Patients with PB due to CHD tend to be younger and have a poorer prognosis than do those with PB due to other comorbidities. In our patient, PB occurred 9 months after the Glenn procedure and was triggered by a respiratory infection, which is in agreement with other reports.[2] The present case highlights the fact that PB should be considered in cyanotic children presenting with asymmetry on chest examination, a history of cardiac surgery, and moderately severe infectious respiratory symptoms. Spontaneously expectorated bronchial casts, as were those observed in the case reported here, usually substantiate the diagnosis. Hypothetically, the incidence of PB in children is likely to be underdiagnosed because of the difficulty in productive expectoration at this age. Bronchoscopy could be a diagnostic and treatment option in PB.[2] In our patient, we managed to remove the bronchial casts during the FB procedure. However, massive casts might require rigid bronchoscopy. Histological examination is important, although not always clinically relevant. In cases of overlapping infection after cardiac surgery, inflammatory casts might be present, as was exemplified in our patient. This is also in line with other reports, because respiratory tract infection in children might be coincidental or causative.[10] In the present case, the results of microscopic examination of the bronchial cast justified the modification of the treatment to the well-known options of azithromycin and systemic corticosteroids. Our patient benefited from the use of nebulized hypertonic saline (3%

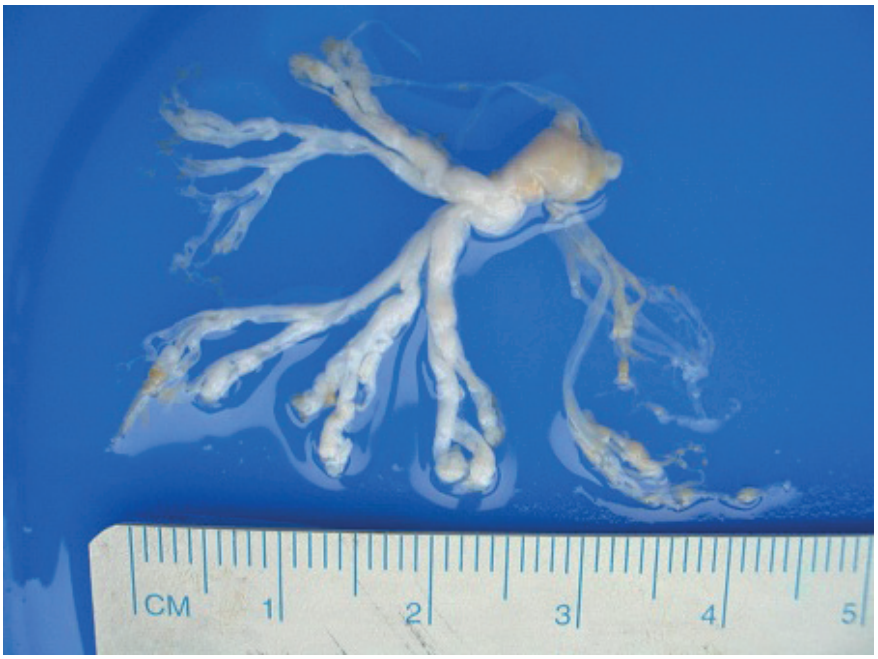

Figure 1 - Branching cast from the left bronchus.

NaCl), which, to our knowledge, was an empirical treatment reported for the first time in a patient with PB. Improvement in expectoration, lack of cast recurrence, and a positive outcome were observed. Other attempts, including the use of aerosolized urokinase, tissue plasminogen activator, and recombinant human DNase, as well as extracorporeal membrane oxygenation, have been reported anecdotally.[8] We did not introduce sildenafil citrate, which has been reported to be used successfully in combination with epoprostenol.[11]

In summary, children with a functionally univentricular heart after a Fontan-type procedure require constant vigilance on the part of physicians for PB, which can be triggered by respiratory tract infection. In some cases, FB might be suitable for the removal of casts. Because of the vast spectrum of underlying comorbidities, therapy should be individualized, and the use of nebulized hypertonic saline might be beneficial.

References

1. Ugurlucan M, Basaran M, Alpagut U, Tireli E. Bidirectional inferior vena cava-pulmonary artery shunt: can it be alternative for older patients presenting single ventricle heart disease in the third world countries? Arch Med Sci. 2008;4:1-6.
2. Madsen P, Shah SA, Rubin BK. Plastic bronchitis: new insight and classification scheme. Paediatric Respir Rev. 2005;6(4):292-300. http://dx.doi.org/10.1016/j.prrv.2005.09.001
3. ElMallah MK, Prabhakaran S, Chesrown SE. Plastic bronchitis: resolution after heart transplantation. Pediatr Pulmonol. 2011;46(8):824-5. http://dx.doi.org/10.1002/ppul.21432
4. Mateos-Corral D, Cutz E, Solomon M, Ratjen F. Plastic bronchitis as an unusual cause of mucus plugging in cystic fibrosis. Pediatr Pulmonol. 2009;44(9):939-40. http://dx.doi.org/10.1002/ppul.21063
5. Seear M, Hui H, Magee F, Bohn D, Cutz E. Bronchial casts in children: a proposed classification based on nine cases and a review of literature. Am J Respir Crit Care Med. 1997;155(1):364-70. http://dx.doi.org/10.1164/ajrccm.155.1.9001337
6. Do P, Randhawa I, Chin T, Parsapour K, Nussbaum E. Successful management of plastic bronchitis in a child post Fontan: case report and literature review. Lung. 2012;190(4):463-8. http://dx.doi.org/10.1007/s00408-012-9384-x
7. Dabo L, Qiyi Z, Jianwen Z, Zhenyun H, Lifeng Z. Perioperative management of plastic bronchitis in children. Int J Pediatr Otorhinolaryng. 2010;74(1):15-21. http://dx.doi.org/10.1016/j.ijporl.2009.09.028
8. Wang G, Wang Y, Luo F, Wang L, Jiang L, Wang L, et al. Effective use of corticosteroids in treatment of plastic bronchitis with hemoptysis in Chinese adults. Acta Pharmacol Sin. 2006;27(9):1206-12. http://dx.doi.org/10.1111/j.1745-7254.2006.00418.x
9. Sledziewska J, Załeska J, Wiatr E, Płodziszewska M, Załeska M, Pirozynski M, et al. Plastic bronchitis and mucoid impaction--uncommon disease syndromes with expectoration mucus plugs [Article in Polish]. Pneumonol Alergol Pol. 2001;69(1-2):50-61.
10. Krenke K, Krenke R, Krauze A, Lange J, Kulus M. Plastic bronchitis: an unusual cause of atelectasis. Respiration. 2010;80(2):146-7. http://dx.doi.org/10.1159/000243711

11. Haseyama K, Satomi G, Yasukochi S, Matsui H, Harada Y, Uchita S. Pulmonary vasodilation therapy with sildenafil citrate in a patient with plastic bronchitis after the Fontan procedure for hypoplastic left heart syndrome. J Thoracic Cardiovasc Surg. 2006;132(5):1232-3. http://dx.doi.org/10.1016/j.jtcvs.2006.05.067

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Tiotropium use and pulmonary function in patients with constrictive bronchiolitis

Uso de tiotrópio e função pulmonar em portadores de bronquiolite constritiva

Alexandre Melo Kawassaki, Letícia Kawano-Dourado, Ronaldo Adib Kairalla

To the Editor:

Tiotropium, a long-acting muscarinic antagonist bronchodilator with well-established use in COPD, has recognized activity in reducing lung hyperinflation, as well as in relieving dyspnea and improving exercise capacity in this population of patients.[1] In a recently published article,[2] tiotropium was shown to be able to attenuate TGF-β-induced airway remodeling. In addition, the combination of albuterol and tiotropium has been shown to elicit an acute response in patients with constrictive bronchiolitis (CB) secondary to graft-versus-host disease after bone marrow transplantation, there being a significant variation in FEV_1, FVC, or both, in 7 of 17 patients tested.[3] Therefore, smooth muscle plays a significant role in CB, and tiotropium might have an inhibitory activity on bronchoconstriction and airway remodeling.

Between January of 2004 and September of 2009, tiotropium was offered (HandiHaler, 18 µg; once a day for 30 days) to 11 consecutive patients with CB. The diagnosis of these patients is described below. Simple spirometric tests were performed before and after tiotropium use, in accordance with the Brazilian guidelines for pulmonary function testing,[4] and 6 patients underwent pre-treatment plethysmography.

Eight patients were female, with the mean age at diagnosis being 49 ± 11.6 years and the mean age at initiation of tiotropium therapy being 54.9 ± 11.0 years. Six patients had a history of smoking, but only 2 had a history of greater than 5 pack-years.

Nine patients had a history of significant exposure (mold, metallurgical material, birds, herbicides, paints, seeds, and plaster). Three patients had a collagen disease (rheumatoid arthritis, in 1; Sjögren's syndrome, in 1; and both, in 1); for these three patients, collagen disease was considered the major etiological factor.

All patients underwent chest CT, which revealed direct signs of small airway disease (bronchial wall thickening, bronchiectasis, bronchiolectasis, centrilobular micronodules or opacities with a tree-in-bud pattern) in 9 patients and an indirect sign of small airway disease (mosaic attenuation) in 2 patients.[5]

Seven biopsies (six surgical biopsies and one transbronchial biopsy) were performed, all of which showed the presence of CB. The 3 patients with rheumatic disease did not undergo lung biopsy because their clinical, functional, and CT findings were consistent with small airway disease, whereas 1 patient did not undergo biopsy because of his severe clinical status, but this patient had clinical, functional, and CT findings of CB.

The treatments instituted before the initiation of tiotropium therapy were as follows: systemic corticosteroid therapy, in 8 patients; inhaled corticosteroid therapy, in 7; long-acting β_2 agonist therapy, in 4; methotrexate therapy, in 4; macrolide therapy, in 3; azathioprine therapy, in 2; chloroquine therapy, in 2; and cyclophosphamide therapy, in 1. Two patients had transient clinical and functional improvement, 1 of whom used methotrexate and 1 of whom used a combination of azathioprine, prednisone, and acetylcysteine.

We analyzed 22 simple spirometric tests (2 per patient; Table 1). The median duration of tiotropium therapy was 21 days (interquartile range, 17.5-42.0), with a minimum of 14 days. The FVC and FEV_1 values before and after tiotropium use are shown in Figure 1. Six patients underwent plethysmography at baseline, and all had normal or increased TLC and increased RV, suggesting air trapping, consistent with the clinical diagnosis of CB. After the initiation of tiotropium therapy, FEV_1 increased from 870 ± 310 mL to 1,060 ± 350 mL (18.7 ± 9.2%; p = 0.0002) and FVC increased from 1,520 ± 500 mL to 1,800 ± 420

Table 1 - FVC and FEV_1 before and after the initiation of tiotropium therapy in the patients studied and percent change.[a]

Patient	Pre-therapy FEV_1, L	Post-therapy FEV_1, L	Δ, %	Pre-therapy FVC, L	Post-therapy FVC, L	Δ, %
1	0.99 (39)	1.41 (56)	30	1.69 (57)	2.06 (70)	18
2	1.09 (55)	1.35 (68)	19	1.39 (56)	1.72 (70)	19
3	0.46 (22)	0.51 (24)	10	1.10 (42)	1.18 (45)	7
4	1.13 (46)	1.22 (50)	7	2.53 (88)	2.51 (88)	−1
5	0.54 (17)	0.77 (23)	30	0.89 (22)	1.61 (40)	45
6	0.98 (27)	1.19 (37)	18	1.85 (42)	2.25 (57)	18
7	1.21 (63)	1.43 (74)	15	1.85 (79)	2.11 (89)	12
8	0.75 (39)	0.88 (46)	15	1.33 (58)	1.45 (63)	8
9	1.29 (60)	1.42 (66)	9	1.88 (72)	1.98 (76)	5
10	0.42 (13)	0.51 (16)	18	0.92 (24)	1.24 (33)	26
11	0.66 (26)	1.02 (37)	35	1.24 (41)	1.64 (51)	24
Mean	0.87 (37)	1.06* (45)	19	1.52 (53)	1.80** (62)	17

[a]Values expressed as n (%). *p = 0.0002. **p = 0.0011.

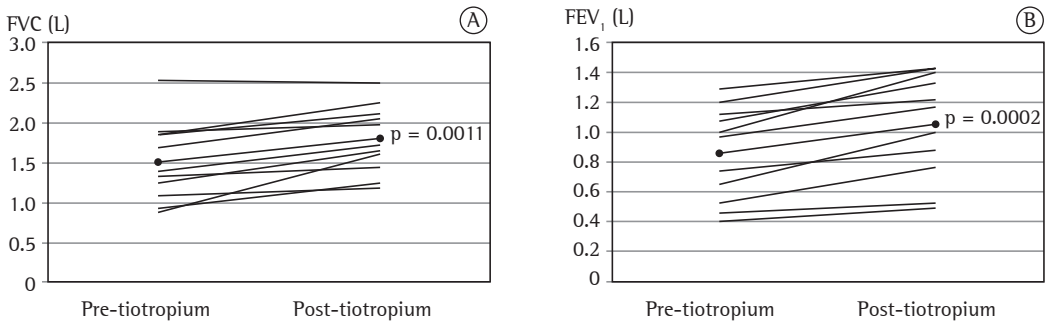

Figure 1 - Variation in FEV_1 (in A) and in FVC (in B) before and after tiotropium use. The darker lines represent the mean values.

mL (16.5 ± 12.6%; p = 0.0011), whereas the FEV_1/FVC showed no significant change (from 0.57 ± 0.11 to 0.58 ± 0.12; p = 0.46). Figure 1 shows the change in FVC and FEV_1 for each patient, as well as the mean values for the group.

The mean functional gain was 280 mL or 16.5% for FVC and 190 mL or 18.7% for FEV_1, values that are similar to those reported in patients with COPD.[1] Only 2 of the 11 patients did not show improvement of greater than 100 mL in FEV_1, FVC, or both, and it was impossible to predict the presence of response solely on the basis of clinical characteristics.

Our findings show that patients with CB have prolonged functional improvement with the use of a drug with a recognized anticholinergic effect, suggesting that acetylcholine plays a role in the pathophysiology of CB through bronchial smooth muscle contraction. To our knowledge, this is the first case series showing spirometric improvement with tiotropium use in patients with CB of different etiologies, which justifies the need for larger and longer studies to evaluate the impact of tiotropium bromide use on the progression of CB.[3,6]

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References

1. Celli B, ZuWallack R, Wang S, Kesten S. Improvement in resting inspiratory capacity and hyperinflation with tiotropium in COPD patients with increased static lung volumes. Chest. 2003;124(5):1743-8. http://dx.doi.org/10.1378/chest.124.5.1743 PMid:14605043
2. Oenema TA, Mensink G, Smedinga L, Halayko AJ, Zaagsma J, Meurs H, et al. Cross-talk between transforming growth factor-β_1 and muscarinic M_2 receptors augments airway smooth muscle proliferation. Am J Respir Cell Mol Biol. 2013;49(1):18-27. http://dx.doi.org/10.1165/rcmb.2012-0261OC PMid:23449734
3. Barisione G, Bacigalupo A, Crimi E, Brusasco V. Acute bronchodilator responsiveness in bronchiolitis obliterans syndrome following hematopoietic stem cell transplantation. Chest. 2011;139(3):633-9. http://dx.doi.org/10.1378/chest.10-1442 PMid:20724742
4. Sociedade Brasileira de Pneumologia e Tisiologia. Diretrizes para testes de função pulmonar. J Pneumol. 2002;28(Suppl 3):S1-S238.
5. Devakonda A, Raoof S, Sung A, Travis WD, Naidich D. Bronchiolar disorders: a clinical-radiological diagnostic algorithm. Chest. 2010;137(4):938-51. http://dx.doi.org/10.1378/chest.09-0800 PMid:20371529
6. Matsuyama W, Yamamoto M, Machida K, Oonakahara K, Watanabe M, Higashimoto I, et al. A case of bronchiolitis obliterans syndrome successfully treated by tiotropium bromide [Article in Japanese]. Nihon Kokyuki Gakkai Zasshi. 2006;44(5):404-9. PMid:16780100

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Interstitial pneumonia following exposure to fluorocarbon polymers

Pneumonia intersticial após exposição a polímeros fluorocarbonados

Eduardo Algranti, Thais Mauad

To the Editor:

Perfluoroalkyl resins are compounds containing hydrophobic alkyl chains, which are partially or fully fluorinated. These resins are heat-resistant (up to 260°C) thermoplastics used as coatings in the metallurgical industry (because of their mechanical and anti-adhesive resistance), as waterproofing agents for coating fabric, in papers used in the food industry, and in surface-active products, waxes, and insecticide formulations. As waterproofing agents, these resins are applied by manually-compressed or motorized spraying systems or by sprays. Reports of respiratory symptoms or epidemics in countries in Europe, Asia, and North America, totaling a few hundred cases, are summarized in a 2009 document by the Public Health Agency of Switzerland.[1] The cases include patients with varying degrees of clinical impairment. We report the first case of interstitial pneumonia caused by exposure to fluorocarbon resins in Brazil.

A 21-year-old male nonsmoker with interstitial pneumonia and no history of respiratory disease was evaluated at our facility. One year earlier, the patient was employed at a furniture factory specializing in the manufacture of sofas and armchairs. He worked as a sofa assembler for three months. Subsequently, he was transferred to an adjacent room, where he filled cushions with synthetic flakes and foams. In that same room, a coworker performed the waterproofing of the fabrics by using a manually-compressed spraying system (Figure 1). The work area was a rectangular enclosure of 30 m^2, with no ventilation/exhaust system, where there were waterproofing product mists. One week later, he had flu-like symptoms that resolved with withdrawal from the workplace. When he returned to work, he developed progressive dyspnea and cough, followed by limitation of physical activities, such as playing soccer and climbing stairs. One month later, he sought treatment from a cardiologist, who started clinical investigation. He continued to work, and the symptoms gradually worsened. Three months later, he had sudden pain in the left hemithorax with worsening dyspnea, a pneumothorax was diagnosed, and there was a finding of diffuse ground-glass infiltration (Figure 2A). Twelve days later, drainage resulted in unsatisfactory lung expansion, and the patient underwent thoracotomy and lung biopsy, which revealed desquamative interstitial pneumonia (Figures 2B and 2C). One month later, he was asymptomatic. A follow-up CT scan showed apical and subpleural bullae and a band in the left hemithorax, which was associated with the area of previous surgical manipulation. His alpha-1-antitrypsin level was normal (183 mg/dL). The patient was started on a 45-day course of prednisone. Spirometry showed that FVC increased from 43%, before the pneumothorax episode, to 72%, twelve months later.

The onset of the condition occurred when the patient was indirectly exposed to waterproofing product mists, the waterproofing agent (Teximper®; Teximper Comércio Importação e Exportação Ltda, São Paulo, Brazil) being composed of perfluoroalkyl resin in a solvent. The parenchymal inflammation was only identified after the pneumothorax. The patient's history included acute, short-term, flu-like symptoms, which started a few days after the change of sectors, followed by progressive dyspnea and cough, which lasted for weeks prior to hospitalization.

Exposure to fumes from fluorocarbon polymers was first described as a cause of flu-like symptoms related to products of thermal degradation of polytetrafluoroethylene (PTFE or Teflon®), being designated "polymer fume fever".[2] Subsequently, cases of respiratory symptoms related to industrial or household exposure to fluorocarbon polymers were described.[1] Waterproofing agents contain fluorocarbon resins, silicones, or waxes as active elements. They are used in the form of sprays—the main use of which is to waterproof shoes. These sprays contain a propellant gas, a resin, and a solvent. When they are applied, the solvent

evaporates and the resin adheres to the fabric. Heinzer et al.[3] reported 6 cases of patients hospitalized for respiratory failure following household exposure between January and March of 2003 in Switzerland. The products used were of different brands; however, a little earlier, the resin supplier had changed the solvent to heptane. During the months in which the new formulation was used, 153 cases of respiratory symptoms were reported in Switzerland.

The mechanism of pulmonary toxicity is unknown. An experimental study raised the hypothesis of a direct effect on the surfactant, because of polymer deposition on the alveolar wall, increasing the surface tension and leading to collapse.[4] A retrospective study evaluated 102 cases of individuals who had respiratory symptoms following household exposure to sprays of acrylic fluorocarbon resins.[5] Those authors concluded that the findings could not be attributed to the solvent present in the formulation because of the high volatility of that solvent, and that the clinical repercussions showed no association with the magnitude of the exposure, or with personal histories of smoking, atopy, and chronic lung disease. Apparently, there is an association between resin toxicity and resin particle diameter.[6] This diameter is a function of the spray generation mechanism (spray systems generate a greater mass of particulate matter < 10 μm than do pump systems) and the solvent (fast-evaporating solvents, such as heptane, generate a greater amount of small-sized particulate matter).[1]

Figure 1 - Manually-compressed resin spraying system with a discharge valve. Note the presence of droplets on the lens of the camera as a result of the product spray.

The CT images described in other case reports[3,7] are similar to the findings of the present case. Histology showed extensive areas of alveolar collapse, without a significant accumulation of intra-alveolar macrophages, and with strong staining of pneumocytes. Wallace & Brown[7] and Ota et al.[8] reported similar findings in cases of patients who underwent transbronchial biopsy.

Most of the cases reported or registered in centers for the treatment of intoxication were cured, either spontaneously or with corticosteroid therapy. There have been few reports of cases in which the DLCO remained abnormal and fibrosis was established.[7,9] Three deaths have been reported.[5,8,10]

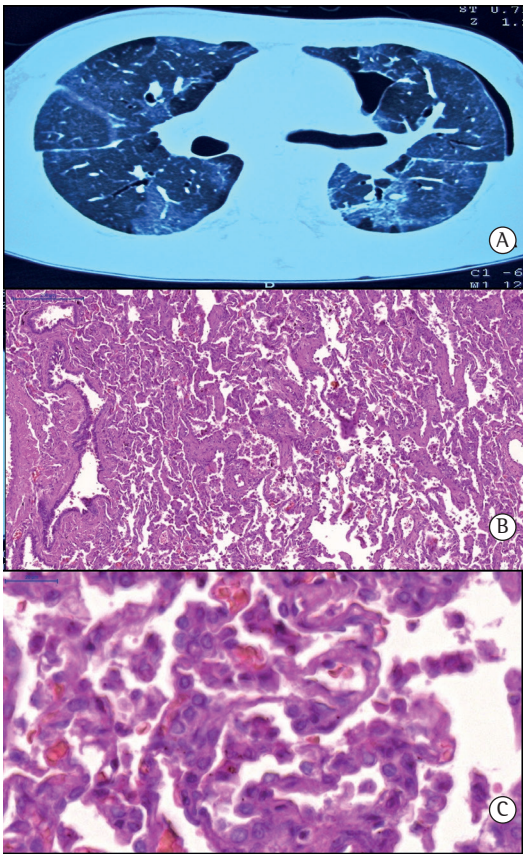

Figure 2 - In A, an HRCT scan showing left pneumothorax and extensive bilateral areas of ground-glass attenuation. In B, findings of desquamative interstitial pneumonitis on histology of an open lung biopsy sample, revealing that the architecture of the lung parenchyma and small airways is intact, with mild interstitial thickening. There are areas of alveolar filling with pooled alveolar macrophages, without granuloma formation (H&E; scale bar, 200 μm). In C, detail of Figure 2B showing alveolar septa with reactive pneumocytes and intra-alveolar macrophage accumulation (H&E; scale bar, 20 μm).

In Brazil, waterproofing sprays for shoes are sold in shoe stores, and the practice of waterproofing upholstered chairs and sofas is common. Items containing Teflon® are also present in households. Little is said about the toxicity of these products, toxicity that might be associated with chemical pneumonias caused by inhalation of aerosols containing fluorocarbon polymers.

Acknowledgments

We would like to thank Professors Fabíola Del Carlo Bernardi and Marisa Dolnikhoff for their assistance in the histological analyses.

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References

1. Federal Office of Public Health. Toxicology of waterproofing sprays. Berne: Federal Office of Public Health of Switzerland; 2009.
2. Shusterman DJ. Polymer fume fever and other fluorocarbon pyrolysis-related syndromes. Occup Med. 1993;8(3):519-31. PMid:8272977
3. Heinzer R, Ribordy V, Kuzoe B, Lazor R, Fitting JW. Recurrence of acute respiratory failure following use of waterproofing sprays. Thorax. 2004;59(6):541-2. PMid:15170049 PMCid:PMC1747044
4. Yamashita M, Tanaka J. Pulmonary collapse and pneumonia due to inhalation of a waterproofing aerosol in female CD-1 mice. J Toxicol Clin Toxicol. 1995;33(6):631-7. http://dx.doi.org/10.3109/15563659509010620
5. Vernez D, Bruzzi R, Kupferschmidt H, De-Batz A, Droz P, Lazor R. Acute respiratory syndrome after inhalation of waterproofing sprays: a posteriori exposure-response assessment in 102 cases. J Occup Environ Hyg. 2006;3(5):250-61. http://dx.doi.org/10.1080/15459620600628845 PMid:16574608
6. Yamashita M, Tanaka J, Yamashita M, Hirai H, Suzuki M, Kajigaya H. Mist particle diameters are related to the toxicity of waterproofing sprays: comparison between toxic and non-toxic products. Vet Hum Toxicol. 1997;39(2):71-4. PMid:9080629
7. Wallace GM, Brown PH. Horse rug lung: toxic pneumonitis due to fluorocarbon inhalation. Occup Environ Med. 2005;62(6):414-6. http://dx.doi.org/10.1136/oem.2004.015784 PMid:15901890 PMCid:PMC1741039
8. Ota H, Koge K, Tanaka H, Akaishi T, Kikuchi K. Acute respiratory failure due to inhalation of aerosol water proof agent [Article in Japanese]. Nihon Kokyuki Gakkai Zasshi. 2000;38(6):485-9. PMid:10979290
9. Schicht R, Hartjen A, Sill V. Alveolitis after inhalation of leather-impregnation spray (author's transl) [Article in German]. Dtsch Med Wochenschr. 1982;107(18):688-91. http://dx.doi.org/10.1055/s-2008-1070003 PMid:7075484
10. Malik MS, Chappell B. Acute respiratory syndrome associated with extreme Superpruf aerosol. Anaesthesia. 2003;58(10):1037-8. http://dx.doi.org/10.1046/j.1365-2044.2003.03415_19.x

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Mixed pneumoconiosis due to silicates and hard metals associated with primary Sjögren's syndrome due to silica

Pneumoconiose mista por silicatos e metais duros associada à síndrome de Sjögren primária por silicatos

Pedro Gonçalo de Silva Ferreira, António Jorge Correia Gouveia Ferreira, Lina Maria Rodrigues de Carvalho, António Segorbe Luís

To the Editor:

Here, we describe the case of a 75-year-old man who presented with a 3-year history of progressive dyspnea on exertion (classified as grade II/III on the modified Medical Research Council scale) and persistent dry cough. He had worked as a professional welder for 35 years, welding alloys, polishing weldments by sandblasting and steel blasting, and regularly performing isolation of fixed appliances with asbestos fibers.

Treated in the primary care setting in the first year, the patient developed recurrent scaly skin lesions (exhibiting a lichenified/desquamative pattern) on the limbs, Raynaud's phenomenon, sicca syndrome, and weight loss (5 kg). Physical examination revealed that he was breathing normally, with an SpO_2 of 95% and auscultatory findings of basal inspiratory crackles, and that there was no digital clubbing.

A chest X-ray showed reticular interstitial changes. A CT scan of the chest showed calcified mediastinal adenopathy exhibiting an "eggshell" pattern, interlobular reticulation, traction bronchiectasis, and septal thickening, as well as areas of ground-glass opacity, alveolar consolidation with a peribronchovascular distribution, and areas of pleural thickening (Figure 1).

The patient underwent a skin biopsy, which showed non-specific lichenoid changes. A BAL, performed at the level of the middle lobe (right bronchus, 4a), revealed a total cell count of 130,000 cells/mL, with 40% lymphocytes and 16% neutrophils, as well as negative microbiological and cytological findings. Immunophenotyping showed a predominance of CD8 T lymphocytes (CD4/CD8 ratio = 0.68) and B lymphocytes (20%). The inorganic fraction showed no asbestos bodies and was sent for determination of the levels of hard metals and silicates by inductively coupled plasma-atomic emission spectrometry. This study showed high levels of silica, copper, cobalt, chromium, rubidium, molybdenum, and zinc.

Laboratory testing revealed that the patient had a hemoglobin level of 11.6 g/dL, normal inflammatory markers, a creatinine level of 1.0 mg/dL, and an inactive urinary sediment, as well as having a beta-2 microglobulin level of 6.56 mg/L and a serum angiotensin-converting enzyme level of 127 U/L. In addition, he had polyclonal hypergammaglobulinemia (IgG and IgA) and positive antinuclear antibodies (anti-SSA60 and anti-SSB antibodies) at high titers. Schirmer's test confirmed xerophthalmia (right eye, 9 mm; left eye, 7 mm).

Functionally, the patient had a moderate restrictive pattern (Tiffeneau index, 80; FEV_1, 70.9%; FVC, 66.8%; TLC, 64.6%; and RV, 68.4%), moderately reduced DLCO (51.2% of predicted), and a short six-minute walk distance with desaturation of 5%.

A surgical lung biopsy showed foci of fibroblast proliferation, macrophages with anthracotic pigmentation and birefringent particles suggestive of silicates, multinucleated giant cells along the bronchoalveolar axes and interlobular septa, as well as alveolar macrophage desquamation and diffuse pleural fibrosis (Figure 2).

A diagnosis of mixed pneumoconiosis due to silica, hard metals, and asbestos, associated with primary Sjögren's syndrome (SS) with possible pulmonary parenchymal involvement, was established. The patient was started on a four-month course of 0.5 mg/kg prednisolone, which resulted in decreased dyspnea on exertion and complete resolution of the skin lesions, although there was only slight improvement in radiological findings and in DLCO.

The concomitant diagnosis of late-onset primary SS, established in accordance with the criteria proposed by the European American

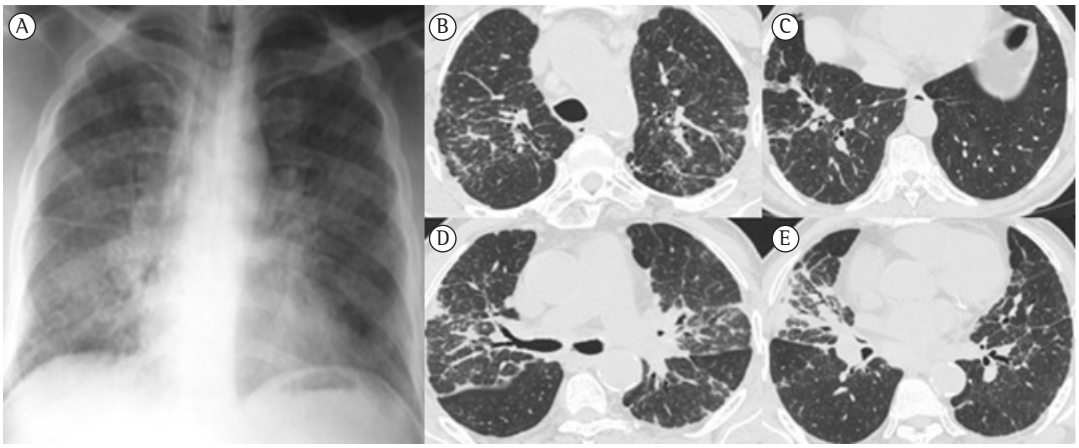

Figure 1 - Initial radiological findings. In A, chest X-ray showing a reticular interstitial pattern predominantly in the lower lung fields, already denoting some loss of volume. In B-E, CT scan showing septal thickening patterns, traction bronchiectasis, small areas of ground-glass opacity, and consolidation with a peribronchovascular distribution.

Consensus Group, may be related to the long-term exposure to silica, which is in agreement with the few existing reports in the literature.[1-3] In fact, it has been shown that intense exposure to silica can lead to the development of autoimmune processes, namely systemic sclerosis,[4] rheumatoid arthritis,[4] and primary SS,[1-4] in a proportion of exposed workers. In this context, alveolar lymphocytosis has been correlated with pulmonary involvement in SS and with unfavorable prognosis.[5] In the present case, the finding of peribronchovascular lymphocytic infiltration with a significant proportion of B lymphocytes may be related to parenchymal infiltration attributable to SS. The correct exclusion of lymphoma was essential.

The pneumoconiotic component, radiologically expressed by inflammatory changes and fibrotic involvement, manifests histologically as a periseptal and peribronchovascular fibroblastic reaction, as well as by the presence of macrophages with anthracotic pigmentation and birefringent particles. The observed patterns of alveolar desquamation and giant cell reaction are the ones that are typically seen in hard metal lung disease.[6-8] The areas of diffuse pleural fibrosis are relatable to exposure to asbestos.

Typical histology of parenchymal disease due to hard metals corresponds to the pattern of interstitial fibrosis with giant cell reaction and foci of desquamative interstitial pneumonia with or without bronchiolitis obliterans.[6-8] In some cases, there can be sarcoid features or only a mixed-dust pneumoconiosis pattern.

Lung mineralogical analysis is useful in the etiological detection of particles in pneumoconiosis.[7] In the present case, the BAL fluid levels of silicates and hard metals were determined by inductively coupled plasma-atomic emission spectrometry. This type of information makes it possible to document occupational exposure, which is often mixed in nature, several decades after exposure was discontinued, assisting in the etiological identification of some occupational respiratory diseases.[9] Although direct analysis of lung biopsy/autopsy specimens is the most direct marker to determine particle accumulation, BAL fluid analysis is simpler and yields results that show good agreement with those obtained from tissue specimens.[9] However, biopsy is essential in cases in which the differential diagnosis with sarcoidosis is required.

The hard metals most widely used in industry are tungsten carbide, molybdenum carbide, and chromium carbide—cobalt and nickel being alloying elements—and they can induce antigen-specific immune responses in the lung as well as innate immune responses characterized by inflammation and triggered by oxidative injury.[8] Of the elements detected in patient BAL fluid samples, silica, chromium, molybdenum, cobalt, and zinc have all been associated with lung fibrosis or pneumoconiosis.[10] It is known, however, that high concentrations of particles in tissues or body fluids indicate significant exposure but not necessarily disease. Nevertheless, when used in cases of heavy exposure and suggestive clinical, radiological, and histological findings, such as the present case, determination of the levels of hard

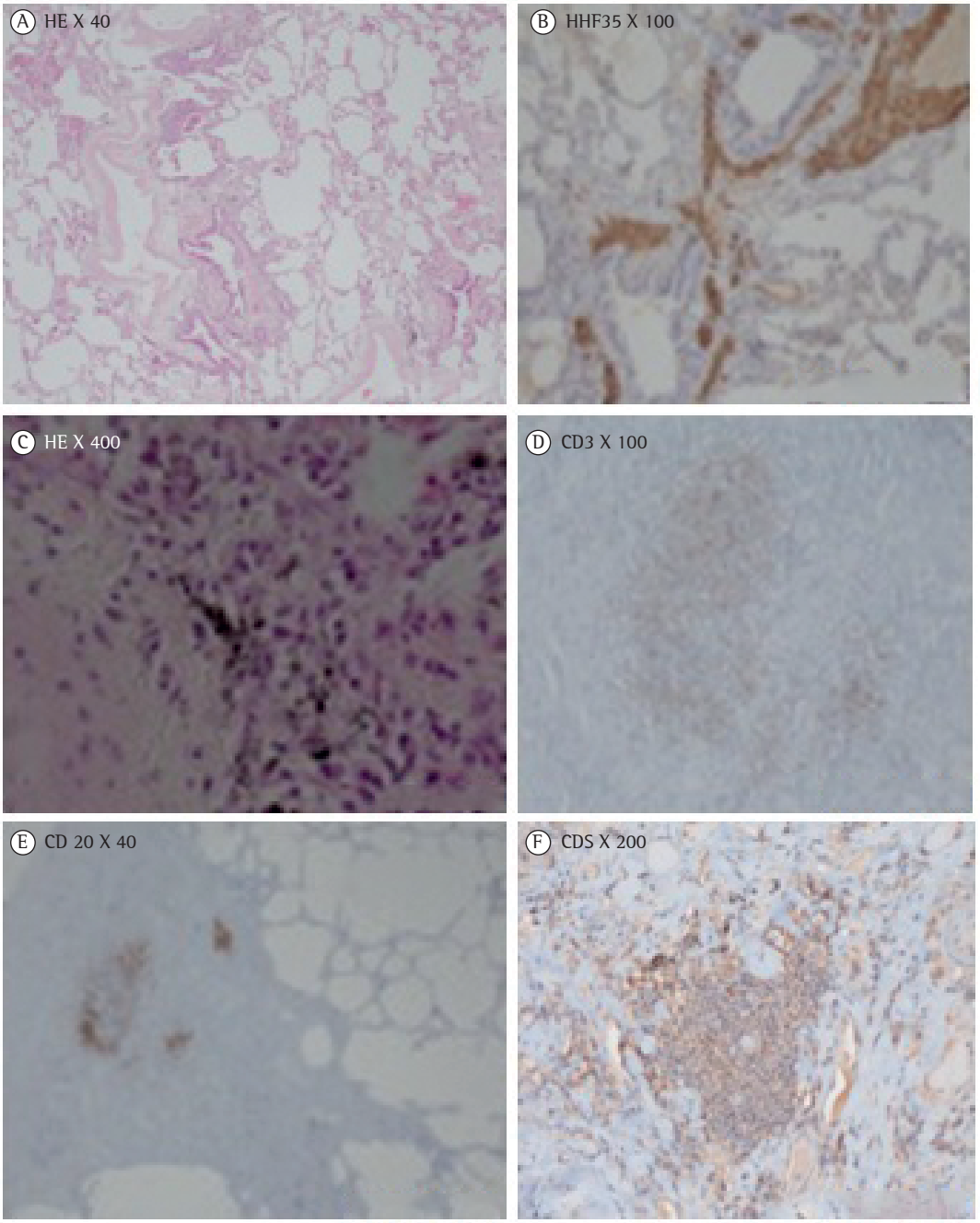

Figure 2 - Photomicrographs of histological sections of surgical lung biopsy specimens. In A, chronic inflammatory infiltrate and septal fibrosing reaction (H&E; magnification, ×40). In B, active fibroblastic foci (HHF35; magnification, ×100). In C, macrophages with anthracotic pigmentation and birefringent silica particles, as well as multinucleated giant cells along the bronchoalveolar axes and interlobular septa (HPX; magnification, ×400). In D, lymphocytic inflammatory infiltrate with T cells (CD3; magnification, ×100). In E, foci of B cells (CD20+) in the chronic inflammatory infiltrate (CD20; magnification, ×40). In F, predominance of T cells with a CD8 immunophenotype (CD8; magnification, ×200).

metals is a valuable element in the diagnosis of less common types of pneumoconiosis, as well as in the understanding of their pathogenesis.[7]

Given the large number of workers involved, a better understanding of the impacts of exposure to welding fumes on pulmonary function will

be important for the development of better prevention strategies.

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References

1. Puisieux F, Hachulla E, Brouillard M, Hatron PY, Devulder B. Silicosis and primary Gougerot-Sjögren syndrome [Article in French]. Rev Med Interne. 1994;15(9):575-9. http://dx.doi.org/10.1016/S0248-8663(05)82502-0
2. Astudillo L, Sailler L, Ecoiffier M, Giron J, Couret B, Arlet-Suau E. Exposure to silica and primary Sjögren's syndrome in a dental technician. Rheumatology (Oxford). 2003;42(10):1268-9. http://dx.doi.org/10.1093/rheumatology/keg334 PMid:14508049
3. Kirwan JR. Out-patient workload. Rheumatology (Oxford). 2003;42(10):1269-70. http://dx.doi.org/10.1093/rheumatology/keg335 PMid:14508050
4. Sanchez-Roman J, Wichmann I, Salaberri J, Varela JM, Nu-ez-Roldan A. Multiple clinical and biological autoimmune manifestations in 50 workers after occupational exposure to silica. Ann Rheum Dis. 1993;52(7):534-8. http://dx.doi.org/10.1136/ard.52.7.534 PMid:8394065 PMCid:PMC1005094
5. Dalavanga YA, Voulgari PV, Georgiadis AN, Leontaridi C, Katsenos S, Vassiliou M, et al. Lymphocytic alveolitis: A surprising index of poor prognosis in patients with primary Sjogren's syndrome. Rheumatol Int. 2006;26(9):799-804. http://dx.doi.org/10.1007/s00296-005-0092-1 PMid:16344933
6. van den Eeckhout AV, Verbeken E, Demedts M. Pulmonary pathology due to cobalt and hard metals [Article in French]. Rev Mal Respir. 1989;6(3):201-7. PMid:2662276
7. Rüttner JR, Spycher MA, Stolkin I. Inorganic particulates in pneumoconiotic lungs of hard metal grinders. Br J Ind Med. 1987;44(10):657-60. PMid:3676118 PMCid:PMC1007897
8. Kelleher P, Pacheco K, Newman LS. Inorganic dust pneumonias: the metal-related parenchymal disorders. Environ Health Perspect. 2000;108 Suppl 4:685-96. PMid:10931787 PMCid:PMC1637664
9. Dumortier P, De Vuyst P, Yernault JC. Non-fibrous inorganic particles in human bronchoalveolar lavage fluids. Scanning Microsc. 1989;3(4):1207-16; discussion 1217-8. PMid:2561220
10. Selden A, Sahle W, Johansson L, Sorenson S, Persson B. Three cases of dental technician's pneumoconiosis related to cobalt-chromium-molybdenum dust exposure. Chest. 1996;109(3):837-42. http://dx.doi.org/10.1378/chest.109.3.837 PMid:8617099

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Mounier-Kuhn syndrome: a rare and often overlooked cause of bronchial dilation and recurrent respiratory tract infections

Síndrome de Mounier-Kuhn: uma causa rara e muitas vezes negligenciada de dilatação brônquica e de infecções recorrentes do trato respiratório

Shailendra Kapoor

To the Editor:

I read with great interest the recent article by García et al.[1] It should be noted that one rare, often overlooked and underrecognized, cause of respiratory tract infections and bronchial dilation is Mounier-Kuhn syndrome (MKS). The primary feature of MKS, also known as "tracheobronchopathia malacia", is congenital tracheal dilation accompanied by dilation of the main bronchi.[2] The dilation occurs secondary to muscular layer degeneration of the trachea and bronchi. Tracheal dilations as large as 36 mm have been reported in MKS. The syndrome most often affects adults between 30 and 40 years of age, predominantly males.[3] It is rarely diagnosed in pediatric patients and usually accompanies disorders such as cutis laxa. There are numerous presentations of MKS. For instance, Randak et al. recently reported the case of a patient with MKS who developed concurrent tracheal diverticula.[4]

Patients with MKS typically develop recurrent lower respiratory tract infections. Such patients can also develop rare forms of bacterial infections. For instance, Arroyo-Cózar et al. recently described the case of a 75-year-old male with MKS who developed a respiratory infection with *Alcaligenes xylosoxidans*.[5] Recurrent bronchiectasis and pneumonia are frequently seen. Patients might also present with intermittent dyspnea. Cough-induced syncope is often seen. Hemoptysis is rare but has been reported. Pulmonary fibrosis can further complicate the course of the disease, as can emphysema. Rapid progression of the disease can result in respiratory failure. Although recently reported by Dincer et al.,[6] vocal cord paralysis is rarely seen in MKS patients.

Imaging with CT goes a long way toward confirming the diagnosis of MKS.[7] Such imaging, especially HRCT scans, typically reveal widening of the trachea and main bronchi. When the tracheal diameter exceeds 30 mm, a formal diagnosis of MKS can be made.[8] Other diagnostic criteria include a right main bronchus diameter greater than 24 mm or a left main bronchus diameter greater than 23 mm. The widening is accompanied by marked bronchiectasis.[3,6] A few patients develop pneumothorax. Some patients initially present with a pneumothorax that reveals the underlying MKS. For instance, in a recent report of the case of a 54-year-old patient presenting with left-sided pneumothorax, further evaluation revealed the underlying cause to be MKS.[9] Significantly dilated airways are typically seen on bronchoscopic evaluation. The results of pulmonary function tests can be normal or abnormal.

The management of MKS primarily involves the institution of supportive measures. Antibiotics need to be started immediately in patients with respiratory tract infections.[5] Chest physiotherapy is advised in most patients. Laser therapy is another emerging alternative. Dutau et al. recently reported the successful management of a patient with MKS by the use of yttrium-aluminum-garnet laser endoscopically.[10] Collapse of the tracheal airway might necessitate endobronchial stenting. Odell et al. recently reported considerable success with such stenting.[11] Another surgical procedure that can be considered in patients with severe forms of MKS is tracheobronchoplasty.

It is obvious that MKS is a rare yet significant cause of respiratory tract infections. It should be included in the differential diagnosis of patients with lower respiratory tract infections and concurrent tracheal dilation on imaging.

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References

1. González-García M, Maldonado Gomez D, Torres-Duque CA, Barrero M, Jaramillo Villegas C, Pérez JM, et al.

Tomographic and functional findings in severe COPD: comparison between the wood smoke-related and smoking-related disease. J Bras Pneumol. 2013;39(2):147-54. http://dx.doi.org/10.1590/S1806-37132013000200005 PMid:23670499
2. Dalar L, Eryüksel E, Kosar F, Karasulu AL, Urer N, Sökücü SN, et al. Central airway obstruction due to malignant fibrous histiocytoma metastasis in a case with Mounier-Kuhn syndrome. Tuberk Toraks. 2012;60(2):167-71. http://dx.doi.org/10.5578/tt.2458 PMid:22779939
3. Marchiori E, Sousa AS Jr, Zanetti G, Hochhegger B. Mounier-Kuhn syndrome: The role of bronchiectasis in clinical presentation. Ann Thorac Med. 2012;7(1):51. http://dx.doi.org/10.4103/1817-1737.91549 PMid:22347353 PMCid:PMC3277044
4. Randak CO, Weinberger M. A child with progressive multiple tracheal diverticulae: a variation of the Mounier-Kuhn syndrome. Pediatr Pulmonol. 2013;48(8):841-3. http://dx.doi.org/10.1002/ppul.22663 PMid:22949127
5. Arroyo-Cózar M, Ruiz-García M, Merlos EM, Vielba D, Macías E. Case report: respiratory infection due to Alcaligenes xylosoxidans in a patient with Mounier-Kuhn syndrome [Article in Spanish]. Rev Chilena Infectol. 2012;29(5):570-1. http://dx.doi.org/10.4067/S0716-10182012000600019 PMid:23282506
6. Dincer HE, Holweger JD. Mounier-Kuhn syndrome and bilateral vocal cord paralysis. J Bronchology Interv Pulmonol. 2012;19(3):255-7. http://dx.doi.org/10.1097/LBR.0b013e318261009e PMid:23207474
7. Jaiswal AK, Munjal S, Singla R, Jain V, Behera D. A 46-year-old man with tracheomegaly, tracheal diverticulosis, and bronchiectasis: Mounier-Kuhn syndrome. Lung India. 2012;29(2):176-8. http://dx.doi.org/10.4103/0970-2113.95337 PMid:22628937 PMCid:PMC3354496
8. Kent BD, Sulaiman I, Akasheh NB, Nadarajan P, Moloney E, Lane SJ. An unusual cause of spontaneous pneumothorax: the Mounier-Kuhn syndrome. Ir Med J. 2011;104(5):152-3. PMid:21736094
9. Celik B, Bilgin S, Yuksel C. Mounier-Kuhn syndrome: a rare cause of bronchial dilation. Tex Heart Inst J. 2011;38(2):194-6. PMid:21494536 PMCid:PMC3066798
10. Dutau H, Maldonado F, Breen DP, Colchen A. Endoscopic successful management of tracheobronchomalacia with laser: apropos of a Mounier-Kuhn syndrome. Eur J Cardiothorac Surg. 2011;39(6):e186-8. http://dx.doi.org/10.1016/j.ejcts.2011.01.074 PMid:21382725
11. Odell DD, Shah A, Gangadharan SP, Majid A, Michaud G, Herth F, et al. Airway stenting and tracheobronchoplasty improve respiratory symptoms in Mounier-Kuhn syndrome. Chest. 2011;140(4):867-73. http://dx.doi.org/10.1378/chest.10-2010 PMid:21493699

Respuesta de los autores:

Luego de leer la interesante descripción del síndrome de Mounier-Kuhn, en la cual cita el artículo de las diferencias tomográficas y funcionales entre la EPOC severa relacionada con humo de leña y con cigarrillo, es importante aclarar que hay diferencias significativas en el compromiso de la vía aérea entre los pacientes con este síndrome y la EPOC por humo de leña. Aunque las dilataciones y engrosamiento bronquial son frecuentes en la EPOC por exposición a humo de leña, no encontramos en las imágenes tomográficas dilatación de la tráquea y los bronquios principales,[1] que es la principal característica del síndrome de Mounier-Kuhn. Los hallazgos en nuestras pacientes de compromiso bronquial y atelectasias, sin daño aparente de tráquea o bronquios fuente, están de acuerdo a la descripción realizada por Moreira et al.[2] en otro artículo del mismo número de la revista. Adicionalmente, los pacientes con EPOC relacionada con el humo de la leña comparten algunas características clínicas con la EPOC por tabaquismo e infrecuentemente se presentan infecciones bacterianas por gérmenes inusuales. Por la presentación de bronquiectasias tanto en la EPOC por leña como en el síndrome de Mounier-Kuhn, las dos entidades deben tenerse en cuenta en el diagnóstico diferencial del adulto con enfermedad bronquial crónica.

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Referencias

1. González-García M, Maldonado Gomez D, Torres-Duque CA, Barrero M, Jaramillo Villegas C, Pérez JM, et al. Tomographic and functional findings in severe COPD: comparison between the wood smoke-related and smoking-related disease. J Bras Pneumol. 2013;39(2):147-54. http://dx.doi.org/10.1590/S1806-37132013000200005 PMid:23670499
2. Moreira MA, Barbosa MA, Queiroz MC, Teixeira KI, Torres PP, de Santana Júnior PJ, et al. Pulmonary changes on HRCT scans in nonsmoking females with COPD due to wood smoke exposure. J Bras Pneumol. 2013;39(2):155-63. http://dx.doi.org/10.1590/S1806-37132013000200006 PMid:23670500

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Erratum

This corrects the article “The chest and aging: radiological findings” published in 2012 n38v5; p. 656-65.

In J Bras Pneumol. 2012;38(5):656-65, Hochhegger B, Meireles GP, Irion K, Zanetti G, Garcia E, Moreira J, Marchiori E. “The chest and aging: radiological findings”, the names of the authors are Bruno Hochhegger, Gustavo Souza Portes Meirelles, Klaus Irion, Gláucia Zanetti, Eduardo Garcia, José Moreira e Edson Marchiori (Hochhegger B, Meirelles GS, Irion K, Zanetti G, Garcia E, Moreira J, Marchiori E).

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Electronic publications

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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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Eventos 2014

NACIONAIS

Curso de Ventilação e Sono
Data: 27 a 29 de março de 2014 Local: Hotel Novotel, São Paulo/SP
Informações: Secretaria da SBPT
Portal: www.sbpt.org.br / Telefone: 0800616218

Curso de Atualização 2014
Data: 24 a 26 de abril de 2014 Local: Hotel Atlântico Búzios, Búzios/RJ.
Informações: Secretaria da SBPT
Portal: www.sbpt.org.br / Telefone: 0800616218

XXXVI Congresso Brasileiro de Pneumologia e Tisiologiaa
Data: 07 a 11 de outubro de 2014 Local: Expogramado, Gramado/RS
Informações: Secretaria da SBPT
Portal: www.sbpt.org.br / Telefone: 0800616218

INTERNACIONAIS

CHEST World Congress
Data: 21 a 24 de março de 2014 Local: Madrid/ Espanha
Informações: www.chestnet.org

ATS 2014
Data: 16 a 21/05/2014
Local: San Diego/CA
Informações: www.thoracic.org

ERS 2014
Data: 06 a 10 de setembro de 2014
Local: Munique/Alemanha
Informações: www.ersnet.org

Chest 2014
Data: 25 a 30 de outubro de 2014
Local: Austin/Texas
Informações: www.chestnet.org

Vannair®

fumarato de formoterol diidratado/budesonida

ÚNICO SPRAY

formoterol/budesonida [1]

- Controle **RÁPIDO** e **SUSTENTADO** da Asma.[1,2]
- **ALCANCE DAS PEQUENAS VIAS AÉREAS,** 50% a 70% de partículas finas.[3]
- **NÃO PRECISA** ser conservado em geladeira.

Referências bibliográficas: 1. Morice AH, Peterson S, Beckman O, Kukova Z. Efficacy and safety of a new pressurised metered-dose inhaler formulation of budesonide/formoterol in children with asthma: a superiority and therapeutic equivalence study. Pulm Pharmacol Ther.2008;21(1):152-9. **2.** Noonan M, Rosenwasser LJ, Martin P, O'Brien CD, O'Dowd L. Efficacy and safety of budesonide and formoterol in one pressurised metered-dose inhaler in adults and adolescents with moderate to severe asthma: a randomised clinical trial. Drugs.2006;66(17):2235-54. **3.** Chambers F, Ludzik A. *In vitro* drug delivery performance of a new budesonide/formoterol pressurized metereddose inhaler. Journal of aerosol medicine and pulmonary drug delivery. 2009 Jun;22(2):113-20.

VANNAIR® 6/100 mcg/inalação e VANNAIR® 6/200 mcg/inalação (fumarato de formoterol di-hidratado/budesonida) VANNAIR® (fumarato de formoterol di-hidratado/budesonida) é composto por substâncias que possuem diferentes modos de ação e que apresentam efeitos aditivos em termos de redução da asma do que outros produtos isoladamente. A budesonida é um glicocorticosteróide que tem uma rápida (dentro de horas) e dose-dependente ação antiinflamatória nas vias aéreas e o formoterol é um agonista beta-2-adrenérgico seletivo de início de ação rápido (1-3 minutos) e de longa duração (pelo menos 12 horas). **Indicações: VANNAIR** está indicado no tratamento da asma nos casos em que o uso de uma associação (corticosteróide inalatório com um beta-2 agonista de ação prolongada) é apropriado. **Contra-indicações: Hipersensibilidade a budesonida, ao formoterol ou a outros componentes da fórmula. Cuidados e Advertências:** Advertências: É recomendado que a dose seja titulada quando o tratamento de longo prazo é descontinuado e este não deve ser interrompido abruptamente. Para minimizar o risco de candidíase orofaríngea, o paciente deve ser instruído a lavar a boca com água após administrar as inalações de **VANNAIR**. Uma deterioração súbita e progressiva do controle da asma é um risco potencial e o paciente deve procurar suporte médico.Pacientes que necessitaram de terapia corticosteróide de alta dose emergencial ou tratamento prolongado de altas doses recomendadas de corticosteróides inalatórios podem exibir sinais e sintomas de insuficiência adrenal quando expostos a situações de estresse grave. Administração de corticosteróide sistêmico adicional deve ser considerada durante situações de estresse ou cirurgia eletiva. **VANNAIR** deve ser administrado com cautela em pacientes com graves alterações cardiovasculares (incluindo anomalias do ritmo cardíaco), *diabetes mellitus*, hipocalemia não tratada ou tireotoxicose. Pacientes com prolongamento do intervalo QTc devem ser cuidadosamente observados (para maiores informações vide bula completa do produto). *Uso durante a gravidez e a lactação:* categoria C de risco de gravidez. Este medicamento não deve ser utilizado por mulheres grávidas sem orientação médica ou do cirurgião-dentista. A administração de **VANNAIR** em mulheres lactantes deve ser apenas considerada se os benefícios esperados para a mãe superarem qualquer possível risco para a criança (para maiores informações vide bula completa do produto). Interações medicamentosas: o metabolismo da budesonida é mediado principalmente pela CYP3A4, uma subfamília do citocromo P450. Portanto, inibidores desta enzima, como o cetoconazol ou suco de *grapefruit* (pomelo), podem aumentar a exposição sistêmica à budesonida. A cimetidina apresenta um leve efeito inibidor sobre o metabolismo hepático da budesonida. Fármacos como a procainamida, fenotiazina, agentes antihistamínicos (terfenadina), inibidor da monoaminooxidase (MAO) e antidepressivos tricíclicos foram relacionados com um intervalo QTc prolongado e um aumento do risco de arritmia ventricular. **Os bloqueadores beta-adrenérgicos (incluindo os colírios oftálmicos) podem atenuar ou inibir o efeito do formoterol** (para maiores informações vide bula completa do produto). **Reações adversas:** as reações adversas que foram associadas à budesonida ou ao formoterol são apresentadas a seguir. *Comum*: palpitações, candidíase na orofaringe, cefaléia, tremor, leve irritação na garganta, tosse, rouquidão. *Incomum*: taquicardia, náusea, cãibras musculares, tontura, agitação, ansiedade, nervosismo eperturbações do sono. (para outras reações adversas, vide bula completa do produto). **Posologia:** a dose de **VANNAIR** deve ser individualizada conforme a gravidade da doença. Quando for obtido o controle da asma, a dose deve ser titulada para a menor dose que permita manter um controle eficaz dos sintomas. **VANNAIR® 6/100 mcg/inalação:** *Adultos (a partir de 18 anos de idade)*: 2 inalações uma ou duas vezes ao dia. Em alguns casos, uma dose máxima de 4 inalações duas vezes ao dia pode ser requerida como dose temporária de manutenção durante a piora da asma. *Adolescentes (12-17 anos)*: 2 inalações uma ou duas vezes ao dia. Durante a piora da asma a dose pode temporariamente ser aumentada para o máximo de 4 inalações duas vezes ao dia. *Crianças (6-11 anos)*: 2 inalações duas vezes ao dia. Dose máxima diária: 4 inalações. **VANNAIR® 6/200 mcg/inalação:** *Adultos (a partir de 18 anos de idade)*: 2 inalações uma ou duas vezes ao dia. Em alguns casos, uma dose máxima de 4 inalações duas vezes ao dia pode ser requerida como dose temporária de manutenção durante a piora da asma. *Adolescentes (12-17 anos)*: 2 inalações uma ou duas vezes ao dia. Durante a piora da asma a dose pode temporariamente ser aumentada para o máximo de 4 inalações duas vezes ao dia. *Instruções de Uso*: vide bula completa do produto. **Superdose:** A superdosagem de formoterol irá provavelmente provocar efeitos típicos dos agonistas beta-2-adrenérgicos: tremor, cefaléia, palpitações e taquicardia. Poderá igualmente ocorrer hipotensão, acidose metabólica, hipocalemia e hiperglicemia. Pode ser indicado um tratamento de suporte e sintomático. A administração de uma dose de 90 mcg durante três horas em pacientes com obstrução brônquica aguda e quando administrada três vezes ao dia como um total de 54 mcg/dia por 3 dias para a estabilidade asmática não suscitou quaisquer problemas de segurança. Não é esperado que uma superdosagem aguda da budesonida, mesmo em doses excessivas, constitua um problema clínico. Quando utilizado cronicamente em doses excessivas, podem ocorrer efeitos glicocorticosteróides sistêmicos (para informações de superdosagem grave vide bula completa do produto). **Apresentações: VANNAIR® 6/100 mcg/inalação:** Aerossol bucal 6/100 mcg/inalação em embalagem com 1 tubo contendo 120 doses. **USO ADULTO E PEDIÁTRICO. VANNAIR® 6/200 mcg/inalação:** Aerossol bucal 6/200 mcg/inalação em embalagem com 1 tubo contendo 120 doses. **USO ADULTO. USO POR INALAÇÃO ORAL. VENDA SOB PRESCRIÇÃO MÉDICA.** Para maiores informações, consulte a bula completa do produto. (VAN005). AstraZeneca do Brasil Ltda., Rod. Raposo Tavares, Km 26,9 - Cotia - SP - CEP 06707-000 Tel.: 0800-0145578. www.astrazeneca.com.br **Vannair®. MS – 1.1618.0234**

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