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HIGHLIGHT

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Facial thermography and noninvasive ventilation

Tuberculosis recurrence

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Contents

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Contents

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Thermography as a tool for monitoring the interface between the noninvasive ventilation mask and the skin

Bruno do Valle Pinheiro[1]

Noninvasive ventilation (NIV) is an important supportive measure for patients with acute respiratory failure. In patients with COPD exacerbation or acute cardiogenic pulmonary edema, for example, NIV is associated with reduced mortality and decreased need for intubation, its use therefore being recommended.[1] In patients with asthma or pneumonia, as well as in the prevention of weaning failure, NIV has been reported to improve clinical and functional parameters and can be used on the basis of clinical judgment.[2]

Although NIV plays an important role in the treatment of acute respiratory failure, NIV failure rates are relatively high, ranging from 5% to 40%.[3] In addition, mortality rates tend to be higher in patients in whom attempts at NIV fail than in those who are intubated without attempt at NIV.[4] Therefore, it is important to identify the risk factors for NIV failure.

Causes of NIV failure include interface-related issues such as air leaks.[3] More often than not, the NIV interface is adjusted incorrectly in an attempt to reduce air leaks, thus resulting in excessive pressure on the skin and, consequently, pressure ulcers, particularly on the nasal dorsum, which is a poorly vascularized area with little tissue between the skin surface and underlying bone.[5]

In the current issue of the JBP, Pontes et al.[6] published the results of a clinical study in which they used a new technology known as skin thermometry or thermography (infrared imaging of the skin) in order to evaluate the effects of NIV on the skin where it was in contact with the interface (an oronasal mask). The two regions of interest were the nasal dorsum and the area of contact between the skin surface and the oronasal mask, the effects being compared between healthy individuals receiving continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BiPAP). The participants (n = 20) were randomized to receive CPAP or BiPAP for 60 min, the exclusion criteria being as follows: having a dermatologic disease, a neurological disease, diabetes, nutritional disorders, or dehydration; currently using creams or chemical substances on the face; being on corticosteroids, anti-inflammatory drugs, or antihistamines; having an axillary temperature outside the normal range; and having excessive sun exposure, which was defined as direct, unprotected sun exposure for more than 30 min before the experiment. CPAP was set at 10 cmH_2O, whereas BiPAP was set to deliver an expiratory pressure of 5 cmH_2O and an inspiratory pressure of 20 cmH_2O (pressure support, 15 cmH_2O). In both groups, the interface for NIV was an oronasal mask. A questionnaire was used in order to determine whether participants had experienced any adverse effects (skin lesions, pain, or other adverse effects). Thermographic imaging was used in order to determine skin temperature, which was subsequently analyzed for correlations with adverse events.

Adverse effects were found to be more intense in the individuals receiving BiPAP than in those receiving CPAP. This is probably due to the fact that pressure levels were higher in the BiPAP group than in the CPAP group, an inspiratory positive airway pressure of 20 cmH_2O being delivered to the individuals in the BiPAP group. In addition, all pressure levels were preset, no adjustments being made to improve patient comfort. In a study published in 2009, a group of authors demonstrated that an increased inspiratory pressure is associated with interface-related side effects, a finding that was confirmed in other studies.[7,8]

The most significant contribution of the study by Pontes et al.[6] was their evaluating the effects of NIV on skin temperature where the skin was in contact with the interface, in an attempt to understand the impact of NIV modes and settings on the local skin microcirculation, as indirectly assessed by infrared thermographic imaging. One interesting finding was a reduction in skin temperature in the areas of contact between the face and the mask and between the nasal dorsum and the mask. The reduction was less pronounced in the area of contact between the nasal dorsum and the mask. However, the baseline temperature of the nasal dorsum skin was lower than was that of the facial skin. This finding was expected and suggests reduced blood flow, probably due to the pressure exerted by the mask. However, it is possible that the airflow provided by the ventilator contributed to the cooling of the skin. Nevertheless, the reduction in skin temperature was found to be less pronounced in the CPAP group than in the BiPAP group, a finding that suggests that the cooling was likely due to ischemia rather than the airflow provided by the ventilator. Given that the airflow provided by the ventilator tends to be higher for BiPAP than for CPAP, particularly at high pressures such as those used in the study by Pontes et al.,[6] its role in cooling the skin should have been more significant in the BiPAP group than in the CPAP group.

Another interesting finding was related to skin temperature after mask removal. In the area of contact between the face and the mask, skin temperature increased at 5 min after mask removal, continuing to rise over the course of the 30-min follow-up period. This increase in local skin temperature was probably due to flows returning to appropriate perfusion levels or even to increased perfusion caused by reactive hyperemia. Although this is expected in situations such as this,

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the same was not true for the nasal dorsum, where skin temperature decreased immediately after mask removal and remained low over the course of the 30-min follow-up period. This finding suggests that skin perfusion was less efficient in the nasal dorsum region, particularly in the presence of pressure levels that can cause ischemia, and explains why pressure ulcers are more likely to occur in that area during NIV, constituting the most significant contribution of the study in my opinion.

According to the authors themselves, one of the limitations of the study was the small sample size, especially if we take into account that the response varied among individuals. Another limitation lies in the possibility that thermography was affected by the temperature of the airflow provided by the ventilator. If that is the case, the use of heated humidification and evaluation of the areas to which the airflow provided by the ventilator was delivered but on which the mask exerted no pressure might aid in clarifying this issue. Finally, the study findings have limited clinical applicability because NIV duration was not long enough to evaluate the studied complications and because the study included healthy individuals (although the effects of NIV on microcirculation might be even worse in diseased individuals). However, none of the aforementioned limitations diminish the relevance of the study findings, because of the pioneering use of a new noninvasive method for monitoring an important side effect of NIV.

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A murine model of elastase- and cigarette smoke-induced emphysema: is it an opportunity to understand CT emphysema in humans?

Alfredo Nicodemos Cruz Santana[1]

COPD is an important public health care problem, being the third leading cause of death in the United States. In addition, researchers say that the prevalence of COPD will rise over the next decades. This fact is explained by the increase in smoking in developing countries and by worldwide aging, considering that COPD is up to three times more prevalent in elderly people (> 60 years of age) than in younger people. Consequently, COPD has been related to accelerated lung aging, including cell senescence and antiaging molecules. Therefore, knowing COPD-related changes that come with aging might help to discover novel therapies against this important disease.[1]

Classically, COPD is defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) as a disease that causes respiratory symptoms and persistent airflow limitation. This airflow limitation is shown by spirometry with reduced FEV_1/FVC ratio (post-bronchodilator FEV_1/FVC < 0.70).[2] However, it has been recently demonstrated that smokers with preserved FEV_1/FVC ratio may already present with respiratory symptoms, respiratory exacerbations, limitation of activities, emphysema, and airway wall thickening on chest CT.[3-5]

In special, people with emphysema on chest CT and preserved FEV_1/FVC ratio present with lower DLCO, altered quality of life, more frequent respiratory exacerbations, and even increased mortality.[3,6] Therefore, we have to pay attention to patients with CT emphysema (CTE) before they present with an altered FEV_1/FVC ratio. However, how can we prevent the progression of CTE to GOLD-defined COPD?

One possibility is to use angiotensin II receptor blockers (A2RB) or angiotensin converting enzyme inhibitors (ACEI). A recent study evaluated 4,472 participants and showed that A2RB and ACEI were associated with a slow progression of CTE.[6] However, this finding merits to be confirmed in randomized clinical trials including patients with CTE and normal FEV_1/FVC ratio, especially considering that, to date, there is no treatment recommended for these people.[2]

Another possibility is to use experimental models in order to study how to prevent the progression of emphysema from an initial to an advanced phase (i.e., from normal respiratory mechanics parameters to altered parameters). At this point, the model proposed by Rodrigues et al. is interesting.[7] It induces initial emphysema with a short course of cigarette smoke exposure due to the potentializing effect of elastase, which facilitates the use of this model by other researchers (because of the short amount of time needed to induce emphysema). However, it is important to use this experimental model in future studies in order to show whether or not emphysema progresses after cigarette smoke exposure cessation. The confirmation of this progression will allow researchers to test interventions to inhibit the worsening of emphysema using this murine model. Possible therapies that are interesting to study are physical activity, use of anti-inflammatory drugs, and use of N-acetylcysteine.

Physical activity was evaluated in a population-based study involving 6,790 participants.[8] The authors found that active smokers who had regular, moderate-to-high-intensity physical activity presented with a slower development of COPD when compared with those who had low-intensity physical activity. However, additional studies in humans as well as in animals are necessary to improve the understanding about these effects and to confirm the possible benefits of physical activity in decreasing the incidence of COPD and preventing COPD progression.

Another point to investigate is the potential role of exercising in asthma-COPD overlap. Recently, studies in humans and in animals have shown beneficial effects of exercise on asthma. Freitas et al.[9] performed a randomized controlled trial involving 52 obese patients with asthma, one group being submitted to a weight loss (WL) program plus exercise and one group submitted to a WL program plus sham (breathing and stretching training). The WL plus exercise group showed improvements in clinical control and pulmonary function, as well as reduced airway and systemic inflammation when compared with the sham group. Additionally, in an animal model of asthma, exercise has also reduced airway inflammation and even airway remodeling.[10]

In summary, this experimental model[7] is easier to use in research and may open new windows for the understanding of the disease and for testing inhibitors of emphysema progression.

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Multiple cavitated nodules

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

A 24-year-old male patient, who was an injection cocaine user, presented with about a 10-day history of cough and fever. A CT scan (Figure 1) showed multiple nodules, some of which were cavitated, with a predominant peripheral distribution.

The differential diagnosis of multiple cavitated nodules includes neoplastic diseases (metastases, lymphomas, etc.) and infectious diseases (septic embolism, granulomatous diseases, etc.), as well as other less frequent etiologies (nodular sarcoidosis, rheumatoid nodules, Wegener's granulomatosis, nodular amyloidosis, etc.).

The most common causes are cavitated metastases and septic embolism. The frequency of cavitation in metastatic nodules is much lower than is that observed in primary tumors. Squamous cell carcinomas are the tumors that most commonly cause cavitated metastases, accounting on average for 70% of such cases. Tumors of the head, neck, reproductive system, and large intestine are the most common primary sites, although any primitive tumor can in principle cause cavitated metastases. In metastases, cavitations originate both from tumor necrosis and from the formation of a check-valve mechanism, because of neoplastic infiltration into the distal airways. The cavitation walls are more frequently thick and irregular, but they can also be thin, similar to cysts.

Septic embolism is caused by embolization of microorganism-infected fragments to the lungs. The disease is most commonly secondary to right-sided endocarditis or to septic thrombophlebitis, but it can occur secondary to the use of infected intravascular catheters, to suppurative processes of the skin, head or neck, or to contamination related to intravenous drug use. CT findings consist of multiple, predominantly peripheral, bilateral, well- or ill-defined nodules exhibiting varying degrees of cavitation. Findings of associated peripheral triangles frequently correspond to infarction due to vascular occlusion. Septic embolism can be accompanied by unilateral or bilateral pleural effusion.

Clinical signs are very important for differential diagnosis. The presence of a known primary tumor should raise the suspicion of lung metastases. Patients with metastases are frequently asymptomatic from a pulmonary standpoint. Septic embolism is clinically characterized by fever, dyspnea, cough, and pleuritic pain. Blood culture can be positive. Laboratory tests can be key to diagnosing rheumatoid nodules or Wegener's granulomatosis. The patient in the case reported here had clinical signs of an infectious process, and blood culture was positive for *Streptococcus viridans*. The final diagnosis was septic embolism secondary to intravenous drug use.

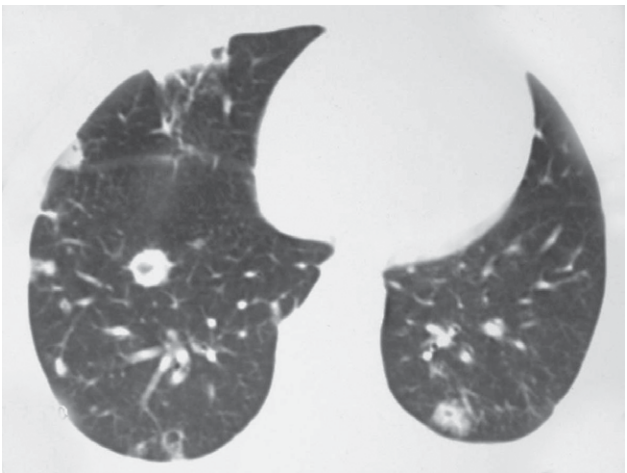

Figure 1. CT scan with lung window settings at the level of the lung bases, showing multiple nodules of various sizes, many of which were cavitated, with a predominant peripheral distribution.

RECOMMENDED READING

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Propensity scores: a tool to help quantify treatment effects in observational studies

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

PRACTICAL SCENARIO

To evaluate the effect of early high-frequency oscillatory mechanical ventilation (MV) vs. conventional MV on duration of MV and in-hospital mortality among children with acute respiratory failure, a retrospective cohort study was conducted using data from a randomized controlled trial (RCT).[1] Multivariable models, adjusted for confounding factors using a propensity score (PS), showed that the children on high-frequency oscillatory MV, when compared with those on conventional MV, were less likely to discontinue MV (hazard ratio = 0.75; 95% CI: 0.64-0.89; p = 0.001) and not at increased risk of in-hospital mortality (odds ratio = 1.28; 95% CI: 0.92-1.79; p = 0.15).

BACKGROUND

To evaluate the effect of interventions on health-related outcomes, RCTs are considered the gold standard study design because randomization gives every study participant a pre-established probability of being assigned to either an intervention or a comparison group. The goal is to prevent selection bias and confounding[2] at baseline by yielding the two groups with a similar distribution of measured and unmeasured confounders so that study results reflect the effect of the intervention on the outcome.

When conducting an RCT is not a feasible or ethical option, observational studies about interventions using PS to mimic randomization effects may be an alternative. The PS is a new composite variable that is created by combining a set of confounding variables that increase the probability of an individual being assigned to a specific intervention (treatment A vs. treatment B) and then incorporated into the analysis. In our example, the goal was to evaluate the effect of two MV strategies (intervention) on duration of MV and in-hospital mortality (outcomes). To mimic the effects of randomization and make both groups similar regarding confounding variables, a PS was created, based on variables clinicians utilize to assign the specific MV strategy and included it in the multivariable analysis as a covariate to adjust for confounders.

PROPENSITY SCORE

Definition: a variable that results from calculating the likelihood (propensity) of each participant receiving a treatment conditional on values of variables thought to influence the decision to prescribe treatment A or B.

Variable selection: Researchers select variables for PS based on their effect as confounders or predictors of the exposure (the intervention). Typical variables included in PS are demographics (age, gender, and socioeconomic status), disease severity, and characteristics of the treatment environment (characteristics of physicians and their practice). The variables are included as exposure variables in a logistic regression model with the intervention as the outcome. This model calculates a score for each participant representing their estimated likelihood of receiving treatment A or B, conditional on a weighed score of the values of that participant on the set of exposure variables used to create the PS.

Analytical methods: Four[3] strategies are typically used in observational studies (Table 1), each having advantages and disadvantages. We recommend consulting with a biostatistician to guide all PS processes.

Table 1. Methods used in order to include propensity scores in observational studies.

Method	Description
Stratification	Strata are created with the participants that present with equal values in the propensity score. Weighted averages within strata are calculated before the multivariable analysis is conducted.
Matching	Each exposed participant (treatment A) is matched to an unexposed participant (treatment B) with same propensity score value before the multivariable analysis is conducted.
Inverse weighting	Two potential samples are created to represent samples that would have been observed if everyone had been exposed to the treatment or no one had been exposed to it.
Covariate adjustment	A regression model of the intervention on the outcome is fit to the both the intervention group (exposure) and the propensity score (covariate).

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ORIGINAL ARTICLE

Influence of the ventilatory mode on acute adverse effects and facial thermography after noninvasive ventilation

Suzy Maria Montenegro Pontes[1], Luiz Henrique de Paula Melo[2], Nathalia Parente de Sousa Maia[3], Andrea da Nóbrega Cirino Nogueira[3], Thiago Brasileiro Vasconcelos[4], Eanes Delgado Barros Pereira[5], Vasco Pinheiro Diógenes Bastos[3], Marcelo Alcantara Holanda[5]

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Study carried out in the Laboratório da Respiração – Resplab – Universidade Federal do Ceará, Fortaleza (CE) Brasil.

ABSTRACT

Objective: To compare the incidence and intensity of acute adverse effects and the variation in the temperature of facial skin by thermography after the use of noninvasive ventilation (NIV). **Methods:** We included 20 healthy volunteers receiving NIV via oronasal mask for 1 h. The volunteers were randomly divided into two groups according to the ventilatory mode: bilevel positive airway pressure (BiPAP) or continuous positive airway pressure (CPAP). Facial thermography was performed in order to determine the temperature of the face where it was in contact with the mask and of the nasal dorsum at various time points. After removal of the mask, the volunteers completed a questionnaire about adverse effects of NIV. **Results:** The incidence and intensity of acute adverse effects were higher in the individuals receiving BiPAP than in those receiving CPAP (16.1% vs. 5.6%). Thermographic analysis showed a significant cooling of the facial skin in the two regions of interest immediately after removal of the mask. The more intense acute adverse effects occurred predominantly among the participants in whom the decrease in the mean temperature of the nasal dorsum was lower (14.4% vs. 7.2%). The thermographic visual analysis of the zones of cooling and heating on the face identified areas of hypoperfusion or reactive hyperemia. **Conclusions:** The use of BiPAP mode was associated with a higher incidence and intensity of NIV-related acute adverse effects. There was an association between acute adverse effects and less cooling of the nasal dorsum immediately after removal of the mask. Cutaneous thermography can be an additional tool to detect adverse effects that the use of NIV has on facial skin.

Keywords: Masks; Noninvasive ventilation; Thermography.

INTRODUCTION

The use of noninvasive ventilation (NIV) in acute respiratory failure is associated with a reduced need for tracheal intubation, decreased length of hospital stay, and decreased mortality.[1-3]

NIV intolerance is one of the reasons for NIV failure.[4,5] NIV failure can occur in 5-40% of cases, being associated with a 4-fold greater likelihood of in-hospital mortality—NIV failure (OR = 3.95; 95% CI: 1.74-8.99).[6] Interface-related problems are the most common adverse effects, accounting for 50-100% of all complications, such as excessive air leaks, discomfort caused by air pressure on the face, claustrophobia, rebreathing of carbon dioxide, skin lesions, facial pain, and oronasal dryness.[7] Acute adverse effects are related to the type of mask and the pressure settings.[8,9]

Rates for the incidence of facial skin lesions resulting from the use of NIV masks range from 10-31% in adults.[10] Pediatric studies have reported a 60% incidence of pressure ulcers associated with the use of medical devices, including masks for NIV.[11] The incidence of pressure ulcers on the face and in the area of the nasal dorsum has been reported to be approximately 17%.[12] The area of the nasal dorsum, with its scarce subcutaneous cellular tissue and its poor vascularization, is more likely to develop severe skin lesions because it is subject to greater contact pressure with the oronasal mask.[13]

Infrared skin thermometry or thermography is the most efficient means to study skin temperature distribution, by means of measurement of the temperature variations caused by greater or lesser irrigation of the microvascular territory.[14,15] Thermography has contributed to the diagnosis and intensity monitoring of various conditions in which skin temperature may reflect an inflammatory process in the underlying tissues or may indicate where the blood flow may increase or decrease.[16]

The hypotheses of the present study were as follows: NIV-related variables (ventilatory mode and pressure settings) have an effect on local skin microcirculation in the zones of contact between the skin and the mask, changing the temperature levels of the facial skin tissue in these zones; and these possible temperature changes in the contact areas are measurable by infrared thermography and can be related to acute adverse effects.

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The objective of the present study was to compare the incidence and intensity of acute adverse effects and the variation in facial skin temperature between NIV modes—continuous positive airway pressure (CPAP) vs. bilevel positive airway pressure (BiPAP)—and to analyze the relationship between acute adverse effects of the application of NIV via oronasal mask and the variations in facial skin temperature in two areas: the zones of contact between the face and the mask; and the nasal dorsum.

METHODS

This was a prospective, analytical intervention study in humans. It was carried out in the Respiratory Laboratory of the *Universidade Federal do Ceará* (UFC, Federal University of Ceará) between March of 2014 and December of 2015. The sample consisted of 20 individuals (18-45 years of age) who were selected by convenience from among the participants in the Respiratory Laboratory and the student body of the UFC campus and who agreed to participate in the study. There were no dropouts or exclusions. All individuals participated in ventilatory mode randomization. The exclusion criteria were as follows: being under dermatological treatment for skin lesions or making use of creams or any type of chemical substance on the face; being on corticosteroids, anti-inflammatory drugs, or antihistamines; having an axillary temperature outside the normal range (36.5°C-36.8°C); having excessive sun exposure, which was previously defined by the researchers as direct, unprotected sun exposure for more than 30 min before starting the experiment; and having a neurological disease, diabetes mellitus, nutritional disorders, or dehydration. The study was submitted to and approved by the UFC Research Ethics Committee (CAAE 20060113.4.0000.5045).

Study protocol

All participants were assessed by the same dermatologist of the UFC Department of Clinical Medicine, who used a specific, dermatological assessment form to check skin integrity and determine skin type and subsequently performed the first thermographic measurement.

Randomization was performed as follows: 20 labels reading either BiPAP or CPAP were placed into an opaque container; and the participants themselves drew a label out of the container.

After this randomization, the ventilator was set up—CPAP = 10 cmH_2O or BiPAP; expiratory positive airway pressure (EPAP) = 5 cmH_2O; inspiratory positive airway pressure (IPAP) = 20 cmH_2O; and pressure support = 15 cmH_2O—and the choice of interface to minimize air leak was made on the basis of the anatomical characteristics of the volunteer's face. The Mirage Quattro FX mask (ResMed, Bella Vista, Australia), which is an oronasal interface equipped with an exhalation valve, was the model made available to the participants.

Subsequently, the mask was gently placed on the participant's face and was connected to the NIV ventilator; the entire system was checked for the presence of leaks, and the necessary corrections were made.

We used two dedicated, single-limb NIV ventilators that can be set in CPAP mode and BiPAP mode, both equipped with a memory card to record data during therapy, without a humidifier. The Auto VPAP (ResMed) was set in BiPAP mode, with an EPAP of 5 cmH_2O and an IPAP of 20 cmH_2O ; the Autoset II (ResMed) was set in CPAP mode, with a fixed pressure of 10 cmH_2O.[17]

The individual remained seated for an initial 10-min period of adaptation to NIV, which was then continued for an additional 50 min, totaling 60 min of NIV.

Immediately after removal of the mask, the second thermographic measurement was performed, and, to prevent any kind of influence by the team, the participants then viewed their own faces in a high-definition digital photographic image in order to complete a questionnaire about NIV-related adverse effects, with a score ranging from zero (no problem) to three (intense problem).[18] The adverse effects were grouped into three categories: skin lesions; pain; and other adverse effects (Appendix 1; available in the online version of the JBP; http://www.jornaldepneumologia.com.br/detalhe_anexo.asp?id=49). Subsequently, thermographic images were taken at 5, 15, and 30 min after removal of the mask, with the participants in the same posture and under the same conditions as those of the previous measurements.

The memory cards of the ventilators were read with ResScan software (ResMed) in order to record leaks occurring around the mask.

The thermographic images taken with a VarioCAM thermographic camera (InfraTec, Jena, Germany) were stored in the memory card of the camera and analyzed with IRBIS® Professional analysis software for thermographic images, version 2.2 (InfraTec). The thermographic images were converted and transferred to MATLAB® simulation software, version 2015a (MathWorks, Natick, MA, USA). On the basis of a reference point established by a piece of styrofoam glued between the participant's eyebrows (Figure 1A), the regions of interest in the original images were cut out in the shape of a trapezoid (Figures 1B and 1C). By means of a specific script, a color-based comparative analysis of the temperature variation in the zones of contact between the skin and the mask was carried out by superimposing the images taken at each of the time points after removal of the mask on those taken at baseline. The room where the protocols were performed was kept well lit at a temperature of 22°C (range, 21.5°C-22.5°C) and at a relative humidity of 60% (range, 57.94%-60.26%). The variation in room temperature did not exceed 1°C over the 20-min period.

Statistical analysis of variables

For descriptive statistics, means and standard deviations or medians and interquartile ranges were

calculated for quantitative variables, depending on the sample distribution. Categorical variables were expressed as absolute and relative frequencies. Categorical parameters were compared by means of Fisher's exact test. Since the scoring of adverse effects resulted from a subjective finding by each volunteer, we chose to group the adverse effects into three categories.[18]

The variation in mean temperature was compared between the two ventilatory modes (CPAP vs. BiPAP) and between the two regions of interest (zone of contact between the nasal dorsum and the mask vs. zone of contact between the face and the mask) by ANOVA, depending on the normality of test results. In addition, Pearson's correlation coefficient between skin temperature and adverse effects was analyzed. The level of statistical significance required to reject the null hypothesis was set at 5% ($p < 0.05$).

RESULTS

Table 1 shows the participant demographic characteristics and the room environmental conditions, by ventilatory mode. The sample consisted of 20 volunteers with a mean age of 28.15 ± 8.08 years (95% CI: 20.07-36.23); the anthropometric characteristics (mean BMI of 23.57 ± 2.51 kg/m² and mean axillary temperature of 36.39°C) were homogeneous. The room environmental conditions were kept under control (mean relative humidity of 59.1 ± 116% and mean room temperature of 22.1 ± 0.31°C). The mean air leak measured by the NIV ventilator during NIV was 2.30 ± 3.19 L/min.

Dermatological assessment showed no dermatological lesions, facial malformations, or changes in touch or pain sensitivity. Skin elasticity was preserved. The oval face shape predominated, being found in 80% of the individuals receiving CPAP and in 90% of those receiving BiPAP. Skin color was light brown in 80% of the volunteers. Skin type was oily in 70% of the individuals.

Table 2 shows the results of the scores for adverse effects in three predefined categories, by ventilatory mode. The effects causing a greater degree of problem or discomfort during BiPAP ventilation were pruritus on the nose, claustrophobia, dryness, and nasal congestion, whereas, during CPAP ventilation, none of the adverse effects reached the maximum degree of discomfort.

When comparing the participants' answers regarding the intensity of each adverse effect individually, by ventilatory mode, we found no significant differences; however (Figure 2A), when grouping the participants' answers to all categories of adverse effects, we found a significant difference in occurrence of the more intense adverse effects in BiPAP mode. We significantly found that moderate and intense adverse effects (scores 2 and 3) were more common immediately after removal of the mask in the group of participants in whom there was no reduction in the temperature of the nasal dorsum (Figure 2B). There was a statistically significant decrease in the mean temperature of the nasal dorsum, as compared

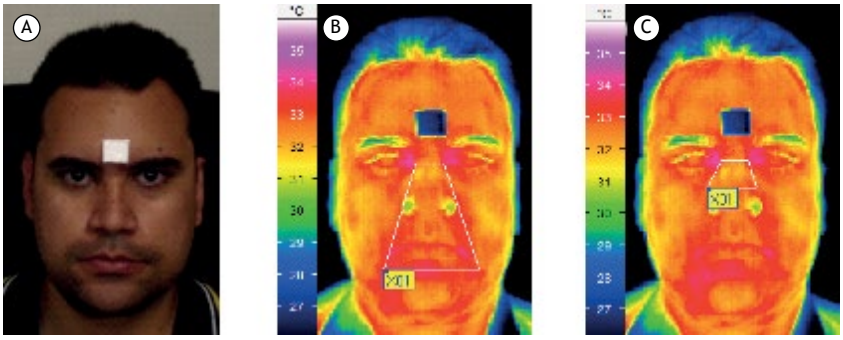

Figure 1. Conventional photograph (in A) and thermographic images of the areas of contact between the face and the mask (in B) and between the nasal dorsum and the mask (in C).

Table 1. Participant demographic characteristics and room environmental conditions, by ventilatory mode.[a]

Characteristic	BiPAP (n = 10)	CPAP (n = 10)	Total (N = 20)
Age, years	27.4 ± 9.20	28.9 ± 7.20	28.15 ± 8.08
Weight, kg	66.3 ± 11.09	69.38 ± 16.84	67.84 ± 13.97
Height, m	1.69 ± 0.07	1.68 ± 0.12	1.68 ± 0.09
BMI, kg/m²	22.92 ± 2.13	24.23 ± 2.80	23.57 ± 2.51
Axillary temperature, °C	36.4 ± 0.39	36.39 ± 0.29	36.39 ± 0.34
Male gender, n (%)	5 (50)	5 (50)	10 (50)
Relative humidity, %	59.3 ± 1.16	58.9 ± 1.19	59.1 ± 1.16
Room temperature, °C	22.14 ± 0.30	22.06 ± 0.33	22.1 ± 0.31
Air leak, L/min	2.16 ± 1.56	2.83 ± 4.31	2.32 ± 3.19

BiPAP: bilevel positive airway pressure; and CPAP: continuous positive airway pressure. [a]Values expressed as mean ± SD, except where otherwise indicated.

Table 2. Classification of adverse effect intensity in the participants, by ventilatory mode.[a]

Adverse effect	Ventilatory mode			
	BiPAP (n = 10)		CPAP (n = 10)	
	No or mild	Moderate or intense	No or mild	Moderate or intense
Category 1 - Skin lesions				
Erythema on the cheek	9 (90)	1 (10)	10 (100)	0 (0)
Erythema on the nasal dorsum	5 (50)	5 (50)	6 (60)	4 (40)
Erythema on the chin	9 (90)	1 (10)	9 (90)	1 (10)
Pruritus on the cheek	8 (80)	2 (20)	10 (100)	0 (0)
Pruritus on the nose	7 (70)	3 (30)	9 (90)	1 (10)
Pruritus on the chin	8 (80)	2 (20)	10 (100)	0 (0)
Category 2 - Pain				
Nasal dorsum	9 (90)	1 (10)	9 (90)	1 (10)
Ear	8 (90)	2 (20)	10 (100)	0 (0)
Paranasal sinuses	9 (90)	1 (10)	10 (100)	0 (0)
Cheek	9 (90)	1 (10)	10 (100)	0 (0)
Chin	10 (100)	0 (0)	10 (100)	0 (0)
Head	10 (100)	0 (0)	9 (90)	1 (10)
Category 3 - Other adverse effects				
Claustrophobia	9 (90)	1 (0)	10 (100)	0 (0)
Air leak	8 (80)	2 (20)	10 (100)	0 (0)
Dryness	6 (60)	4 (40)	9 (90)	1(10)
Nasal congestion	8 (80)	2 (20)	10 (100)	0 (0)
Respiratory distress	9 (90)	1 (10)	9 (90)	1 (10)
Chest discomfort	10 (100)	0 (0)	10 (100)	0 (0)

BiPAP: bilevel positive airway pressure; and CPAP: continuous positive airway pressure. [a]Data expressed as n (%).

with baseline, immediately, at 5 min, at 15 min, and at 30 min after removal of the mask. Figure 3A depicts the mean temperature in the areas of contact between the face and the mask and between the nasal dorsum and the mask before and immediately after 60 min of NIV, as well as at 5, 15, and 30 min after removal of the mask. We observed a significantly different behavior between the two areas. In the area of contact between the face and the mask immediately after removal of the mask, there was a decrease in temperature; however, at the subsequent time points (at 5, 15, and 30 min after removal of the mask), there was a trend toward a return to baseline values. In the area of contact between the nasal dorsum and the mask, there was a decrease in mean temperature immediately after removal of the mask, and the cooling persisted at the subsequent time points. Figure 3B depicts the temperature variation in the area of the nasal dorsum by ventilatory mode. We observed that the decrease in temperature persisted in CPAP mode.

In the qualitative assessment (Figure 4) of the superimposed images taken before NIV and at each of the other time points (immediately, at 5 min, at 15 min, and at 30 min after removal of the mask), we found that the blue color (maximum cooling) predominated in CPAP mode and the red color (maximum heating) predominated in BiPAP mode.

There were no statistically significant correlations between adverse effects and the temperature variation in the two regions of interest when Pearson's correlation coefficient was used (See table in Appendix 2; available in the online version of the JBP; http://www.jornaldepneumologia.com.br/detalhe_anexo.asp?id=49).

DISCUSSION

The incidence and intensity of acute adverse effects resulting from the use of NIV (claustrophobia, dryness, and nasal congestion) were higher in the participants receiving BiPAP than in those receiving CPAP. Thermographic analysis of the oronasal region showed cooling in the area of contact between the facial skin and the mask and in the area of the nasal dorsum immediately after removal of the mask. The area of the nasal dorsum varied less relative to the baseline temperature, showing less cooling than the zone of contact between the facial skin and the mask. In the area of contact between the facial skin and the mask, the temperature gradually returned to its baseline value, that is, it increased at the subsequent time points. Visual analysis of the zones of cooling and heating on the face over time showed coexisting areas of hypoperfusion or reactive hyperemia from acute use of NIV after removal of the mask, with a trend toward an increase in temperature in the group receiving BiPAP.

The more intense acute adverse effects assessed immediately after removal of the mask occurred

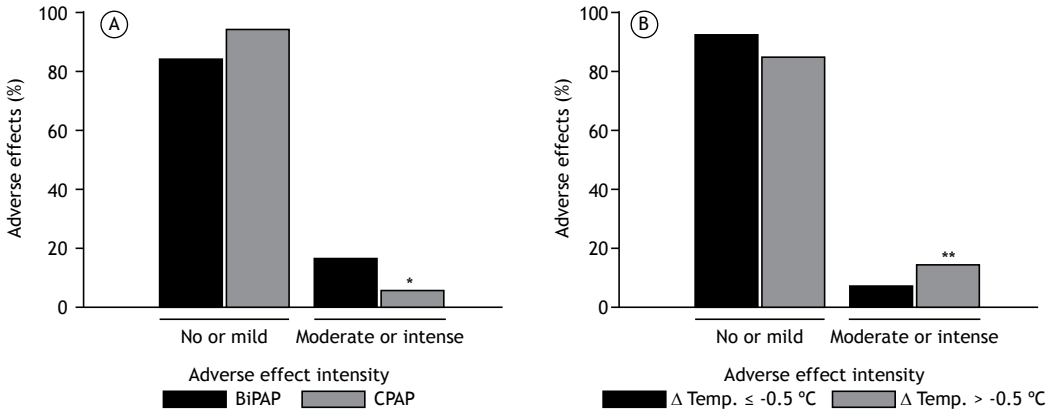

Figure 2. In A, proportion of participant-reported adverse effects by ventilatory mode. In B, proportion of participant-reported adverse effects by temperature variation in the area of the nasal dorsum immediately after removal of the mask. ΔTemp: temperature variation between baseline and immediately after removal of the mask; BiPAP: bilevel positive airway pressure; and CPAP: continuous positive airway pressure. *p = 0.001; **p = 0.04. Total number of reported adverse events = 360.

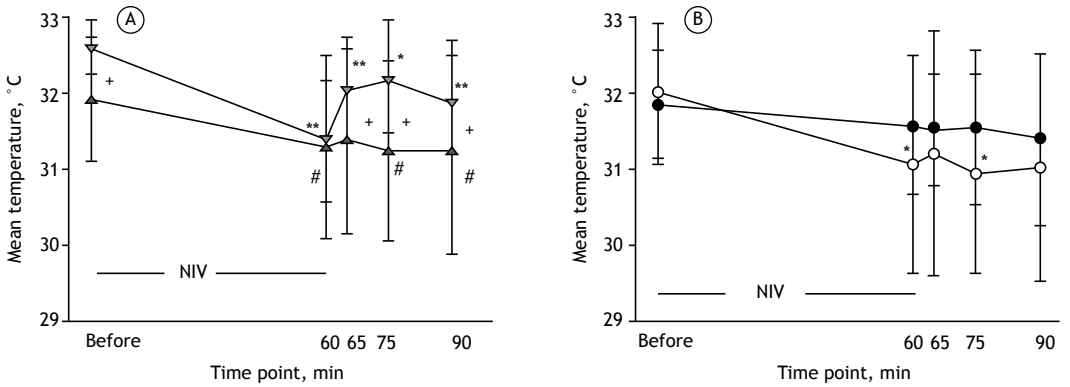

Figure 3. In A, mean temperature in the areas of contact between the face and the mask (inverted triangles) and between the nasal dorsum and the mask (gray triangles) before and immediately after 60 min of noninvasive ventilation (NIV), as well as at 5 min (65 min), 15 min (75 min), and 30 min (90 min) after removal of the mask. In B, mean temperature in the area of contact between the nasal dorsum and the mask at the same time points, by ventilatory mode—bilevel positive airway pressure (black circles) and continuous positive airway pressure (white circles). Figure 3A: *p < 0.05 and **p < 0.01 vs. baseline temperature; $^{+}$p < 0.05 area of contact between the nasal dorsum and the mask vs. area of contact between the face and the mask; $^{\#}$p < 0.05 area of contact between the nasal dorsum and the mask vs. baseline temperature. Figure 3B: *p < 0.05 continuous positive airway pressure mode vs. baseline.

among the participants in whom the nasal dorsum skin showed less cooling.

The present study is the first to use thermographic analysis of the facial skin before and after the use of NIV at various time points and to test the association of these findings, for BiPAP and CPAP, with acute adverse effects. The facial skin temperature data of the present study are consistent with those obtained by Haddad et al.,[19] demonstrating the validity of our methodology.

Holanda et al.[8] studied three types of masks and the acute adverse effects related to their use by comparing two different NIV pressure settings in healthy individuals: a lower pressure setting (IPAP = 11 cmH_2O and EPAP = 6 cmH_2O); and a higher pressure setting (IPAP = 15 cmH_2O and EPAP = 10 cmH_2O). The increase in pressure increased the incidence of acute adverse effects for the three masks. It is possible to infer that, in the present study, BiPAP was associated with a higher incidence and intensity of acute adverse effects, as compared with CPAP, probably because of higher levels of IPAP (20 cmH_2O vs. 10 cmH_2O).

Although microcirculation in the area of contact between the mask and the skin was not subjected to direct measurement, it may have been compromised by decreased blood supply (immediately after removal of the mask), which would result in cooling of the contact area, probably caused by pressure ischemia; subsequently, the temperature returned to its baseline values or even surpassed them, resulting in heating of the area, presumably because of reactive hyperemia. In the area of the nasal dorsum, initially there was a smaller decrease in mean temperature relative to the baseline temperature. On average, there was no return to the baseline values (before NIV); however, in some individuals, heating occurred in this area,

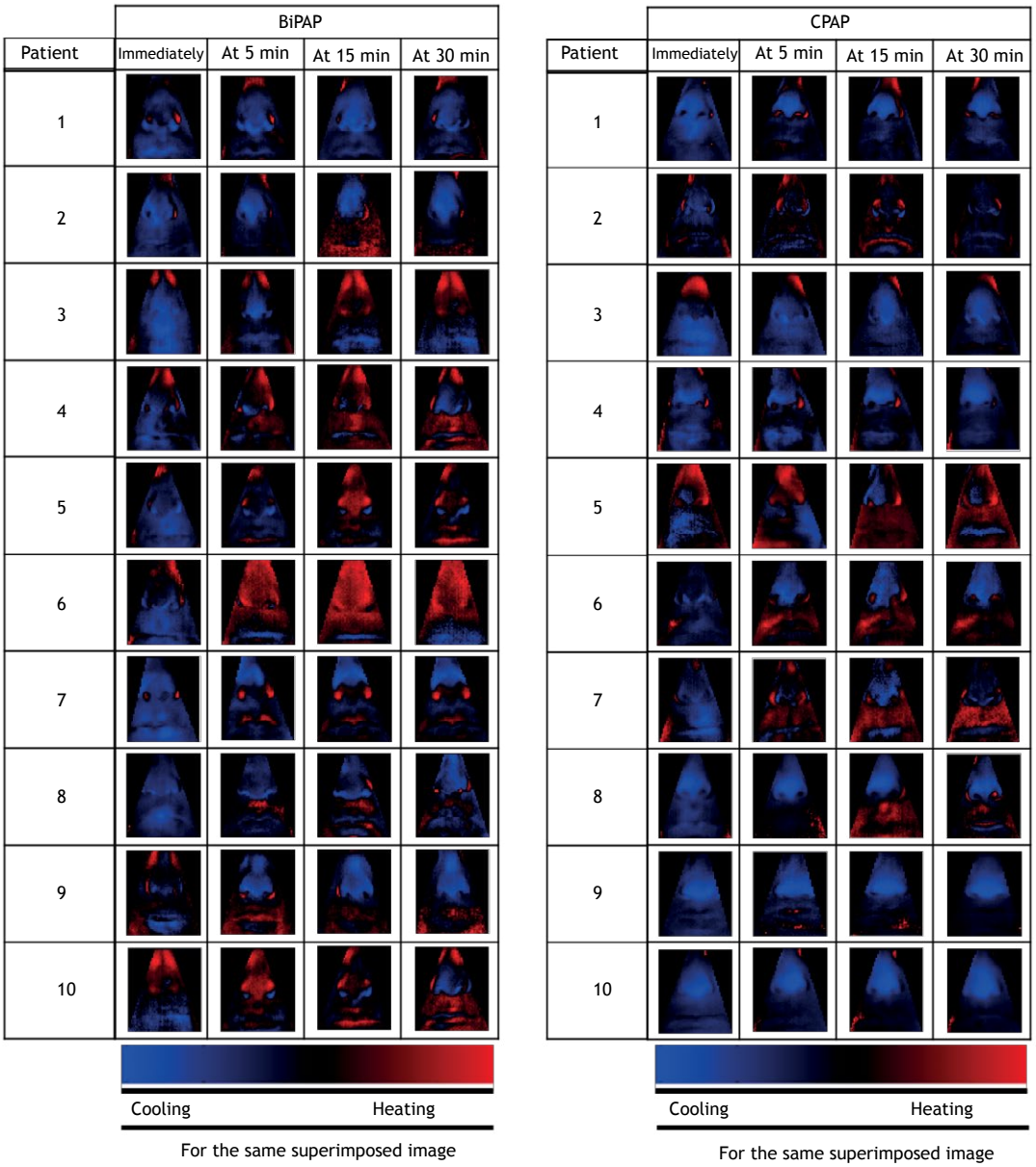

Figure 4. Qualitative assessment of the superimposed images taken before noninvasive ventilation and at each of the other time points: immediately, at 5 min, at 15 min, and at 30 min after removal of the mask. The visual color bar scale ranging from maximum cooling (blue) to maximum heating (red) was used for each superimposed image. BiPAP: bilevel positive airway pressure; and CPAP: continuous positive airway pressure.

demonstrating that the response to the application of NIV is quite individual and varied.

The phenomenon of reactive hyperemia would explain the findings of the present study, or the poor vascularization of the cutaneous territory of the nasal dorsum would be a reason for the smaller impact of the mask pressure on the temperature variation in this area. Visual analysis of the zones of cooling and heating on the face over time showed that the response to the application of NIV is quite individual and varied.

Capillary perfusion pressure plays an important role in skin tissue integrity. The pressures leading to capillary collapse usually range from 12 to 32 mmHg or from 20 to 40 cmH_2O. Direct application of a higher pressure than capillary closing pressure on the skin and soft tissues will cause hypoxia in the area, culminating in tissue ischemia and anoxia.[20] By removing pressure after a short period of time, blood flow is restored through reactive hyperemia. If there is prolonged, persistent application of pressure, the risk for ischemic injury increases, which might cause the onset of a pressure ulcer.[21] In the present study, there was a higher incidence of more intense acute adverse events in the group of participants with a smaller decrease in the mean temperature of the

nasal dorsum, emphasizing the predisposition of this particular area to skin perfusion disturbances. Souto et al.[13] emphasized that the oronasal mask has several areas that are subject to critical tension values for the development of skin lesions, the most relevant being in the upper lateral region of the nose.

Weng,[22] seeking preventive measures against the development of skin lesions in patients using face masks for BiPAP ventilation, found a proportion of 96% of stage I pressure ulcers with hyperemia on the nasal dorsum, which is in line with data from clinical studies in terms of the susceptibility of the area of the nasal dorsum to skin lesions, including its anatomical characteristic of a thin layer of poorly vascularized epidermis covering the bone surface.

We concluded that the incidence and intensity of acute adverse effects were higher in the participants receiving BiPAP ventilation. There was an association between acute adverse effects of the application of NIV via oronasal mask and less cooling or greater reactive hyperemia in the area of the nasal dorsum after removal of the mask. Thermography can be an additional tool to detect skin areas at high risk of developing skin lesions.

Methodological rigor in preparing the environment and the participants and a literature review on the optimal conditions to perform thermography are the strengths of this study. However, the study has limitations. The sample was small, involving healthy participants, and the results would probably be different in situations in which other risk factors (age, nutritional status, medication use, presence of comorbidities, and level of consciousness) were present.[12,21,23] Another important limitation was the lack of a control group receiving heated humidification.[24,25]

The practical implication is to underscore the importance of monitoring acute adverse effects on the skin of patients receiving NIV. The use of pressure masks is associated with the development of facial skin lesions, probably because of impaired perfusion.[26-29] Thermography would be an additional tool for more accurate determination of facial skin areas at high risk of NIV-related pressure lesions or ulcers. Therefore, the results stimulate interest in future clinical trials assessing this perspective.

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ORIGINAL ARTICLE

A murine model of elastase- and cigarette smoke-induced emphysema

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ABSTRACT

Objective: To describe a murine model of emphysema induced by a combination of exposure to cigarette smoke (CS) and instillation of porcine pancreatic elastase (PPE). **Methods:** A total of 38 C57BL/6 mice were randomly divided into four groups: control (one intranasal instillation of 0.9% saline solution); PPE (two intranasal instillations of PPE); CS (CS exposure for 60 days); and CS + PPE (two intranasal instillations of PPE + CS exposure for 60 days). At the end of the experimental protocol, all animals were anesthetized and tracheostomized for calculation of respiratory mechanics parameters. Subsequently, all animals were euthanized and their lungs were removed for measurement of the mean linear intercept (Lm) and determination of the numbers of cells that were immunoreactive to macrophage (MAC)-2 antigen, matrix metalloproteinase (MMP)-12, and glycosylated 91-kDa glycoprotein (gp91*phox*) in the distal lung parenchyma and peribronchial region. **Results:** Although there were no differences among the four groups regarding the respiratory mechanics parameters assessed, there was an increase in the Lm in the CS + PPE group. The numbers of MAC-2-positive cells in the peribronchial region and distal lung parenchyma were higher in the CS + PPE group than in the other groups, as were the numbers of cells that were positive for MMP-12 and gp91*phox*, although only in the distal lung parenchyma. **Conclusions:** Our model of emphysema induced by a combination of PPE instillation and CS exposure results in a significant degree of parenchymal destruction in a shorter time frame than that employed in other models of CS-induced emphysema, reinforcing the importance of protease-antiprotease imbalance and oxidant-antioxidant imbalance in the pathogenesis of emphysema.

Keywords: Tobacco; Models, animal; Emphysema; Respiratory physiological phenomena; Lung injury.

INTRODUCTION

Animal models of emphysema have been extensively used in order to provide a better understanding of the pathogenesis of the disease. This is due to the fact that studies involving human participants focus exclusively on morphological and molecular analysis of lung tissue fragments from patients undergoing surgical procedures or are in vitro studies conducted at a single time point.

The cigarette smoke (CS) and elastase models of emphysema are the most commonly used murine models of the disease, and both can produce pathological changes resembling human emphysema. However, given that neither can closely mimic the disease in humans, it is important to understand the advantages and disadvantages of each.[1] Although CS-induced emphysema models appear to best represent the pathogenesis of human emphysema, one major limitation of such models is that, regardless of how long animals are exposed to CS, the resulting alveolar enlargement is mild in comparison with that resulting from animal models of elastase-induced emphysema.[1-3] Depending on the dose, intratracheal or intranasal instillation of elastase can induce severe emphysema in a short time,[1,4-7] as well as a significant increase in alveolar enlargement, collagen fibers, and elastic fibers, suggesting a process of lung parenchymal remodeling.[4,6] However, the main disadvantage of elastase models of emphysema is that they do not trigger all of the physiological events that CS models do, their relevance for therapeutic approaches therefore being limited.[1]

Animal models of CS- and elastase-induced emphysema have been used not only to elucidate the structural changes in lung tissue but also to clarify the mechanistic insights involved in emphysema development. Although the protease-antiprotease imbalance hypothesis remains the most widely accepted hypothesis to explain the parenchymal destruction of emphysema,[8-11] oxidative stress should also be taken into account, given that the oxidant burden is increased in smokers as a response to CS compounds.[12,13] In an attempt to reduce the smoke exposure time required to induce emphysema and mimic as closely as possible the pathological features of human

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emphysema, we developed an experimental model of emphysema induced by a combination of instillation of porcine pancreatic elastase (PPE) and exposure to CS for 2 months only.

METHODS

The present study was approved by the Human and Animal Research Ethics Committee of the University of São Paulo School of Medicine, located in the city of São Paulo, Brazil. Six- to eight-week-old male C57BL/6 mice (weighing 20-25 g) were used in the study. All animals received humane care in compliance with the US National Institutes of Health Guide for the Care and Use of Laboratory Animals (NIH Publication no. 85-23, revised in 1996).

For emphysema induction, the animals were anesthetized with a combination of xylazine and ketamine (i.m., 5 mg/kg and 40 mg/kg, respectively) and then challenged with an intranasal instillation of 50 µL of type I PPE (E1250; Sigma-Aldrich, St. Louis, MO, USA) at a lower dose (i.e., 0.33 IU) than that used in other models of PPE-induced emphysema, given that our goal was to induce emphysema by combining instillation of PPE and exposure to CS.[14] The animals received a total of two doses of PPE (one dose at day 0 and one dose at day 30). Control animals received 50 µL of 0.9% saline solution (vehicle).

For animals undergoing CS exposure, the protocol began on day 1. The animals were exposed to CS in a 28-L inhalation chamber with two inlets (one for air and one for smoke), one outlet, and a fan for better mixing of air and smoke inside the chamber. One of the inlets was set to deliver synthetic air flow at 2 L/min, and the other was set to deliver synthetic air flow coming from a Venturi system connected to a lit cigarette, suctioning the CS into the chamber. It was possible to change that flow rate to increase or decrease the amount of smoke in the chamber. After several measurements of the concentration of CO in the chamber, the flow rate was set to 1.5 L/min, which produced CO levels ranging from 250 ppm to 350 ppm. Carboxyhemoglobin levels were maintained at 10 ± 1.3% in all mice undergoing CS exposure. The animals were exposed to smoke from 12 ± 1 commercial filter cigarettes (each containing 0.8 mg of nicotine, 10 mg of tar, and 10 mg of CO), at a total particulate matter concentration of 411.4 ± 30 µg/m^3 per day. Exposure duration was 60 min per day (i.e., two 30-min exposure periods) 5 days a week for 2 months. Control mice were exposed to room air.[15]

A total of 38 C57BL/6 mice were randomly divided into four groups (Figure 1):

1. control (n = 9), comprising mice receiving an intranasal instillation of 0.9% saline solution on day 0 and euthanized on day 60
2. PPE (n = 9), comprising mice receiving two intranasal instillations of PPE (one on day 0 and one on day 30) and euthanized on day 60
3. CS (n = 10), comprising mice exposed to CS twice a day 5 days a week for 60 days and euthanized on day 60
4. CS + PPE (n = 10), comprising mice receiving two intranasal instillations of PPE (one on day 0 and one on day 30), undergoing the aforementioned CS exposure protocol from day 1 onward, and euthanized on day 60

At the end of the experimental protocol, all animals were deeply anesthetized with an intraperitoneal injection of thiopental (70 mg/kg), tracheostomized, and then connected to a ventilator for small animals (flexiVent™; SCIREQ, Montreal, QC, Canada), the ventilator being set to a tidal volume of 10 mL/kg and an RR of 120 breaths/min. All animals received an intraperitoneal injection of pancuronium bromide (0.2 mg/kg) in order to avoid increased work of breathing.[15] Respiratory system input impedance was measured by the forced oscillation technique, a 16-s perturbation (at frequencies of 0.25-9.125 Hz) being applied and the exhalation valve being kept closed.[16] Pressure was generated, and impedance was calculated as a function of the different frequencies. In order to calculate respiratory mechanics parameters such as airway resistance, tissue damping, and tissue elastance, we used a constant phase model described elsewhere.[17]

After calculation of the aforementioned parameters, a 2-cm incision was made in the abdomen and the animals were euthanized by exsanguination from the abdominal aorta. Subsequently, the anterior chest wall was opened and the lungs were removed *en bloc* and fixed in 4% formaldehyde at a constant pressure of 20 cmH_2O for 24 h, conventional histology being subsequently performed. In brief, lower- and upper-lobe specimens were embedded in paraffin and cut into 5-µm sections that were stained with hematoxylin and eosin in order to measure the mean linear intercept (Lm), which is an indicator of mean alveolar diameter.[18]

The lung tissue was immunostained with the following antibodies: rat anti-mouse macrophage (MAC)-2 monoclonal antibody (1:50,000; CEDARLANE®, Burlington, ON, Canada); polyclonal goat anti-mouse matrix metalloproteinase (MMP)-12 (1:500; Santa Cruz Biotechnology, Inc., Santa Cruz, CA, USA); and polyclonal goat anti-mouse glycosylated 91-kDa glycoprotein (gp91*phox*; 1:300; Santa Cruz Biotechnology, Inc.).

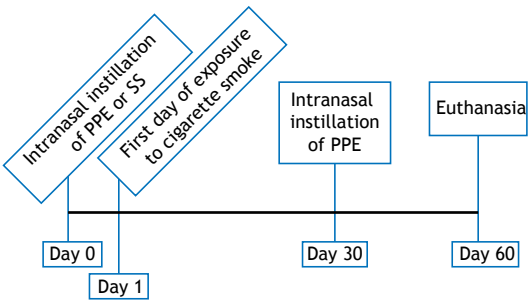

Figure 1. Timeline of the experimental protocol. PPE: porcine pancreatic elastase; and SS: saline solution.

A biotin-streptavidin-peroxidase method was used. Secondary antibodies included anti-rabbit VECTASTAIN® ABC kit, anti-goat VECTASTAIN® ABC kit, and anti-rat VECTASTAIN® ABC kit (Vector Laboratories, Inc., Burlingame, CA, USA), which were also used without a primary antibody, serving as a negative control.[19]

For histomorphometry, a 100-point ocular grid of known area was placed in the microscope eyepiece.[20] For each animal, 20 randomly selected nonoverlapping fields of lung parenchyma were examined under light microscopy (magnification, ×200). The Lm was measured by counting how many times the grid lines intercepted the alveolar walls, being calculated by the following equation:

$$Lm = Ltotal/NI$$

where *Ltotal* is the sum of all grid segments, calculated by measuring each segment with a ruler (Carl Zeiss Microscopy GmbH, Jena, Germany) under the microscope, and *NI* is the average number of times that the lines intersected the alveolar walls. All Lm values were expressed in micrometers (μm).

Histomorphometry was also used in order to determine the numbers of cells that were immunoreactive to MAC-2, MMP-12, and gp91*phox* in the distal lung parenchyma and peribronchial region by a point-counting technique with the aforementioned grid placed in the microscope eyepiece (magnification, ×400). For each animal, 15 fields of lung parenchyma and 5 airways were randomly selected. The results were expressed in cells/μm^2.[21-24]

Statistical analysis was performed with the program SigmaStat, version 11 (Systat Software, Inc., San Jose, CA, USA). The four groups of mice were compared by one-way ANOVA. Differences were considered significant at $p < 0.05$.

RESULTS

On day 60 of the experimental protocol, no significant differences were found among the four groups of mice regarding the respiratory mechanics parameters assessed (i.e., airway resistance, tissue damping, and tissue elastance; Figure 2). The Lm was found to be higher in the CS + PPE group than in the other groups ($p < 0.05$; Figure 3), an increased Lm being a hallmark of pulmonary emphysema.

Figure 4 shows the numbers of cells that were positive for MAC-2 in the peribronchial region and distal lung parenchyma. An increased number of macrophages in the peribronchial region ($p < 0.05$) and distal lung parenchyma ($p < 0.005$) were found in the CS + PPE group.

There were no significant differences among the four groups regarding the number of cells that were positive for MMP-12 in the peribronchial region (Figure 5A). However, in the distal lung parenchyma, the number of cells that were positive for MMP-12 was higher in the CS + PPE group than in the control group ($p = 0.007$; Figure 5B).

The number of cells that were positive for gp91*phox* in the peribronchial region was higher in the CS group than in the control and PPE groups ($p = 0.001$; Figure 6A). In the distal lung parenchyma, the number of cells that were positive for gp91*phox* was higher in the CS group than in the control group ($p = 0.03$), as well as being higher in the CS + PPE group than in the control and PPE groups ($p < 0.003$; Figure 6B).

DISCUSSION

In the present study, we tested an experimental model of emphysema induced by a combination of short-term exposure to CS and instillation of PPE. After 2 months, there was an increase in the Lm, as well as macrophage infiltration in the peribronchial region and distal lung parenchyma, together with an increase in the numbers of cells that were positive for MMP-12 and gp91*phox* in the distal lung parenchyma.

The fact that no functional changes were found in the present study is probably due to the fact that there

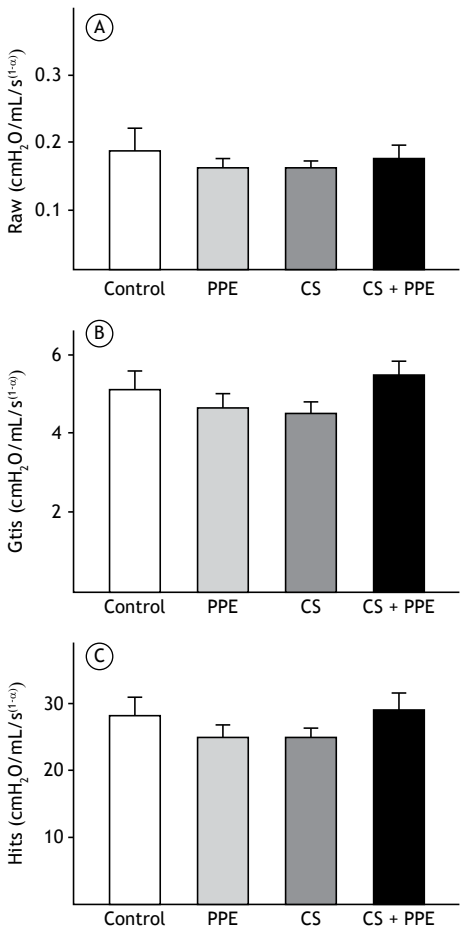

Figure 2. Respiratory mechanics parameters in the four experimental groups, expressed as mean ± SE. In A, airway resistance (Raw); in B, tissue damping (Gtis); and in C, tissue elastance (Hits). There were no significant differences in any of the parameters assessed among the experimental groups. PPE: porcine pancreatic elastase; and CS: cigarette smoke.

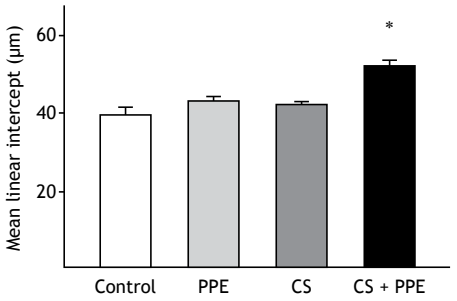

Figure 3. Mean linear intercept (Lm) values measured in the four experimental groups, expressed as mean ± SE. The CS + PPE group showed an increase in Lm values in comparison with the other groups. PPE: porcine pancreatic elastase; and CS: cigarette smoke. *p < 0.05 vs. control, PPE, and CS groups.

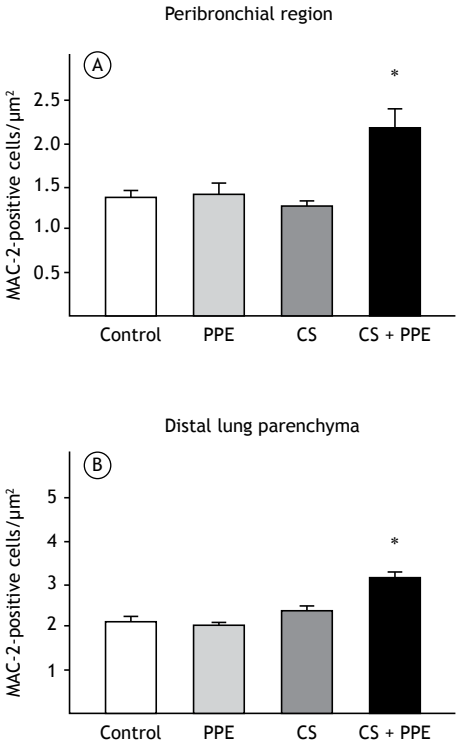

Figure 4. Number of positive cells for macrophage (MAC)-2 in the four experimental groups, expressed as mean ± SE. There was an increase in the number of positive cells for MAC-2 in the peribronchial region (in A; *p < 0.05) and distal lung parenchyma (in B; *p < 0.005) in the CS + PPE group in comparison with the other groups. PPE: porcine pancreatic elastase; and CS: cigarette smoke.

was less alveolar enlargement in our study than in studies involving models of PPE-induced emphysema and higher doses of elastase[25] or in studies involving models of CS-induced emphysema and longer exposure times.[15] In addition, some studies have shown that assessment of respiratory mechanics does not reflect the presence of emphysema as well as does morphometric analysis.[21,26] Foronjy et al.[27] found no changes in lung compliance despite the presence of

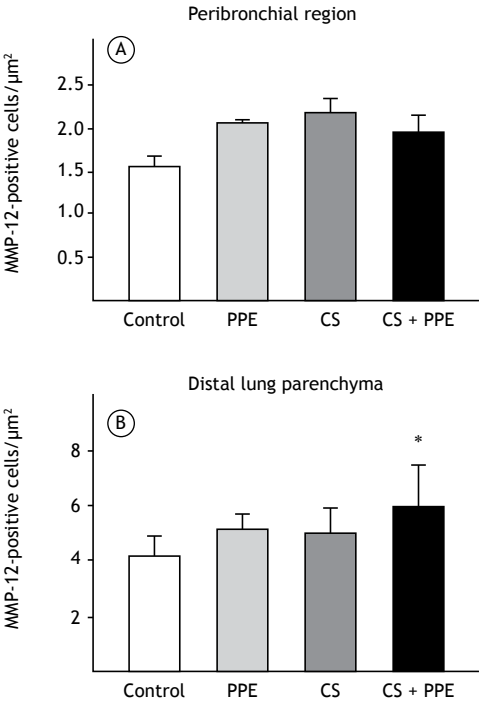

Figure 5. Number of positive cells for matrix metalloproteinase (MMP)-12 in the four experimental groups, expressed as mean ± SE. There were no differences among the experimental groups regarding the number of MMP-12-positive cells in the peribronchial region (in A). The number of positive cells for MMP-12 in the distal lung parenchyma was higher in the CS + PPE group than in the control group (in B; *p = 0.007). PPE: porcine pancreatic elastase; and CS: cigarette smoke.

significant emphysema, with no correlation between emphysema as measured by morphometric analysis and lung compliance. They concluded that this lack of correlation occurs because the mechanisms involved in anatomic emphysema might be distinct from those that cause the loss of elastic recoil.[27]

An imbalance between protease and antiprotease activity in the lung remains the most widely accepted mechanism for parenchymal destruction in emphysema.[10,14,28-30] In addition, studies have shown that MMPs, particularly MMP-12, play an important role in attacking the protein components of the lung parenchymal extracellular matrix.[31,32]

MMP-12 is mainly produced by alveolar macrophages[33] and is recognized to play an important role in emphysema. One group of authors exposed MMP-12 knockout mice to CS 6 days a week for 6 months and observed no increase in macrophage number or parenchymal destruction.[34] In addition, there have been reports of increased MMP-12 expression in macrophages in smokers and greater MMP-12 activity in the sputum of patients with COPD than in that of smokers without airflow limitation.[35,36]

In the present study, there was an increase in macrophages in the peribronchial region and distal lung parenchyma, as well as an increase in the number of cells that were positive for MMP-12 in comparison

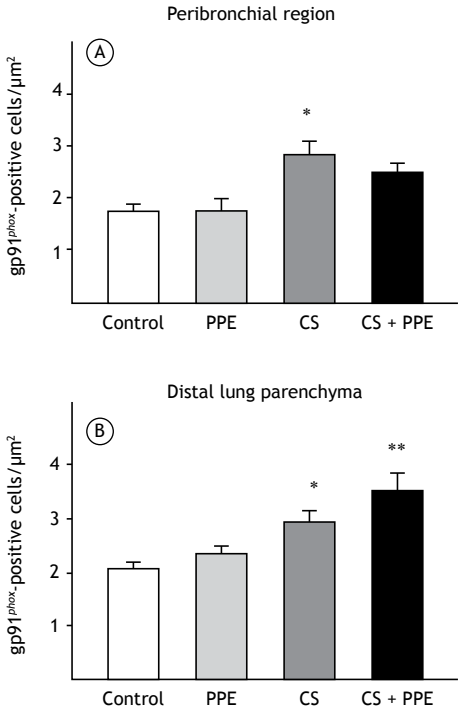

Figure 6. Number of positive cells for glycosylated 91-kDa glycoprotein (gp91*phox*) in the four experimental groups, expressed as mean ± SE. The number of gp91*phox*-positive cells in the peribronchial region was higher in the CS group than in the control and PPE groups (in A; *p = 0.001). In the distal lung parenchyma, the number of gp91*phox*-positive cells was higher in the CS group than in the control group (in B; *p = 0.03), as well as being higher in the CS + PPE group than in the control and PPE groups (in B; **p < 0.003). PPE: porcine pancreatic elastase; and CS: cigarette smoke.

with the control group, although only in the distal lung parenchyma. Although MMP-12 levels were higher in the PPE and CS groups than in the control group, the difference was not significant. These findings are consistent with the structural changes observed in the distal lung parenchyma.

In the present study, the Lm was found to be higher in the CS + PPE group than in the other groups. A similar increase in the Lm has previously been observed, although only after 6 months of CS exposure[15] or with the use of twice as much PPE as was used in the present study.[25,37]

In the present study, oxidative stress was measured by determining the number of positive cells for gp91*phox*, which is the heme-binding subunit of the superoxide-generating NADPH oxidase.[38] CS contains many oxidants and reactive oxygen species promoting an environmental oxidant burden, which is augmented by additional release of oxidants from inflammatory cells, culminating in body tissue destruction.[39,40] Alveolar macrophages release more reactive oxygen species in smokers than in nonsmokers, plasma antioxidant capacity being reduced in the former.[39] In the present study, exposure to CS was found to result in an increase in gp91*phox*-positive cells in the peribronchial region and distal lung parenchyma. The number of gp91*phox*-positive cells in the peribronchial region was higher in the CS group than in the control and PPE groups. In addition, there was an increase in gp91*phox*-positive cells in the distal lung parenchyma in the CS and CS + PPE groups. This increase was enhanced by a combination of CS exposure and PPE instillation, the presence of alveolar enlargement suggesting that oxidants play an important role in our murine model of emphysema.

Although oxidative stress has been described as an important mechanism in the development of emphysema,[41-43] NADPH oxidase has been shown to play an important role in restraining MMP activity in macrophages, MMP-12 activity in vitro having been shown to be greater in oxidant-deficient macrophages than in gp91*phox*-null and wild-type macrophages.[44] In addition, spontaneous, progressive emphysema similar to that observed in wild-type animals exposed to CS has been shown to develop in vivo in gp91*phox* knockout mice.[44] The differences between our results and those of the aforementioned study[44] might be due to differences in experimental protocols between the two studies.

Our model of emphysema induced by a combination of CS exposure and PPE instillation results in a significant degree of parenchymal destruction in a shorter time frame than that employed in previous studies, reinforcing the importance of protease-antiprotease imbalance and oxidant-antioxidant imbalance in the pathogenesis of emphysema. Given the diversity of experimental models in the literature, it is important to choose carefully the best model for each purpose. A murine model of emphysema induced by a combination of CS exposure and PPE instillation might be useful for evaluating structural changes occurring during the processes of parenchymal destruction and remodeling in emphysema.

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ORIGINAL ARTICLE

Spontaneous pneumomediastinum: experience in 18 patients during the last 12 years

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ABSTRACT

Objective: To characterize clinically all of the patients with spontaneous pneumomediastinum (SPM) admitted to an adult pulmonology ward in Lisbon, Portugal. **Methods:** This was a retrospective descriptive study of all adult patients (≥ 18 years of age) diagnosed with SPM between January of 2004 and September of 2015. **Results:** At least one predisposing factor was identified in most (88.9%) of the 18 patients who presented with SPM during the study period. With regard to precipitating factors, bouts of cough were present in 50.0% of the patients. Other precipitating factors included a sudden increase in tobacco consumption, inhaled drug use, occupational inhalation of varnish fumes, intense exercise, and vomiting. The most common complaints were dyspnea (in 83.3%) and chest pain (in 77.8%). Other complaints included cough, neck pain, dysphagia, and odynophagia. Subcutaneous emphysema was found in most of the patients. The diagnosis of SPM was based on chest X-ray findings in 61.1% of the patients. **Conclusions:** Although SPM is a rare condition, it should be considered in the differential diagnosis of chest pain and dyspnea. It can develop without a triggering event or conclusive findings on a chest X-ray, which is usually sufficient for diagnosis.

Keywords: Mediastinal emphysema; Subcutaneous emphysema; Dyspnea.

INTRODUCTION

Spontaneous pneumomediastinum (SPM) or spontaneous mediastinal emphysema is a rare condition characterized by free air in the mediastinum not preceded by thoracic trauma, surgery, or any other medical procedure.[1-3] It was first described by Louis Hamman in 1939, which is why it is also known as Hamman's syndrome.[1,2,4-7] However, secondary pneumomediastinum had previously been reported as a traumatic complication, by René Laennec in 1819.[7] SPM is a benign and usually self-limiting condition that primarily affects young males. In many cases, the precipitating factor or underlying disease cannot be identified.[1,8] The literature describes pre-existing factors/conditions that facilitate the onset of SPM, known as predisposing factors, and events/conditions that trigger it, known as precipitating factors.[7]

The pathophysiology of SPM was first described in 1944 by Macklin and Macklin, who suggested the presence of an alveolar-interstitial pressure gradient. Increased airway pressure leads to alveolar rupture and, consequently, dissection of air along the bronchovascular sheath toward the mediastinum, which can extend to the cervical subcutaneous tissue, pleura, pericardium, peritoneal cavity, and epidural space.[2,5,9,10] The increase in pressure in the intrapleural space and in the airway is due to predisposing factors, such as smoking, bronchial asthma, respiratory infection, and interstitial lung disease,[1,2] in combination with precipitating factors, such as bouts of cough, emesis, and vigorous exercise.[4] In some cases, no identifiable cause is found.[4] SPM has also been associated with inhaled drug use—including marijuana, cocaine, and ecstasy use—which is related to various mechanisms, including performance of the Valsalva maneuver, strong pulmonary vasoconstriction, and direct effects on the alveolar membrane.[6] Although SPM has been associated with noninvasive ventilation[11] and dental procedures involving the use of a high-speed air-turbine handpiece,[12,13] such cases are best classified as iatrogenic.

The most common symptoms and signs of SPM are dyspnea, chest pain, neck pain, and subcutaneous emphysema.[4,5,14] On chest auscultation, a crunching sound synchronous with the heartbeat (Hamman's sign) can sometimes be heard.[1,4] Pneumomediastinum is typically diagnosed on the basis of posteroanterior and lateral chest X-rays.[3]

SPM can go unnoticed for various reasons. First, it is a rare condition, the incidence of which ranges from 1:7,000 to 1:45,000 hospital admissions.[7] Second, it is a poorly recognized disease; the only published studies to date are reports of isolated clinical cases or small case series. Finally, patient complaints are not specific to SPM and are common in numerous other cardiopulmonary diseases.[3,5,8,14]

The prognosis is usually excellent with conservative treatment, i.e., rest, oxygen therapy, and analgesia (if

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necessary). Although SPM is rare, patients should be monitored for complications such as hypertensive pneumothorax, pneumopericardium, pneumomediastinum, pneumoperitoneum, pneumorrhachis, and mediastinitis. Although the risk of recurrence is low, secondary causes should be excluded,[2,4] including iatrogenic/traumatic perforation of the esophagus or trachea/respiratory tract and intrathoracic infection.[2]

The objective of the present study was to characterize clinically all SPM patients admitted to the Pulmonology Ward of *Centro Hospitalar Lisboa Norte Hospital de Santa Maria*, in the city of Lisbon, Portugal, in the last 11 years, by analyzing their progression and response to conservative treatment.

METHODS

This was a retrospective descriptive study aimed at identifying all of the adult patients (≥ 18 years of age) who were admitted to the aforementioned ward with a diagnosis of SPM in the period between January of 2004 and September of 2015. To that end, all discharge documents issued during the study period were reviewed. Secondary causes of pneumomediastinum were excluded, including thoracic trauma, surgery, invasive tests, and upper aerodigestive tract manipulation. All patients were admitted via the emergency department of our hospital, either directly or referred by other hospitals.

All data were collected in accordance with a previously established protocol and included the following information: demographic data; possible predisposing and precipitating factors; symptoms and signs; additional diagnostic tests; treatment received during hospital stay; clinical course; length of hospital stay; and readmissions. When data on symptoms and signs were collected, information regarding the presence of cough, dyspnea, dysphagia, odynophagia, neck pain, chest pain, and subcutaneous emphysema was actively sought. Outpatient files were also reviewed, in order to identify any recurrences.

Statistical analysis was performed with Microsoft Office Excel 2013, proportions, means, and standard deviations being calculated. The study was approved by the Research Ethics Committee of *Centro Hospitalar Lisboa Norte*.

RESULTS

Over a period of 11 years and 9 months, a total of 1,835,817 adult patients (≥ 18 years of age) sought emergency room treatment at *Hospital de Santa Maria*, patients presenting with gynecological/obstetric conditions not being taken into account. During the same period, a total of 8,581 patients were admitted to our pulmonology ward. Of those, 18 were diagnosed with SPM. Therefore, the incidence of SPM in our study was approximately 1:102,000. Of the 18 patients diagnosed with SPM, 66.7% were male (the youngest being 18 years old and the oldest being 87 years old), and the mean age was 35.4 ± 24.7 years. The mean length of hospital stay was 10.5 ± 9.9 days.

As can be seen in Table 1, at least one predisposing factor was identified in most of the patients (88.9%), as follows: 44.4% were current smokers; 22.2% were former smokers; 44.4% had a history of recent respiratory infection; 27.8% had a diagnosis of bronchial asthma; 22.2% had a history of bronchial hyperreactivity (without bronchial asthma); and 11.1% had a history of interstitial lung disease. With regard to precipitating factors (Table 2), 50.0% of the cases of SPM were related to bouts of cough; 2 were related to bouts of vomiting; 2 were related to inhaled drug use; 1 was related to a sudden increase in tobacco consumption; 1 was related to occupational inhalation of varnish fumes; and 1 was related to intense physical activity. In 2 (11.1%) of the patients, no potential precipitating factor was identified.

As can be seen in Table 3, the following symptoms were identified: dyspnea, in 83.3% of the patients; chest pain, in 77.8%; cough, in 55.6%; neck pain, in 55.6%; dysphagia, in 27.8%; and odynophagia, in 16.7%. Physical examination revealed subcutaneous emphysema in 83.3% and Hamman's sign in only 1 patient (Table 3).

All patients underwent the following tests: complete blood count; blood coagulation testing; renal function testing; hepatic function testing; determination of serum electrolyte levels; and arterial blood gas analysis. At emergency room admission, mean leukocyte count was 12,540 × 10^9 cells/L (range, 3,500 × 10^9 cells/L to 20,570 × 10^9 cells/L). Of the total of patients, 10 had leukocytosis and 12 had neutrophilia (> 70% of the relative leukocyte count). All patients underwent chest X-rays, diagnosis being based on chest X-ray findings in 11 (61.1%). The remaining patients underwent chest CT scans in order to clarify the diagnosis. Of the 2 patients in whom SPM was related to a bout of vomiting, 1 underwent barium esophagography and 1 underwent upper gastrointestinal endoscopy, which excluded esophageal discontinuity. In most (11) of the patients, there were no complications directly related to SPM. Of the remaining 7 patients, 5 had pneumothorax and 2 had pneumorrhachis.[15] Although 1 patient died—an 81-year-old male with a history of chronic hypersensitivity pneumonitis—the cause of death was unrelated to SPM. His death was attributed to nosocomial pneumonia with type II respiratory failure. Although the patient required noninvasive ventilation, SPM had been diagnosed before the initiation of noninvasive ventilation.

All of the patients received conservative medical treatment for SPM. Treatment consisted of bed rest, analgesia, oxygen therapy, and serial chest X-rays. Of the 18 patients, 7 received antibiotic therapy for concomitant respiratory tract infection. There were no recurrences in the 13 patients who were subsequently followed as outpatients, the duration of follow-up having ranged from 1 month to 76 months. Of the

Table 1. Predisposing factors for spontaneous pneumomediastinum (N = 18).

Predisposing factor	n	%
Current smoking	8	44.4
Recent respiratory infection	8	44.4
Bronchial asthma	5	27.8
Past smoking	4	22.2
Bronchial hyperreactivity (without bronchial asthma)	4	22.2
Interstitial lung disease	2	11.1

Table 2. Precipitating factors for spontaneous pneumomediastinum (N = 18).

Precipitating factor	n	%
Cough	9	50.0
Vomiting	2	11.1
Inhaled drug use	2	11.1
Intense exercise	1	5.6
Occupational inhalation of varnish fumes	1	5.6
Sudden increase in tobacco consumption	1	5.6
Unidentified	2	11.1

Table 3. Symptoms and signs present on admission (N = 18).

Symptoms and signs	n	%
Dyspnea	15	83.3
Subcutaneous emphysema	15	83.3
Chest pain	14	77.8
Cough	10	55.6
Neck pain	10	55.6
Dysphagia	5	27.8
Odynophagia	3	16.7
Hamman's sign	1	5.6

remaining 5 patients, 4 were lost to follow-up and 1 died (as previously mentioned).

As previously mentioned, there have been few reports of pneumomediastinum related to dental procedures involving the use of high-speed air-turbine handpieces. Therefore, we decided to mention here the case of a patient who was admitted to our pulmonology ward during the study period. It was not included in our statistical analysis because it was considered to be a case of iatrogenic/secondary pneumomediastinum. The patient was a 36-year-old nonsmoking female who had had sudden-onset cervical subcutaneous emphysema, chest pain, and neck pain during a dental cleaning procedure with the use of a high-speed air-turbine handpiece. Diagnosis was based on chest X-ray findings, and the patient received conservative treatment. She had no recurrence during her hospital stay and was discharged after 5 days.

DISCUSSION

Although the true incidence of SPM is unknown, it is probably underestimated because few practitioners are aware of this condition, the diagnosis of which requires a high level of suspicion.[16] In Portugal, no published studies have been found that have examined this issue, and there had been no estimates of the incidence of SPM in the country before the present study. The incidence of SPM in our study (1:102,000) is much lower than that reported in other studies. Although this suggests that SPM is underdiagnosed, further studies are needed in order to confirm that.

The demographic characteristics of our sample are also different from those reported in the literature. The mean age was relatively higher in the present study, which is probably due to the fact that our patients varied widely in age. In agreement with other studies,[3,17] there was a predominance of males in the present study (2:1).

In most studies, the proportion of SPM cases associated with a precipitating factor ranges from 21.0% to 75.0%.[2,4-6,14,17,18] In the present study, however, that proportion was substantially higher (88.9%). This might be due to the fact that all of the patients in the present study were admitted to a pulmonology ward where precipitating factors were actively investigated. Most of the cases of SPM in the present study were found to be related to the Valsalva maneuver performed during bouts of cough or vomiting, a finding that is in accordance with other studies.[5,6,10,14,19] In the cases in which SPM was associated with a sudden increase in tobacco consumption, with occupational inhalation of varnish fumes, or with inhaled drug use, SPM was also attributed to the Valsalva maneuver, performed

either during inhalation or during the bouts of cough triggered by airway irritation. While reviewing the discharge documents, we found no reference to patients being systematically questioned about inhaled drug abuse and the type(s) of drug(s) used.

In a systematic review of 27 studies of SPM (including a total of 600 patients), at least one predisposing factor was identified in 22.0% of the cases. The most common predisposing factor was bronchial asthma, followed by interstitial lung disease, COPD, bronchiectasis, bullae, thoracic neoplasms, cystic disease, and respiratory tract infection.[17] In the present study, the most common predisposing factor was current or past smoking (in 12 of the 18 patients), which led to respiratory tract inflammation and, consequently, bouts of cough. The fact that current or past smoking was considered a predisposing factor for SPM in the present study significantly increased the number of patients with at least one predisposing factor for SPM.

In all of the patients in the present study, SPM presented as an acute or subacute condition with no signs of hemodynamic instability or exuberant inflammatory response. With regard to the symptoms most commonly associated with SPM, our findings are consistent with those of most studies,[2-6,10,14,17-20] as is our finding of a mild to moderate inflammatory response to SPM.[4-6,18]

In the present study, the diagnosis of SPM was based on chest X-ray findings in most (61.1%) of the patients. Thoracic CT was used only in cases of uncertainty, as recommended elsewhere.[6,16] However, one group of authors[9] reported that pneumomediastinum was visible on chest X-rays in only 52.9% of patients. This difference in proportions across studies might be due to the different medical or surgical specialties of the physicians involved and to the different hospital departments to which patients were admitted.

In the present study, the clinical course of SPM was invariably benign, and all patients received conservative treatment. The mean length of hospital stay was 10.5 ± 9.9 days, significantly longer than that reported in a systematic review published in 2013 (4.1 ± 2.3 days).[17] This discrepancy is explained by the fact that the mean age of the patients in the present study was higher and by the presence of associated conditions, such as interstitial lung diseases. In the 13 patients who were followed as outpatients, there were no recurrences, a finding that is consistent with the literature.[17]

Invasive procedures have rarely been described in SPM. Their use is reserved for tension pneumomediastinum with respiratory distress,[21] significant cardiorespiratory compromise, such as in cases of pneumopericardium resulting in air tamponade,[22] and specific cases of esophageal tear.[23]

Although SPM is a rare condition, it should be considered in the differential diagnosis of chest pain and dyspnea, which focuses on cardiovascular and pulmonary sources, including acute coronary syndromes, pericarditis, aortic dissection, pulmonary thromboembolism, pneumonia, pleural effusion, and pneumothorax.[2] Musculoskeletal pain, gastroesophageal reflux disease, esophageal perforation, and spasm are also included in the differential diagnosis.[2]

The present study confirms that SPM can develop without a triggering event and with no conclusive findings on a chest X-ray. Because they are usually sufficient for diagnosis, posteroanterior and lateral chest X-rays should be performed first, thoracic CT being reserved for cases in which chest X-ray findings are inconclusive. Likewise, esophagography and thoracic CT should be performed only if there is a history or clinical evidence of esophageal rupture, whereas fiberoptic bronchoscopy and thoracic CT should be performed only in cases of suspected tracheal rupture. Despite an excellent prognosis with conservative treatment and a low risk of recurrence, secondary causes should be excluded, and patients should be monitored for complications. Our findings suggest that it might be useful for pulmonology departments to implement protocols that allow early diagnosis of pneumomediastinum by including specific questions regarding inhaled drug use, as well as drug testing.

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ORIGINAL ARTICLE

Tuberculosis recurrence in a priority city in the state of São Paulo, Brazil

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ABSTRACT

Objective: To describe cases of tuberculosis recurrence (TBR), stratified by temporal classification (early or late TBR), and to identify possible predictors of such recurrence. **Methods:** This was an analytical retrospective observational epidemiological study involving a cohort of 963 new cases of pulmonary tuberculosis, reported and treated via the Tuberculosis Control Program in the city of Carapicuíba, Brazil. The study period was from 2000 to 2010. All of the pulmonary tuberculosis patients who successfully completed the treatment (with or without confirmation of cure) were selected and followed until December 31, 2012. **Results:** Of the 963 cases, TBR occurred in 47 (4.88%). The mean time between the first and second tuberculosis episodes was 36.12 months. Of the 47 TBR cases, 16 (34.04%) occurred within the first 18 months after the completion of the initial treatment (early TBR) and 31 (65.96%) occurred thereafter (late TBR). There were statistically significant differences between the early and late TBR groups only regarding level of education (≤ 3 vs. > 3 years of schooling; $p < 0.004$) and weight gain at completion of the initial treatment (1.78 kg vs. 5.31 kg; $p < 0.045$)—not regarding any of the other variables studied. **Conclusions:** A low level of education might translate to poor treatment adherence, which impedes the killing of bacilli and facilitates their survival in a latent state, making it appear as if the treatment was effective. Minimal or no weight gain at completion of the initial treatment might be a reliable biomarker to be used by health care facilities that provide tuberculosis treatment.

Keywords: Recurrence; Tuberculosis; Risk factors.

INTRODUCTION

Tuberculosis, which is considered to be a curable disease, is one of the oldest diseases known to mankind. Short-term treatment regimens combining rifampin, isoniazid, pyrazinamide, and ethambutol have an efficacy of nearly 100% provided that the drugs are administered in the correct doses and for the appropriate amount of time in drug-susceptible patients; however, tuberculosis remains a serious public health problem in the 21st century.[1-4] The World Health Organization estimates that over 9 million people have had tuberculosis; of those, 1.5 million have died, whereas 300,000 have developed the disease again after having been treated and considered cured,[3] constituting cases of tuberculosis recurrence (TBR).

Studies have shown that the risk of TBR is higher in previously treated tuberculosis patients than in the general population, being up to four times higher in the former than in the latter depending on the epidemiological profile of the disease at the study site.[5,6] A major concern for tuberculosis control programs (TCPs), TBR is overlooked and understudied by researchers and health authorities alike. TBR rates vary widely, being 0.4% in patients receiving directly observed treatment, short-course (DOTS) and over 30% in appropriately treated patients receiving self-administered treatment.[7-9]

TBR is due to endogenous reactivation (also known as relapse), caused by the same bacterial strain that caused the first episode of tuberculosis (probably because of bacillary persistence), or exogenous infection (also known as reinfection) with a new strain of *Mycobacterium tuberculosis*. Although there is no clinical difference between relapse and reinfection, they can be differentiated by using molecular biology techniques, which are usually unavailable in routine clinical practice.[5,8,10-12] According to the British Medical Research Council, 91% of relapses occur before post-discharge month 12, and a recent review of the latest clinical trials of new tuberculosis treatment regimens showed that 94% of relapses occurred within the first 18 months after treatment completion.[13] TBR can be classified as early TBR or late TBR; the former is defined as TBR occurring within the first 18 months after treatment completion, whereas the latter is defined as TBR occurring thereafter.[6,8,12,14]

A better knowledge and understanding of TBR will improve the surveillance and follow-up of tuberculosis patients discharged from treatment, thus improving disease control and contributing to breaking the chain of transmission. The objective of the present study was to describe cases of early and late TBR in a cohort of patients treated via a municipal TCP and to identify possible predictors of such recurrence.

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METHODS

Characterization of the study site

The present study was conducted in the city of Carapicuíba, Brazil, a bedroom community in the greater metropolitan area of São Paulo. The latest census showed that Carapicuíba had a population of 369,908 inhabitants, being one of the most densely populated cities in the country (i.e., 10,576 people/km^2). In 1995, the *Programa Nacional de Controle da Tuberculose* (PNCT, Brazilian National Tuberculosis Control Program) identified the city of Carapicuíba as a priority because of its high burden of tuberculosis, with a mean incidence of 41.77 cases per 100,000 population in the last 5 years.[15] The local TCP was launched in the 1990s and, on the basis of epidemiological criteria, has been considered a priority by the Brazilian National Ministry of Health since then. In 2004, the DOTS strategy was implemented in all primary care clinics in the city via the local TCP, the decentralization of diagnosis being achieved by actively searching for patients with respiratory symptoms and collecting samples for smear microscopy at all public health care facilities. A rapid molecular biology-based assay has recently been implemented.

Study design

This was an analytical retrospective observational epidemiological study involving a cohort of new cases of tuberculosis, reported and treated via the TCP in the city of Carapicuíba. The study period was from 2000 to 2010. All of the pulmonary tuberculosis (PTB) patients who successfully completed the treatment (with or without confirmation of cure, as defined by the PNCT) were selected and followed until December 31, 2012 (Figure 1). The inclusion, exclusion, and follow-up criteria were those used in a larger study approved by the Research Ethics Committee of the Federal University of São Paulo (Protocol no. 0690/11).[15] TBR (the dependent variable) was defined as a second episode of tuberculosis after completion of the initial treatment, being classified as early or late TBR. Early TBR was defined as PTB occurring within the first 18 months after treatment completion. Late TBR was defined as PTB occurring more than 18 months after treatment completion.

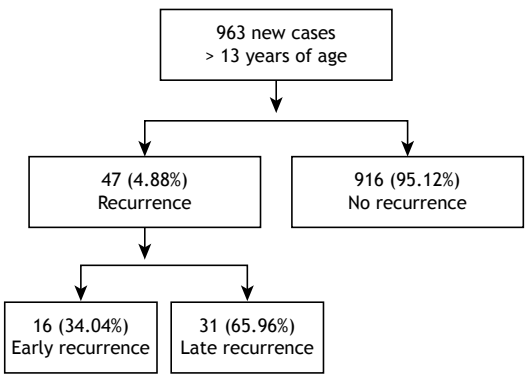

Figure 1. Flowchart of pulmonary tuberculosis cases in the city of Carapicuíba, Brazil, in the 2000-2012 period.

Data source and variables analyzed

Data were collected from the São Paulo State Epidemiological Surveillance Tuberculosis System (Epi-TB database) and the Online Epidemiological Surveillance Tuberculosis System (TBweb database) for the 2000-2005 and 2006-2010 periods, respectively. All data collected from the TBweb database were collected in real time. After identification of the medical record numbers, patient medical records were retrieved for data collection. Data were collected with the use of questionnaires developed specifically for the present study, being subsequently entered into an Epi Info 3.3 database. Double data entry and the Epi Info "data compare" tool were used in order to verify data consistency and eliminate typographical errors.

For the first episode of PTB, the following independent variables were analyzed: sociodemographic variables (gender, age, level of education, occupation—in accordance with the Brazilian Institute of Geography and Statistics—and household contact); comorbidities/unhealthy habits (diabetes mellitus, HIV infection, alcoholism, smoking, and drug addiction); signs and symptoms (time from onset of signs and symptoms to treatment, cough, fever, and sweating); clinical variables (active PTB, bilateral pulmonary involvement, and pulmonary cavitation); health and diagnostic equipment (place of treatment and type of facility); and treatment-related variables (number of doses taken during self-administered treatment, number of doses taken during DOTS, number of doses missed during DOTS, weight gain—in kg—in the attack phase, weight gain—in kg—at discharge from treatment, negative smear results in the attack phase, adverse events during treatment, and home contact with active tuberculosis during follow-up).

Statistical analysis

A frequency distribution table showing absolute and relative values was constructed to describe the characteristics of TBR cases. In order to determine the association between independent variables and the dependent variable (early or late TBR), the chi-square test was used, Yates' correction or Fisher's exact test being used when necessary; for risk assessment, prevalence ratios (PRs) were used, with a 95% CI and a significance level of $p \leq 0.05$; for continuous variables related to early or late TBR (independent groups), the Student's t-test (Levene's test) or the Mann-Whitney (Kruskal-Wallis) test was used, with a significance level of $p \leq 0.05$. All statistical analyses were performed with the IBM SPSS Statistics software package, version 20 (IBM Corporation, Armonk, NY, USA).

RESULTS

By the end of the follow-up period, TBR had occurred in 47 (4.88%) of the 963 PTB patients in our cohort;

in half of the cases, TBR occurred within 34 months after treatment completion. The mean time between treatment and TBR was 36.12 months (range, 2.52-98.04 months). Of the 47 cases of TBR, 7 (14.89%) occurred within the first 6 months after treatment completion, whereas 13 (27.66%) and 16 (34.04%) occurred within the first 12 and 18 months, respectively, and were therefore considered to be cases of recent TBR; the remaining 31 TBR cases (65.96%) occurred more than 18 months after treatment completion and were therefore considered to be cases of late TBR (Figure 2).

Of the 47 patients in whom there was TBR, 35 (74.47%) were male, and the mean age was 32.77 years. Approximately 45% had had ≥ 8 years of schooling. Most of the patients were currently employed (70.22%) and had home contacts (93.62%). The most prevalent comorbidity was diabetes mellitus (in 14.89%), and the most prevalent unhealthy habit was smoking (in 44.68%). Cough was reported by most of the patients (97.87%). With regard to the clinical variables, 80.85% of the patients had active tuberculosis (positive smear results at diagnosis), 63.83% had bilateral pulmonary involvement, and 57.45% had imaging findings suggestive of pulmonary parenchymal cavitation; only 8.51% had been diagnosed at private facilities, and slightly more than half had been diagnosed in an emergency room or hospital.

The mean number of doses taken during self-administered treatment was 92.27, and the mean number of doses taken during DOTS was 84.73; although 46.81% of the patients experienced adverse events during the initial treatment, only 1 (4.54%) experienced a major adverse event (drug hepatotoxicity), with no need to change the standard regimen. There was weight gain at the end of the attack phase in 74.47% and at discharge from treatment in 82.98%. In addition, approximately 15% had household contacts with active tuberculosis during treatment.

A bivariate analysis of the association between categorical variables and early or late TBR (Table 1) showed that the level of education was the only significant variable ($p \leq 0.05$); that is, a lower level of education translated to a greater association with early TBR (PR = 1.70 for up to 3 years of schooling; PR = 1.59 for 4-7 years of schooling). None of the other categorical variables were found to have statistical significance. A bivariate analysis of the association between quantitative variables and early or late TBR (Table 2) showed that weight gain (in kg) at discharge from treatment was the only significant variable, the mean weight gain being 1.78 kg for the early TBR group and 5.31 kg for the late TBR group.

DISCUSSION

The proportions of TBR cases vary widely across studies, ranging from 0.4% to 61.7%[4,6,9,16-20]; the incidence of TBR in the present study is consistent with that reported in locations where there are well-structured TCPs (i.e., 5-6%).[21,22] The incidence of TBR in the present study is also consistent with that reported in locations where the reported incidence of tuberculosis is low, such as North America and Australia,[16,18] moderate, such as Brazil and Spain,[19,20] and high, such as South Africa and Ethiopia,[4,20] regardless of heterogeneity and tuberculosis burden.[3,4,6,12,16-20]

Cases of relapse occur toward the end of the treatment period, primarily between months 6 and

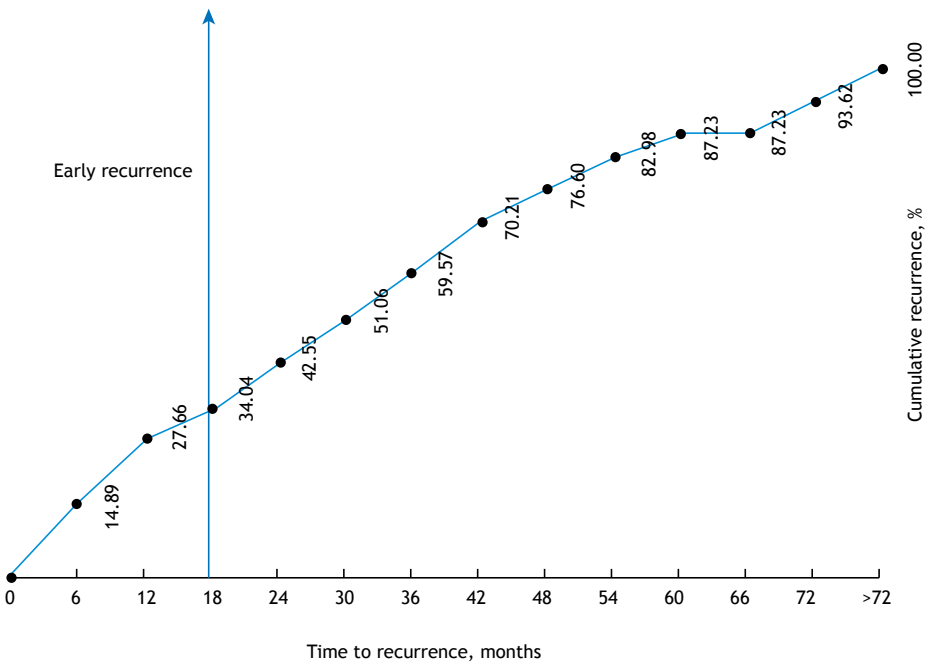

Figure 2. Cumulative recurrence of pulmonary tuberculosis during follow-up (in months) in the city of Carapicuíba, Brazil, in the 2000-2012 period.

Table 1. Frequency distribution and prevalence ratio, by type of pulmonary tuberculosis recurrence, in the city of Carapicuíba, Brazil, in the 2000-2012 period.

Variable	Total	%	Recurrence				PR	95% CI	p
			Early		Late				
			n	%	n	%			
TOTAL	47	100.00	16	34.04	31	65.96			
Gender									
Male	35	74.47	11	31.43	24	68.57		0.58-3.04	0.518
Female	12	25.53	5	41.67	7	58.33	1.33		
Level of education, number of years of schooling									
≤ 3	8	17.02	6	75.00	2	25.00	1.70	1.19-2.42	0.004
4-7	18	38.30	4	22.22	14	77.78	1.59	1.11-2.27	0.011
≥ 8	21	44.68	6	28.57	15	71.43			
Occupation									
Unemployed	7	14.89	4	57.14	3	42.86	1.39	0.94-2.06	0.102
Employed	33	70.22	8	24.24	25	75.76	1.00	0.60-1.68	1.000
Other	7	14.89	3	42.86	4	57.14			
Household contact									
No	3	6.38	0	0.00	3	100.00			
Yes	44	93.62	16	36.36	28	63.64			
Diabetes									
No	40	85.11	13	32.50	27	67.50			
Yes	7	14.89	3	42.86	4	57.14	1.32	0.50-3.46	0.676
HIV infection									
No	45	95.74	15	33.33	30	66.67			
Yes	2	4.26	1	50.00	1	50.00	1.50	0.35-6.37	0.626
Alcoholism									
No	33	70.21	12	36.36	21	63.64	1.27	0.50-3.27	0.742
Yes	14	29.79	4	28.57	10	71.43			
Smoking									
No	26	55.32	10	38.46	16	61.54	1.35	0.59-3.10	0.477
Yes	21	44.68	6	28.57	15	71.43			
Drug addiction									
No	41	87.23	15	36.58	26	63.42	2.20	0.35-13.74	0.648
Yes	6	12.77	1	16.67	5	83.33			
Time from onset of signs/symptoms to treatment, weeks									
≤ 3	4	8.51	1	25.00	3	75.00			
≥ 4	43	91.49	15	34.88	28	65.12	1.40	0.24-8.00	0.690
Cough									
No	1	2.13	1	100.00	0	0.00			
Yes	46	97.87	15	32.61	31	67.39			
Fever									
No	8	17.02	3	37.50	5	62.50	1.13	0.41-3.05	0.821
Yes	39	82.98	13	33.33	26	66.67			
Sweating									
No	7	14.89	3	42.86	4	57.14	1.32	0.50-3.46	0.676
Yes	40	85.11	13	32.50	27	67.50			
Active tuberculosis									
No	9	19.15	5	55.56	4	44.44	1.92	0.89-441	0.239
Yes	38	80.85	11	28.95	27	71.05			
Bilateral involvement									
No	17	36.17	5	21.41	12	78.59			
Yes	30	63.83	11	36.67	19	63.33	1.25	0.52-2.99	0.614
Pulmonary cavitation									
No	20	42.55	6	30.00	14	60.00			
Yes	27	57.45	10	37.04	17	62.96	1.23	0.54-2.83	0.615
Place of treatment									
Outpatient clinic	23	48.93	9	39.13	14	60.87	1.34	0.60-3.00	0.471
Other[a]	24	51.07	7	29.17	17	70.83			
Type of facility									
Public	43	91.49	14	32.56	29	67.44			
Private	4	8.51	2	50.00	2	50.00	1.54	0.53-4.48	0.598
Negative smear results in the attack phase									
Yes	33	70.21	10	30.30	23	69.70			
No	14	29.79	6	42.86	8	57.14	1.41	0.64-3.13	0.406
DOTS									
No	28	59.57	10	35.71	18	64.29	1.13	0.49-2.59	0.769
Yes	19	40.43	6	31.58	13	68.42			
Adverse events									
No	25	53.19	8	32.00	17	68.00			
Yes	22	46.81	8	36.36	14	63.64	1.14	0.51-2.52	0.753
Home contacts with active tuberculosis									
No	40	85.11	13	32.50	27	67.50			
Yes	7	14.89	3	42.86	4	57.14	1.32	0.50-3.46	0.676

PR: prevalence ratio; and DOTS: directly observed treatment, short-course. [a]Emergency room or hospital.

Table 2. Variables, by recurrence type, in the city of Carapicuíba, Brazil, in the 2000-2012 period.

Variable	Recurrence		Difference[a]	p
	Early	Late		
	Mean	Mean		
Age, years	37.94	30.10	7.84	0.096
Doses taken during SAT, n	99.57	88.50	11.07	0.667
Doses taken during DOTS, n	85.00	84.89	0.11	0.419
Doses missed during DOTS, n	11.22	2.19	9.03	0.119
Weight gain within 60 days after treatment initiation, kg	1.11	3.39	2.27	0.108
Weight gain at treatment completion, kg	1.78	5.31	3.53	0.045

SAT: self-administered treatment; and DOTS: directly observed treatment, short-course. [a]Expressed as absolute values.

12[13,14]; therefore, in phase III clinical trials examining the efficacy of new drugs or treatment regimens for tuberculosis, patients are followed until 18 months after discharge from treatment (cure).[13] Relapse, which is also known as endogenous reactivation, is caused by the same bacterial strain that caused the first episode of tuberculosis (probably because of bacillary persistence). The term persistence refers to the ability of bacilli to survive dormant within alveolar macrophages or in caseous areas even when they are sensitive to antituberculosis drugs and when bactericidal concentrations of chemotherapeutic agents are adequate during treatment. When conditions are favorable, these bacilli become metabolically active and multiply. When they multiply during treatment, they are completely eliminated by chemotherapy; however, if they resume their metabolic activity after discharge from treatment, TBR occurs.[13,23-26]

Several studies[8,12,19,26-30] have shown that TBR resulting from exogenous reinfection occurs long after treatment completion, more consistently over time and predominantly in locations where the burden of tuberculosis is moderate or high, because the chain of transmission is active. This was confirmed experimentally in a laboratory setting,[21] cured animals having subsequently developed a transient specific antigenic immune response that decreased over time. This transient resistance appears to prevent hematogenous spread of new bacilli and, consequently, a second episode of tuberculosis caused by early exogenous infection.

In the present study, a low level of education was found to be a risk factor for early TBR, possibly interfering with treatment adherence. The number of doses taken during self-administered treatment was higher in the early TBR group than in the late TBR group, although the difference was not statistically significant; however, it was impossible to determine the exact number of doses taken during treatment. It can be hypothesized that treatment adherence was lower in the early TBR group, a hypothesis that supports the recommendation of the World Health Organization and several groups of authors that DOTS be used.[3,14,16,19,24] Tuberculosis is a disease that has long been associated with poverty and low socioeconomic development, as indirectly measured by little or no schooling[9,10,12,31]; therefore, poverty can be associated with poor health status, or the latter can affect work and working conditions or limit job opportunities. This can also have an impact on treatment adherence,[14,16,19,24] thus explaining the aforementioned biological mechanism for bacillary persistence in cases of TBR, a mechanism that has been confirmed in other studies.[32,33]

In the present study, early TBR was found to be associated with reduced weight gain at discharge from treatment, a finding that suggests greater activation of tuberculosis-related chemical mediators, slower normalization of those mediators, or a combination of the two. In a clinical trial,[34] it was found that, among individuals who were underweight at diagnosis, weight gain of 5% or less during treatment was associated with an increased risk of TBR. An association between weight loss and TBR has been found in observational studies[35-37] and in laboratory animal studies,[23,33] as well as having been found in an operational study conducted in Bangladesh.[38] Weight loss and malnutrition are common in patients with tuberculosis; however, it is difficult to distinguish between cause and effect. The fact that TNF-α is released into the bloodstream of tuberculosis patients by sensitized phagocytic cells and that TNF-α is related to weight loss and cachexia can partially explain why weight loss is a common complaint in patients with tuberculosis.[32-36] In addition to TNF-α, the concentrations of IL-1, IL-6, IFN-γ, and prostaglandins are altered in individuals with cachexia, emphasizing the role of chronic diseases, such as tuberculosis, in the process of weight loss.[37]

Potential limitations of the present study include recall and information biases. It is possible that the answers that the patients themselves or their legal guardians gave to questions regarding some of the exposure variables, such as time from onset of signs and symptoms to treatment, cough, fever, and sweating, resulted in recall bias. It is also possible that their answers to questions regarding comorbidities and unhealthy habits, such as alcoholism, smoking, and drug addiction, resulted in information bias. Therefore, there is a possibility that these two potential biases affected the significance of the aforementioned variables. Another limitation is that it was impossible to control for confounding variables because of the small number of TBR cases during the follow-up period, a stratified or multivariate statistical analysis of early and late TBR therefore being impossible. Yet another limitation

is that it was impossible to distinguish between TBR resulting from endogenous reactivation and TBR resulting from exogenous reinfection. Molecular biology methods are not routinely used in Brazil as they are in countries such as the United States. However, this does not invalidate the results of the present study. One strength of the present study is that it was a retrospective observational study of secondary data from a municipal TCP, such data being much more representative of daily clinical and operational practices than are those from controlled clinical trials.

In summary, the present study showed that TBR cases occurring within the first 18 months after treatment completion (early TBR cases) were more common than late TBR cases, the occurrence of which increased consistently thereafter, a finding that is consistent with the literature. A low level of education might translate to poor treatment adherence, which impedes the elimination of bacilli and facilitates their survival in a latent state, making it appear as if the treatment was effective, as observed in the present study. One strategy to reduce early TBR, as well as for cases in which there is minimal or no weight gain at treatment completion, is to prolong treatment on the basis of the number of doses missed during DOTS, as recommended by the PNCT. Although minimal or no weight gain at treatment completion might be a reliable biomarker to be used by health care facilities that provide tuberculosis treatment, further studies of TBR are needed in order to confirm that.

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Estimated rates of recurrence, cure, and treatment abandonment in patients with pulmonary tuberculosis treated with a four-drug fixed-dose combination regimen at a tertiary health care facility in the city of Rio de Janeiro, Brazil

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ABSTRACT

Objective: To estimate the rates of recurrence, cure, and treatment abandonment in patients with pulmonary tuberculosis treated with a four-drug fixed-dose combination (FDC) regimen, as well as to evaluate possible associated factors. **Methods:** This was a retrospective observational study involving 208 patients with a confirmed diagnosis of pulmonary tuberculosis enrolled in the Hospital Tuberculosis Control Program at the Institute for Thoracic Diseases, located in the city of Rio de Janeiro, Brazil. Between January of 2007 and October of 2010, the patients were treated with the rifampin-isoniazid-pyrazinamide (RHZ) regimen, whereas, between November of 2010 and June of 2013, the patients were treated with the rifampin-isoniazid-pyrazinamide-ethambutol FDC (RHZE/FDC) regimen. Data regarding tuberculosis recurrence and mortality in the patients studied were retrieved from the Brazilian Case Registry Database and the Brazilian Mortality Database, respectively. The follow-up period comprised two years after treatment completion. **Results:** The rates of cure, treatment abandonment, and death were 90.4%, 4.8%, and 4.8%, respectively. There were 7 cases of recurrence during the follow-up period. No significant differences in the recurrence rate were found between the RHZ and RHZE/FDC regimen groups (p = 0.13). We identified no factors associated with the occurrence of recurrence; nor were there any statistically significant differences between the treatment groups regarding adverse effects or rates of cure, treatment abandonment, or death. **Conclusions:** The adoption of the RHZE/FDC regimen produced no statistically significant differences in the rates of recurrence, cure, or treatment abandonment; nor did it have any effect on the occurrence of adverse effects, in comparison with the use of the RHZ regimen.

Keywords: Tuberculosis, pulmonary, Drug combinations; Recurrence.

INTRODUCTION

Tuberculosis remains a serious global public health problem and is one of the leading causes of death in the world, according to data from the World Health Organization. Brazil is one of the 22 countries that collectively account for 80.0% of all cases of pulmonary tuberculosis worldwide, ranking 18th. In 2014, the tuberculosis incidence rate in Brazil was 44 cases per 100,000 population, with a rate of tuberculosis/HIV coinfection of 17%. The mortality rate from tuberculosis/HIV was 1.2 cases per 100,000 population.[1] The state of Rio de Janeiro has one of the highest tuberculosis incidence rates in the country (54.5 cases/100,000 population), second only to the state of Amazonas, as well as having the highest mortality rate from tuberculosis in the country (5.1 cases/100,000 population) and a rate of tuberculosis/HIV coinfection of 8.9%.[2] Tuberculosis is related to poverty, malnutrition, and social exclusion,[3] predominating in men aged 45 to 59 years.[3,4]

Since 1994, the World Health Organization and the International Union against Tuberculosis and Lung Diseases have recommended the use of fixed-dose combinations (FDCs), proposing the change in previous treatments with the justification that treatment adherence would be better and selection of drug-resistant mutant bacilli would be reduced,[4-8] which would translate to higher cure rates and lower rates of treatment abandonment, recurrence, and death.

On the basis of data from the Second National Survey on Antituberculosis Drug Resistance (2007-2008),[4,9] which showed an increase in primary resistance to isoniazid (from 3.5% to 6%) and rifampin (from 0.2% to 1.5%) between 1997 and 2007, the Brazilian National Tuberculosis Control Program/Ministry of Health decided,

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in 2009, to change the regimen used, which had been in use since 1979. The regimen that had been used until then, known as regimen I—2 months of rifampin, isoniazid, and pyrazinamide (RHZ), followed by 4 months of rifampin and isoniazid (RH)—was changed by adding a fourth drug, ethambutol, to the (2-month) intensive phase of treatment, the new regimen being designated 2RHZE/4RH. In the 2-month intensive phase of treatment, capsules were replaced by FDC tablets containing RHZE (RHZE/FDC), whereas, in the 4-month continuation phase of treatment, FDC capsules containing RH were used. In adults, the doses of isoniazid and pyrazinamide were adjusted to 300 mg/day and 1,600 mg/day, respectively.[4,9]

The objective of the present study was to determine the rate of recurrence of pulmonary tuberculosis with the use of the RHZE/FDC regimen, in comparison with the use of regimen I (RHZ), and to identify possible risk factors leading to recurrence, in addition to determining the rates of cure, treatment abandonment, and death, as well as the occurrence of adverse effects.

METHODS

This was a retrospective observational study conducted between January of 2007 and June of 2013 at the *Instituto de Doenças do Tórax* (IDT, Institute for Thoracic Diseases) of *Hospital Universitário Clementino Fraga Filho* (HUCFF, Clementino Fraga Filho University Hospital), which is a tertiary hospital complex affiliated with the Federal University of Rio de Janeiro and is located in the north area of the city of Rio de Janeiro, Brazil. The hospital is a referral center for the treatment of patients with HIV/AIDS, patients with diseases requiring complex treatment, such as transplantation, patients with autoimmune diseases, cancer patients, and patients with diabetes mellitus; therefore, comorbidities are common. The study was approved by the HUCFF/IDT Research Ethics Committee in November of 2013 (Protocol no. 465.507).

At the HUCFF/IDT, there is the *Programa de Controle da Tuberculose Hospitalar* (PCTH, Hospital Tuberculosis Control Program), which was established in 1998. The program includes active surveillance for tuberculosis in inpatients, outpatient treatment for patients suspected of having tuberculosis, isolation of patients with suspected or confirmed pulmonary tuberculosis, routine sputum smear microscopy and mycobacterial culture, prompt availability of laboratory results, and continuing education of health care professionals. It is a multidisciplinary integrated care program, and all enrolled patients are followed for 2 years after treatment completion.[10]

The medical records of all patients treated at the PCTH outpatient clinic during the study period were reviewed by using a data collection instrument, and confidentiality was maintained. In addition to information on sociodemographic variables (gender, age, and level of education), information was collected on clinical and epidemiological variables (nutritional status, date of the first episode of tuberculosis, date of recurrence, and HIV serology), lifestyle habits (alcohol consumption, smoking, smoking history, and illicit drug use), and presence of comorbidities. All patients enrolled in the PCTH for treatment were followed for 2 years after treatment completion in order to determine whether or not there were recurrences. Patient data on recurrence and mortality during the 2-year follow-up period were retrieved from the Brazilian Ministry of Health National Case Registry Database and the Brazilian Mortality Database, respectively. The search was done using the patient's name, the patient's mother's name, and the patient's date of birth.

During treatment through the PCTH, all patients were followed monthly and were asked about the occurrence of adverse effects, by using a standardized data collection instrument, which included adverse reactions; these data were entered into a PCTH database. Adverse effects were classified as minor and major. Major adverse effects, namely, hepatitis, rifampin-induced thrombocytopenia, hemolytic anemia, acute renal failure, thrombotic thrombocytopenic purpura, ethambutol--induced optic neuritis, and pyrazinamide-induced acute gouty arthritis, require discontinuation of the offending drug and a change in the initial regimen.[6] Minor adverse effects include skin rash, acne, itching, arthralgia, and mild gastrointestinal symptoms, such as nausea, vomiting, loss of appetite, and abdominal pain; in cases of patients exhibiting these effects, it is usually not necessary to change treatment, and patient management consists of symptomatic therapy and a change in the administration schedule.[6]

Statistical analysis was performed with the Statistical Analysis System, version 6.11 (SAS Institute Inc., Cary, NC, USA). Descriptive statistics were expressed as frequency (n) and proportion (%) for categorical data and as mean and standard deviation for numerical data. In order to determine whether sociodemographic variables, comorbidities, and adverse effects were significantly associated with recurrence, categorical data were compared by using the chi-square test or Fisher's exact test, and numerical data (continuous variables with normal distribution) were compared by using the Student's t-test for independent samples. The level of statistical significance was set at 5% ($p < 0.05$).

RESULTS

Of the 466 patients treated for pulmonary tuberculosis through the PCTH during the study period, 275 were included. All of those 275 patients were 18 years of age or older; had a diagnosis of pulmonary tuberculosis confirmed by culture, which was performed through the PCTH; and were considered cured or completed treatment, either with regimen I (RHZ) between January of 2007 and October of 2010 or with the RHZE/FDC regimen between November of 2010 and June of 2013. Sixty-seven patients were excluded for different reasons (Figure 1). The final sample for the analysis of the rates of cure, treatment abandonment, and death, as well as for the assessment of adverse

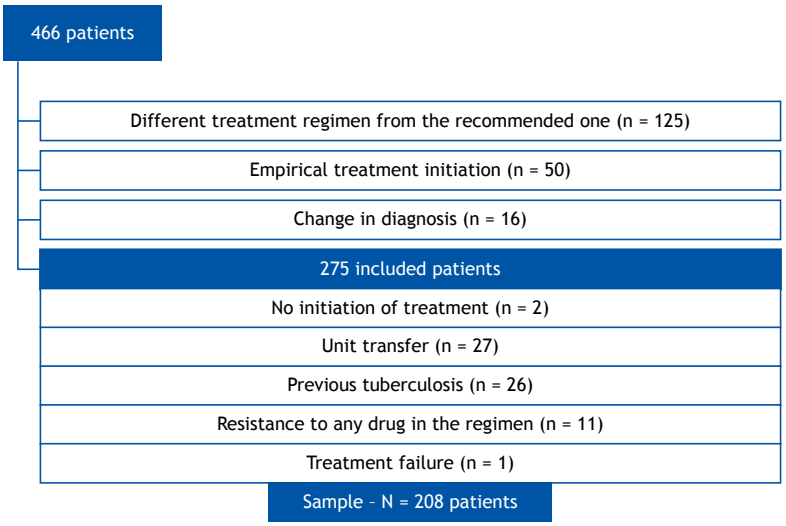

Figure 1. Selection of patients diagnosed with pulmonary tuberculosis for inclusion in the study.

effects, consisted of 208 patients, all of whom underwent self-administered treatment (Figure 1).

In the sample of 208 patients for the assessment of adverse effects and analysis of the rates of cure, treatment abandonment, and death, 125 patients (60.1%) received the RHZ regimen (in capsules and tablets) e 83 patients (39.9%) received the RHZE/FDC regimen.

The pattern of involvement by tuberculosis (first episode), with sociodemographic and clinical variables being stratified by treatment regimen (two groups), is shown in Table 1.

Among the 203 patients for whom data on adverse effects were available (information unavailable for 5), 139 experienced adverse effects (68.5%). There were no significant differences in the occurrence of adverse effects between the two treatment groups (Table 2).

Table 3 shows data on treatment status and outcomes by treatment regimen. The overall cure rate was 90.4%, and the rates of treatment abandonment and death before treatment completion were both 4.8%. During the 2-year follow-up period, 11 patients died from various causes. There were no significant differences in those rates between the two treatment groups. It was necessary to change the initial treatment because of the occurrence of adverse effects in 24 patients (18 in the RHZ group and 6 in the RHZE/FDC group), with no statistical difference ($p = 0.11$; Table 3).

For the analysis of the recurrence rate, we excluded 21 cases of death from any cause during treatment or during the 2-year follow-up period after treatment completion (4 of which experienced adverse effects and had a change in treatment regimen); 10 cases of treatment abandonment (1 of which experienced adverse effects and had a change in treatment regimen); and 24 cases of change in treatment regimen due to drug intolerance. Therefore, for this analysis, we excluded 50 patients, and the final sample consisted of 158 patients (78.9%). There were 7 recurrences throughout the follow-up period (recurrence rate = 4.4%), 6 of which occurred in the RHZ group and 1 of which occurred in the RHZE/FDC group, with no statistical difference ($p = 0.13$). Only 4 recurrences occurred within 2 years after treatment (RHZ = 3 patients and RHZE/FDC = 1 patient), the recurrence rate in this period being 2.5%. The other 3 recurrences occurred later than the two years of treatment and follow-up.

Smoking, illicit drug use, alcoholism, positive HIV serology, and body mass index (BMI) < 18.5 kg/cm^2 were not risk factors for recurrence (Table 4), nor was the presence of comorbidities, the presence of cavitation on chest X-ray, or the occurrence of a positive culture at 2 months of treatment. Time to culture conversion (2 months) was not different between the groups ($p = 0.36$). There were only 7 cases of positive culture at 2 months (4.8%). This information was available for 145 patients (69.7%).

Of the 208 patients, 146 (70.2%) had comorbidities when they developed tuberculosis. Among those who had recurrence, comorbidity-related characteristics were as follows: hepatitis, in 1; systemic arterial hypertension, in 2; diabetes mellitus, in 1; insulin dependence, in 1; chronic renal failure, in 1; connective tissue disease, in 2; use of immunosuppressants, in 2; use of corticosteroids, in 2; and lung disease, in 2. None of the comorbidities were found to be statistically associated with the recurrence outcome. There were no associations between the occurrence of major or minor adverse effects and recurrence.

DISCUSSION

Our study did not find statistically significant differences in the recurrence rate between the RHZ and RHZE/FDC groups, nor did it find associations of this outcome with the clinical factors investigated. There were no statistically significant differences in the occurrence of adverse effects between the groups, either. Malnutrition ($p = 0.079$), connective tissue

Table 1. Sociodemographic and clinical variables by treatment regimen.

Variable	Treatment regimen				p
	RHZ (n = 125)		RHZE/FDC (n = 83)		
	n	%	n	%	
Gender					
Male	81	64.8	45	54.2	0.13
Female	44	35.2	38	45.8	
Age, years[a]	46 ± 17		42 ± 15		0.11*
Age group, years					
≤ 30	29	23.2	21	25.3	0.65*
31-44	31	24.8	26	31.3	
45-55	33	26.4	18	21.7	
> 55	32	25.6	18	21.7	
Race[b]					
White	63	50.4	39	47.6	0.015
Biracial	32	25.6	34	41.5	
Black	30	24	9	11.0	
Level of education[c]					
Illiterate/≤ 9 years of schooling	65	54.6	38	48.1	0.46
High school (incomplete/complete)	38	31.9	32	40.5	
College (incomplete/complete)	16	13.4	9	11.4	
Smoking[c]					
Yes	18	14.6	8	9.6	0.45
Former smoker	43	35	27	32.5	
No	62	50.4	48	57.8	
Smoking history, pack-years[c]					
0	62	54.9	48	63.2	0.43
≤ 20	18	15.9	12	15.8	
> 20	33	29.2	16	21.1	
Drug use[c]					
Yes	9	7.5	4	4.9	0.47
No	111	92.5	77	95.1	
BMI classification[c]					
Underweight	19	23.2	16	27.6	0.83
Normal weight	47	57.3	31	53.4	
Overweight/obese	16	19.5	11	19.0	
Alcoholism[c]					
Yes	23	18.5	8	9.8	0.084
No	101	81.5	74	90.2	
HIV serology[c]					
Positive	18	15.3	6	9.0	0.22
Negative	100	84.7	61	91.0	

RHZ: rifampin-isoniazid-pyrazinamide; RHZE/FDC: rifampin-isoniazid-pyrazinamide-ethambutol fixed-dose combination; and BMI: body mass index. [a]Values expressed as mean ± SD. [b]One patient was indigenous (RHZE/FDC). [c]Lack of information on the following variables: level of education (n = 10); smoking (n = 2); smoking history (n = 19); drug use (n =7); BMI classification (n = 68); alcoholism (n = 2); and HIV serology (n = 23). *Student's t-test for independent samples.

disease (p = 0.12), and use of immunosuppressants or corticosteroids showed a trend toward an association with recurrence, although the association was not statistically significant. There were no differences in the rates of cure, treatment abandonment, or death between the treatment groups, the change in treatment to RHZE/FDC not translating to improvement in those rates, as has been reported in the literature.[8,11-16]

Tuberculosis was predominant in males (60.6%), in the economically active age group (27.4%), in Whites (49.0%), and in patients with a low level of education (52.0%). A low level of education suggests low socioeconomic status and limited access to health care.[3,17] There were no differences in sociodemographic variables between the treatment groups (RHZ vs. RHZE/FDC), showing that the groups were comparable.

In our sample, 89 patients (43.4%) had chest X-ray findings suggestive of tuberculosis with cavitation, and there were only 7 cases (4.8%) of positive culture at 2 months of treatment. Although it has been reported

Table 2. Adverse effects by treatment regimen.[a]

Adverse effects	Treatment regimen				p
	RHZ		RHZE/FDC		
	n	%	n	%	
Total					
Yes	86	69.9	53	66.3	0.35
No	37	30.1	27	33.8	
Minor					
Yes	78	63.4	48	60.0	0.37
No	45	36.6	32	40.0	
Major					
Yes	14	11.4	7	8.8	0.36
No	109	88.6	73	91.3	
Acne/itching					
Yes	31	25.2	13	16.3	0.089
No	92	74.8	67	83.8	
Arthralgia					
Yes	34	27.6	15	18.8	0.099
No	89	72.4	65	81.3	
Anorexia/vomiting/abdominal pain/nausea					
Yes	39	31.7	26	32.5	0.51
No	84	68.3	54	67.5	
Paresthesia					
Yes	21	17.1	15	18.8	0.45
No	102	82.9	65	81.3	
Hepatotoxicity					
Yes	13	10.6	6	7.5	0.32
No	110	89.4	74	92.5	
Optic neuritis					
Yes	0	0	0	0	N/A
No	123	100	80	100	
Exanthema					
Yes	1	0.8	1	1.3	0.63
No	122	99.2	79	98.8	

RHZ: rifampin-isoniazid-pyrazinamide; and RHZE/FDC: rifampin-isoniazid-pyrazinamide-ethambutol fixed-dose combination. [a]Lack of information on 5 patients (2 in the RHZ group and 3 in the RHZE/FDC group). Patients could experience more than one adverse effect.

Table 3. Treatment status and variables by treatment regimen.[a]

Variable	Treatment regimen				p
	RHZ (n = 125)		RHZE/FDC (n = 83)		
	n	%	n	%	
Treatment status					
Cure	114	91.2	74	89.2	
Treatment abandonment	4	3.2	6	7.2	0.32
Death	7	5.6	3	3.6	
Positive culture at 2 months of treatment					
Yes	3	3.7	4	6.3	0.36
No	79	96.3	59	93.7	
Change in initial treatment					
Yes	18	14.4	6	7.2	0.11
No	107	85.6	77	92.8	
Recurrence					
Yes	6	4.8	1	1.2	0.13
No	119	95.2	82	98.8	

RHZ: rifampin-isoniazid-pyrazinamide; and RHZE/FDC: rifampin-isoniazid-pyrazinamide-ethambutol fixed-dose combination.

Table 4. Sociodemographic and clinical variables by recurrence status (N = 158).

Variable	Recurrence		No recurrence		p
	n	%	n	%	
Gender					
Male	4	57.1	88	58.3	0.62
Female	3	42.9	63	41.7	
Age, years[a]	44 ± 15		42 ± 15		
Age group, years					
≤ 30	1	14.3	42	27.8	0.61
31-44	2	28.6	42	27.8	
45-55	3	42.9	34	22.5	
> 55	1	14.3	33	21.9	
Race					
White	2	28.6	69	46.0	0.45
Biracial	4	57.1	51	34	
Black	1	14.3	30	20.0	
Level of education					
Illiterate/≤ 9 years of schooling	3	42.9	75	52.1	0.87
High school (incomplete/complete)	3	42.9	49	34.0	
College (incomplete/complete)	1	14.3	20	13.9	
Smoking					
Yes	1	14.3	20	13.4	0.97
Former smoker	2	28.6	49	32.9	
No	4	57.1	80	53.7	
Smoking history, pack-years[b]					
0	4	66.7	80	59.3	0.33
≤ 20	2	33.3	24	17.8	
> 20	0	0.0	31	23.0	
Drug use					
Yes	1	14.3	10	6.8	0.41
No	6	85.7	136	93.2	
BMI classification[b]					
Underweight	3	75	24	24.7	0.079
Normal weight	1	25	53	54.6	
Overweight/obese	0	0.0	20	20.6	
Alcoholism					
Yes	1	14.3	21	14.1	0.66
No	6	85.7	128	85.9	
HIV serology					
Positive	1	14.3	18	13.2	0.64
Negative	6	85.7	118	86.8	

BMI: body mass index. [a]Values expressed as mean ± SD. [b]Unavailable information on patients with recurrence: smoking history, in 1; and BMI classification, in 3.

in the literature that cavitation is a risk factor for recurrence[1,18-21], as is the occurrence of a positive culture at 2 months of treatment,[18 20,22] this was not observed in the present study.

There was a trend toward increased occurrence of cutaneous adverse effects (acne/itching) and arthralgia in the RHZ regimen group. This trend might be explained by the higher dose concentrations of isoniazid and pyrazinamide in the RHZ regimen, in comparison with the RHZE/FDC regimen. Despite the possibility that the addition of ethambutol could cause more cases of optic neuritis, no such cases were observed. Some studies have not found differences in the occurrence of adverse effects between single-drug regimens and FDC regimens, corroborating our study results.[9,13-15] Gravendeel et al. found increased occurrence of adverse effects in the single-drug regimen group, and gastrointestinal and musculoskeletal adverse effects predominated.[12] According to the literature, the main advantages of changing treatment to FDCs include improving adherence, simplifying treatment, and preventing monotherapy and subsequent selection of drug-resistant mutant bacilli.[6,11,23,24]

Only 4 recurrences occurred within 2 years after treatment (RHZ = 3 patients and RHZE/FDC = 1 patient), the recurrence rate in this period being

2.5%, which is similar to previous reports.[13,25] There was a trend toward increased recurrence in the RHZ regimen group. Some authors have found that changing treatment to RHZE/FDCs led to a trend toward increased recurrence.[11,25-27] In contrast, other studies have found no differences in the recurrence rate between the groups (FDC vs. single-drug formulation).[8,15] A recently published review found little or no difference in the rates of death or in the frequency of adverse effects between the groups.[27] FDCs had no effect in reducing the treatment abandonment rate or the irregular use of drugs.[5,9,13,15,23] The treatment abandonment rate in our study did not vary in a statistically significant way in the two groups, possibly because of the integrated multidisciplinary care provided through the PCTH.[10]

Our study has some limitations, such as the sample size, that may have prevented us from detecting significant associations. A convenience sample was used, because this was a study limited to the operational routine of a single facility. The fact that it was retrospective is another limitation, since data collection by using a data collection instrument and reviewing medical charts may have prevented the gathering of some information. In addition, patients with tuberculosis having access to the HUCFF/IDT meant that most of them had comorbidities, limiting the external validity of the findings. The sample size was not calculated to compare the recurrence rate with RHZE/FDC and RHZ or to compare patients with and without recurrence. However, the fact that this was a study conducted at a tuberculosis treatment facility that provides integrated multidisciplinary care,[10] associated with bacteriological confirmation with routine profiling of sensitivity to the drugs in the regimens used, post-cure follow-up, standardized routines, and systematic data collection, may contribute to the analysis of the effects that the RHZE/FDC regimen has, under optimal operational conditions, on the care of patients with active tuberculosis.

In conclusion, changing treatment to a four-drug FDC produced no statistically significant differences in the rates of recurrence, in comparison with the use of the previous regimen. We identified a trend toward a BMI < 18.5 kg/cm^2 and connective tissue disease being risk factors for recurrence, a trend that may not have reached the level of statistical significance because of the sample size. There were no statistically significant differences in the rates of treatment abandonment, death, or cure or in the occurrence of major or minor adverse effects between the groups. However, the RHZ regimen group showed a trend toward a higher incidence of cutaneous adverse effects (acne/itching) and arthralgia than did the RHZE/FDC regimen group. Further studies involving larger samples and data on different operational routines than that of the PCTH/HUCFF/IDT could contribute to elucidating the impact of the use of the RHZE/FDC regimen in Brazil.

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Sweat test and cystic fibrosis: overview of test performance at public and private centers in the state of São Paulo, Brazil

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ABSTRACT

Objective: The sweat test (ST) measures chloride levels in sweat and is considered the gold standard for the diagnosis of cystic fibrosis (CF). However, the reliability of a ST depends on their being performed by experienced technicians and in accordance with strict guidelines. Our aim was to evaluate how sweat stimulation, sweat collection, and chloride measurement are performed at 14 centers (9 public centers and 5 private centers) that routinely perform STs in the state of São Paulo, which has the highest frequency of CF in Brazil. **Methods:** This was a cross-sectional cohort study, using a standardized questionnaire administered in loco to the staff responsible for conducting STs. **Results:** No uniformity regarding the procedures was found among the centers. Most centers were noncompliant with the international guidelines, especially regarding the collection of sweat (the samples were insufficient in 10-50% of the subjects tested); availability of stimulation equipment (which was limited at 2 centers); modernity and certification of stimulation equipment (most of the equipment having been used for 3-23 years); and written protocols (which were lacking at 12 centers). Knowledge of ST guidelines was evaluated at only 1 center. **Conclusions:** Our results show that STs largely deviate from internationally accepted guidelines at the participating centers. Therefore, there is an urgent need for standardization of STs, training of qualified personnel, and acquisition/certification of suitable equipment. These are essential conditions for a reliable diagnosis of CF, especially with the increasing demand due to newborn screening nationwide, and for the assessment of a possible clinical benefit from the use of modulator drugs.

Keywords: Cystic fibrosis/diagnosis; Cystic fibrosis/prevention & control; Sweat.

INTRODUCTION

The early observations of salty sweat in cystic fibrosis (CF) led to the development of the "still" gold standard test for CF diagnosis, consisting in the measurement of sweat chloride (Cl^-) and sodium (Na^+) concentrations. For most of the patients with CF, at least those with classical CF, this assay will reveal elevated levels of both electrolytes, confirming a diagnosis of CF by this relatively straightforward sweat test (ST).

As in many other countries,[1] the implementation of newborn screening (NBS) for CF in Brazil challenged the diagnosis paradigm by leading to the routine diagnosis of various asymptomatic children. In 2001, NBS was initiated in some states in Brazil, the Brazilian Unified Health Care System providing a nationwide coverage in 2014 (Appendix 1; available in the online version of the JBP; http://www.jornaldepneumologia.com.br/detalhe_anexo.asp?id=48). Although the incidence of CF ranges from 1:2,500 to 1:6,000 live births in Europe and North America,[2] the estimated incidence is 1:10,000 live births in Brazil.[3] Based on these data, it is estimated that 60 new CF cases occur per year in the state of São Paulo (SP). NBS for CF caused an increase in the survival of these patients since it enabled the early diagnosis of CF and allowed the adoption of nutritional and therapeutic approaches before the advent of clinical manifestations and complications of the disease,[4-6] being economically justifiable for the public health care initiative.[7] In the first month of life of an individual, NBS is carried out by two determinations of the level of immunoreactive trypsinogen. However, the follow-up of the patients with positive results in NBS requires the confirmation of a diagnosis of CF. This is achieved by ST values ≥ 60 mEq/L in two different samples and/or the identification of two mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene.[8]

Although the ST remains the most sensitive indicator of CF, in order to be considered as the "gold standard", it should be performed using the Gibson and Cooke (GC)

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technique, also called the quantitative pilocarpine iontophoresis ST.[9]

For the GC method to be reliable, it needs to be performed in laboratories with experienced and skilled technicians according to strict guidelines,[10] requiring that sweating be stimulated by pilocarpine iontophoresis; sweat is collected on a filter paper or gauze pad, weighed, eluted, and analyzed for Na^+ and Cl^- using a variety of validated methods described below. The Cystic Fibrosis Foundation summarized its guidelines in 23 topics in order to ensure the appropriate quality of STs.[11,12] The topics are based on the classical GC method of pilocarpine stimulation,[9] use of filter paper or Macroduct® Sweat Collection System (MSCS; EliTechGroup, Paris, France) for sweat collection, and determination of Cl^- by manual titration or by a coulometric quantitative test.[9,10,12-15] The qualitative method is not accepted for confirming a definitive diagnosis of CF.[10,13,16]

Indeed, the ST is complex, and its accuracy is related to the competence and commitment of the professional who carries out its various steps.[9,10] For this reason, various countries organized standardized protocols for STs. The first country to publish a consensus standardization and external quality control for STs was the USA in 1994, followed by the United Kingdom in 2000.[17-20] Since then, numerous guidelines have been published, enforcing specific rules to be adopted while carrying out STs, as well as demanding accreditation and periodic monitoring of the laboratories by official regulatory agencies.[13]

Nevertheless, even in countries where the standardization of STs is well established, there are details in the performance and interpretation of the tests that are often omitted and overlooked from center to center.[12,21] Moreover, the ST has also become a major outcome measure in clinical trials, namely those involving CFTR modulators that rescue the function of the dysfunctional mutant protein.[22,23] Therefore, it has become increasingly relevant that the performance and the standard procedures of STs should be reviewed at present times.

Taking into account the socioeconomic status and the miscegenation of the Brazilian population, the importance of STs and other methods for the diagnosis of CF is even more relevant.[24-28] In Brazil, to date, there is no critical and comparative analysis regarding the performance and the interpretation of STs. We selected the state of SP because it is the most populous in Brazil, with approximately 45 million inhabitants in 2016 (Appendix 2 ; available in the online version of the JBP; http://www.jornaldepneumologia.com.br/detalhe_anexo.asp?id=48).[29]

The objective of the present study was to evaluate how STs are performed and interpreted at the centers that agreed to participate in the study and that routinely perform these tests in various cities in the state of SP, comparing their routine with those specified in international guidelines. These centers, altogether, carry out approximately 4,500 tests per year.

METHODS

This was an observational, descriptive, cross-sectional cohort study. A total of 18 centers that routinely perform STs in the state of SP were invited to participate in the study in 2013. The study was approved by the Research Ethics Committee of the Universidade Estadual de Campinas (State University of Campinas; Protocol no. 86624/2012) and was carried out in accordance with the Declaration of Helsinki. All participants gave written informed consent.

A questionnaire was developed, consisting of 54 questions that comprised all of the steps for performing STs: sweat stimulation; collection of sweat; and determination of the level of Cl^-[12,13] (Appendix 3 ; available in the online version of the JBP; http://www.jornaldepneumologia.com.br/detalhe_anexo.asp?id=48). The questionnaire was given to the staff responsible for conducting the STs at all of the centers included in the study. In our study, two researchers performed the interviews simultaneously. The data were compiled in Excel spreadsheets, and the results were presented in tables and figures.

RESULTS

A total of 18 centers were identified as performing STs as part of their routine (9 were private and 9 were public). Of the 18 centers, 14 agreed to participate in the study, 5 (35.7%) being private institutions and 9 (64.3%) being public health care centers (Figure 1). At the moment of the visit, 4 of the centers were not performing STs by lack of supplies. The 14 centers included in the study perform approximately 4,500 STs/year, 4,000 of those being carried out at public centers. The number of STs/year per center is shown in Figure 2. Among the 14 centers, the length of experience in performing STs ranged from 1 to > 20 years (Appendix 4 ; available in the online version of the JBP; http://www.jornaldepneumologia.com.br/detalhe_anexo.asp?id=48).

We interviewed the professionals involved in the performance of the three stages of STs at the participating centers. Regarding their occupation, one was a physician, seven were biomedical technicians, two were biologists, four were nurses, and seven were nursing technicians. Among the 14 centers, 11 professionals were trained by colleagues from the same center (internal training), 2 were trained at another center (external training), and 1 had both internal and external training. Only 1 of the centers was aware of the ST guidelines and had a printed version of the standard operating procedure manual.

Among the 14 centers, 2 had no equipment for sweat stimulation. Some centers used more than one device, the equipment used being nine MSCS; one CF-Indicator® (Polychrome Medical Inc., Brooklyn Center, MN, USA); five Iontokit® (Advanced Instruments Inc., Norwood, MA, USA); and one produced by Qualiterm (Qualiterm, São Paulo, Brazil). The five devices connected to a power grid were as follows: three Iontokit® (Advanced

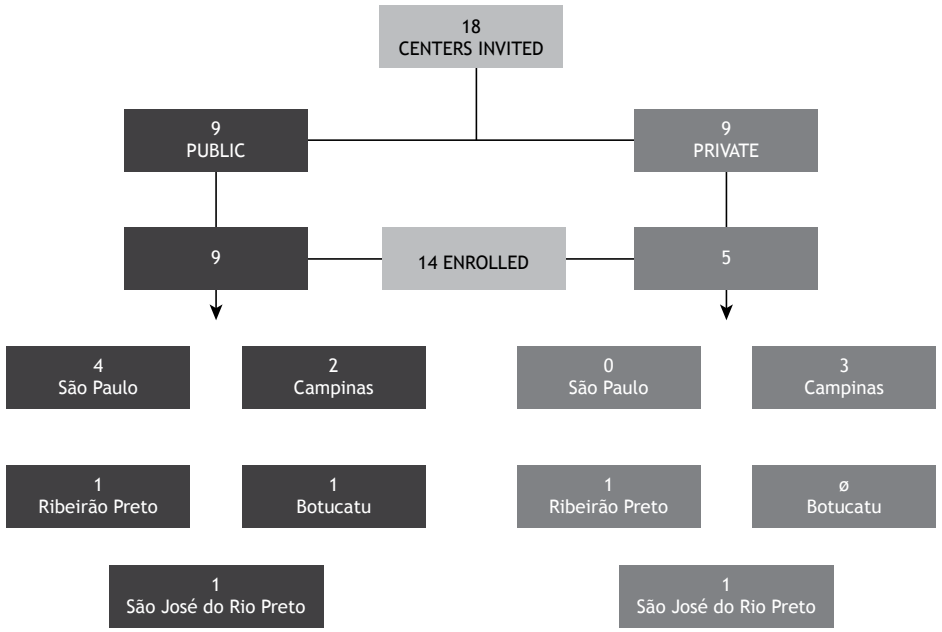

Figure 1. Participating referral centers for cystic fibrosis in the state of São Paulo according to the cities where they are located in.

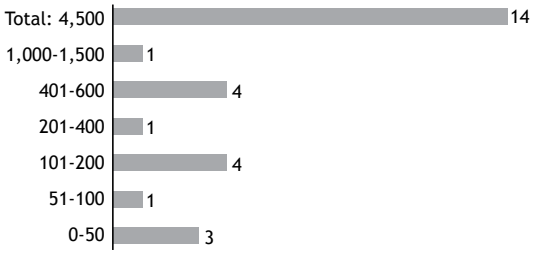

Figure 2. Number of sweat tests performed per year per center. From 0 to 50 tests: two private centers and one public center; from 51 to 100 tests: one private center; from 101 to 200 tests: three public centers and one private center; from 201 to 400 tests: one private center; and from 401 to 1,500 tests: five public centers. Total = 4,500 tests/year at the 14 centers.

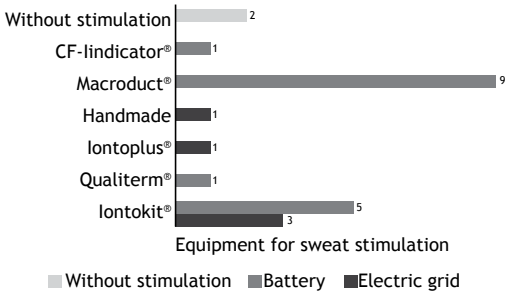

Figure 3. Sweat stimulation equipment used in the centers regarding the energy source used. None was licensed by the Brazilian National Health Oversight Agency. CF-Indicator® (Polychrome Medical Inc., Brooklyn Center, MN, USA); Macroduct® Sweat Collection System (EliTechGroup, Paris, France); Iontoplus® (NAIMCO Inc., Chattanooga, TN, USA); Qualiterm (Qualiterm, São Paulo, Brazil); and Iontokit® (Advanced Instruments Inc., Norwood, MA, USA).

Instruments Inc.), one Iontoplus® (NAIMCO Inc., Chattanooga, TN, USA); and one handmade craft. These devices were older, with a mean usage time of 15 years (Figure 3).

There were 21 pieces of stimulation equipment at 12 of the centers altogether. None of the pieces of equipment had an official registration for the clinical diagnosis of CF in the country. Among these, there were 8 MSCS, 7 of which not being in operation due to lack of spare parts or supplies, or because they broke down less than a year ago. Among the 12 centers that carried out sweat stimulation, 8 used the forearm/arm for electrode placement, whereas the other 4 used other sites (Figure 4A). Sweat stimulation was achieved by one or more of the following techniques: use of a blanket, at 6 centers; use of a coat, at 6; running or walking outdoors, at 4; skin lock with plastic wrap, at 2; use of a bandage, at 1; and Parafilm wrapping, at 1. Sweat was collected from the patient with the help of a disposable spoon and placed into a sterile tube for the determination of the level of Cl^- at 1 center. At 2 private centers, sweat was induced without stimulation by iontophoresis devices (Appendix 5 ; available in the online version of the JBP; http://www.jornaldepneumologia.com.br/detalhe_anexo.asp?id=48).

The electrical stimulation time to induce sweat ranged from 3 to 10 min (Figure 4B). The type of current used was known at only 3 of the 14 centers (direct current) and unknown at 9, 5 of which also failed to report the intensity of the current used. The intensity of the current was known at 5 centers (Figure 4C). At 4 centers (28.6%), it was reported that the electrical stimulation procedure had caused skin burn in some

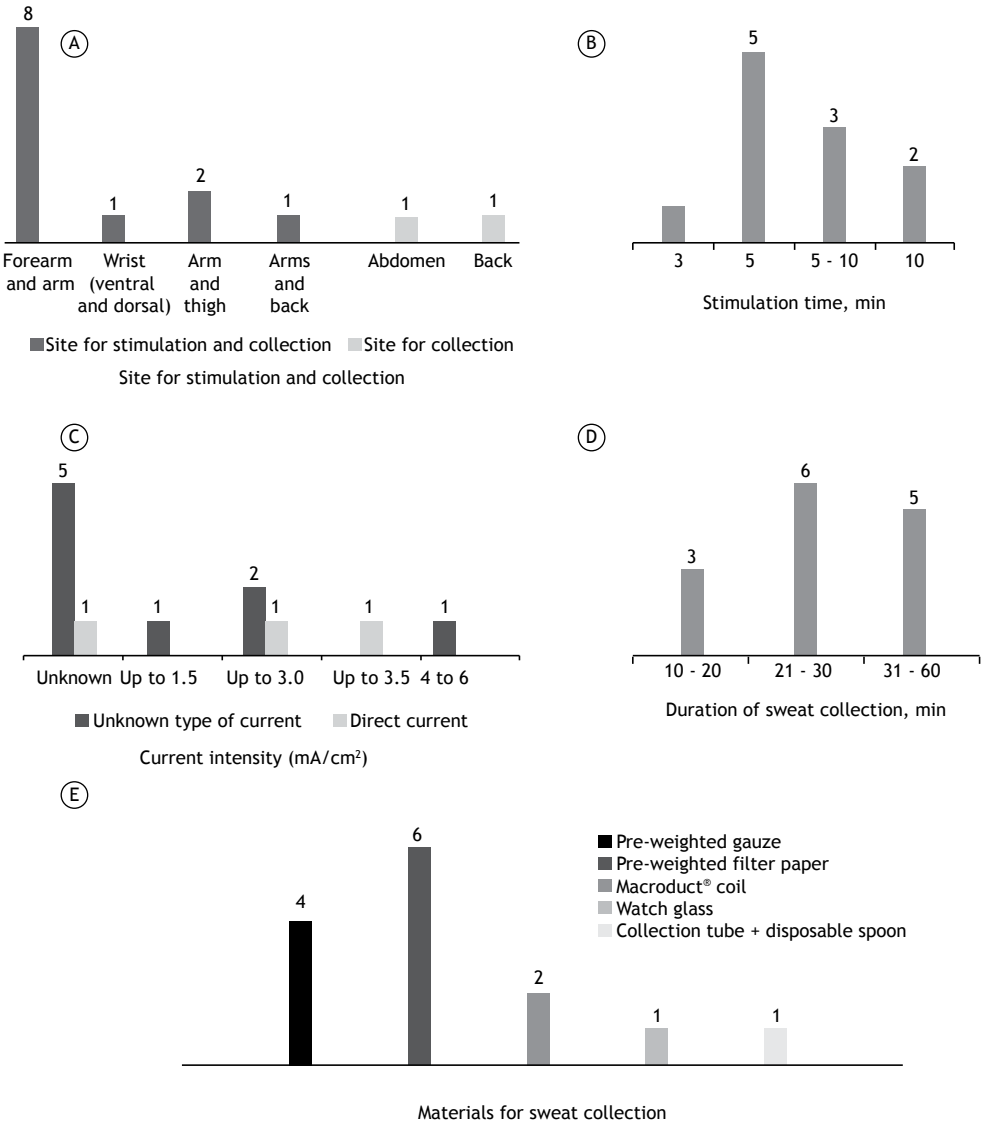

Figure 4. In A, site for stimulation and collection of sweat in the 12 participating centers that performed sweat stimulation. In B, stimulation time to induce sweat per center. In C, information available regarding the type and the intensity of the current applied for sweat stimulation per center. In D, duration of sweat collection per center. In E, materials employed for sweat collection per center.

patients; however, 5 centers (35.7%) reported that it had never occurred with any of their patients, whereas 3 centers (21.4%) were unable to report that information since the interviewees had been recently working at those centers. Finally, 2 centers (14.3%) did not use electrical stimulation.

The duration of sweat collection ranged from 10 to 60 min (Figure 4D). The materials employed for sweat collection at the 14 centers are described in Figure 4E. It is of note that 2 centers were using unusual materials/techniques: a watch glass was placed over the site of pilocarpine stimulation, then fixed with tape, and the sweat droplets were collected using a sterile pipette or a disposable spoon into a sterile tube at 1 of the centers, whereas the other center did not have appropriate precision scales for weighing the collected material. In addition, 2 centers did not perform sweat stimulation using any kind of equipment and, therefore, were disregarded regarding this issue.

The Cl^- level was determined by using the manual titration technique and the quantitative coulometric test (chloridometer), at 6 centers each. Among the latter, 1 center was not in operation. The need to repeat a ST was due to insufficient sweating and unknown causes at 10 and 4 of the centers, respectively. The rate of repeat STs was 5%, at 1 center; 10-20%, at 7; 30%, at 1; and > 50%, at 1.

The number of people who collected sweat and conducted the STs is summarized in Figure 5A. The same professional was responsible for the collection and the performance of the ST at 6 centers. The

minimum acceptable amount of sweat in order to conduct a reliable ST considerably varied among the centers and is summarized in Figure 5B. At 11 centers that used filter paper or gauze to collect sweat, the amount of sweat considerably ranged from 50 to 100 mg, and 1 center had no knowledge of the acceptable value (Figure 5B). Regarding the 3 centers using the MSCS, the acceptable volume of sweat was 15 µL, 20 µL, and no standard. The center that used the watch glass reported that the required minimum volume was 20 µL. Most of the professionals at the centers were unaware of the correct number of tests with positive results ($Cl^- \geq 60$ mEq/L) for a definitive diagnosis of CF (Figure 5C). Figure 6 shows how compliant with the Cystic Fibrosis Foundation guidelines[13] each of the 14 centers was.

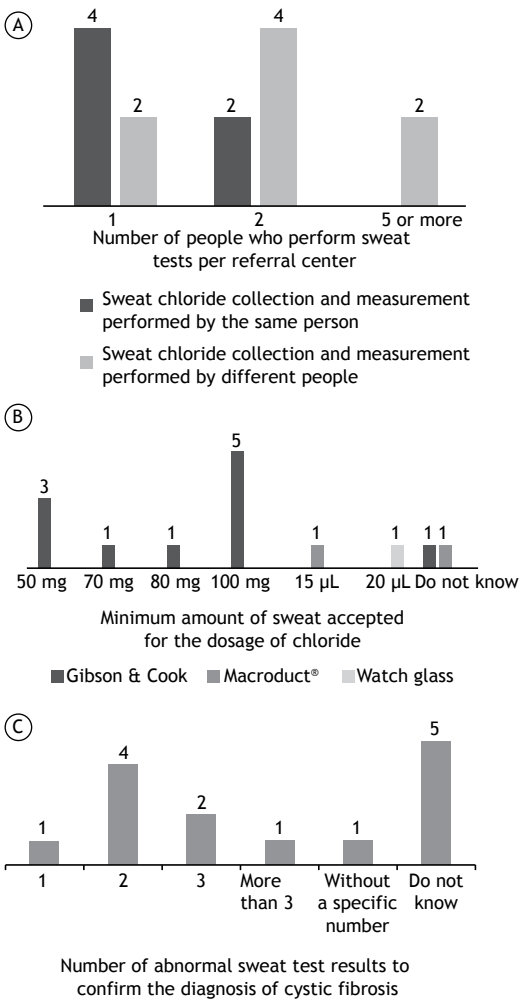

Figure 5. In A, number of people who perform sweat tests (collection and quantification of chloride) per center. In six centers, the staff is responsible for collecting sweat and determining the level of chloride in it. In eight centers, the staff that collects sweat is not the same as that determining the level of chloride. In those centers, the laboratory team is responsible for determining the level of chloride. In B, knowledge of the professionals involved in the performance of sweat tests about the minimum acceptable amount of sweat for chloride level determination per collection method per center. In C, knowledge of the professionals involved in the performance of sweat tests about the necessary number of abnormal test results in order to confirm the diagnosis of cystic fibrosis per center.

DISCUSSION

In Brazil, the diversity of expression of the disease is conditioned by miscegenation, which highly increases the genetic diversity expressed in a variability of mutations in the *CFTR* gene in our population, thus rendering the genetic diagnosis difficult and costly. The monitoring of CF patients in Brazil is performed at referral centers, most of which are public and linked to the Brazilian Unified National Health Care System with public financial support and generally associated with universities. The state of SP has the second per capita income in the country and has the largest number of referral centers for CF (n = 7), all of which being public health care centers (Appendix 6 ; available in the online version of the JBP; http://www.jornaldepneumologia.com.br/detalhe_anexo.asp?id=48).

The present study on the performance of STs at 14 centers, which perform 4,500 tests/year altogether, revealed that there is no uniformity in the ST procedures and that there are serious difficulties in its performance and significantly inadequate conditions, which largely deviate it from internationally accepted guidelines.

Similar studies, however, had been previously performed regarding the quality of STs at various centers in several other countries, also presenting significant diversity and inconsistent results.[12,30,31] The diagnostic confirmation of CF enables health care centers to provide better care and monitoring, which translates into higher life expectancy for the patients.[8] This was also found at our referral center.[32] The standardization of STs is key to a reliable diagnosis of CF.

In particular, the present study has shown that there is no uniformity in the performance of ST in its three stages (stimulation, collection, and quantification) at the participating centers. The main issues and possible alternatives to the three steps can be summarized as follows:

(i) Stimulation: the lack of awareness about the existence of adequate equipment for sweat stimulation and its usage was present at approximately 30% of the participating centers. Alternative methods of stimulation, noncompliant with the international guidelines (e.g. exposure to the sun with a blanket, exposure to the sun inside a car, usage of noncertified sweat induction equipment, and lack of knowledge of stimulation techniques), were in practice at 4 of the centers and might even impair the health of patients (e.g. skin burning, dehydration, or even death). In addition, those 4 centers also collected inadequate sweat samples for determining the level of Cl^-. Every center should rely on the iontophoresis stimulation technique with pilocarpine, use certified stimulation equipment, and carry out its regular maintenance and calibration

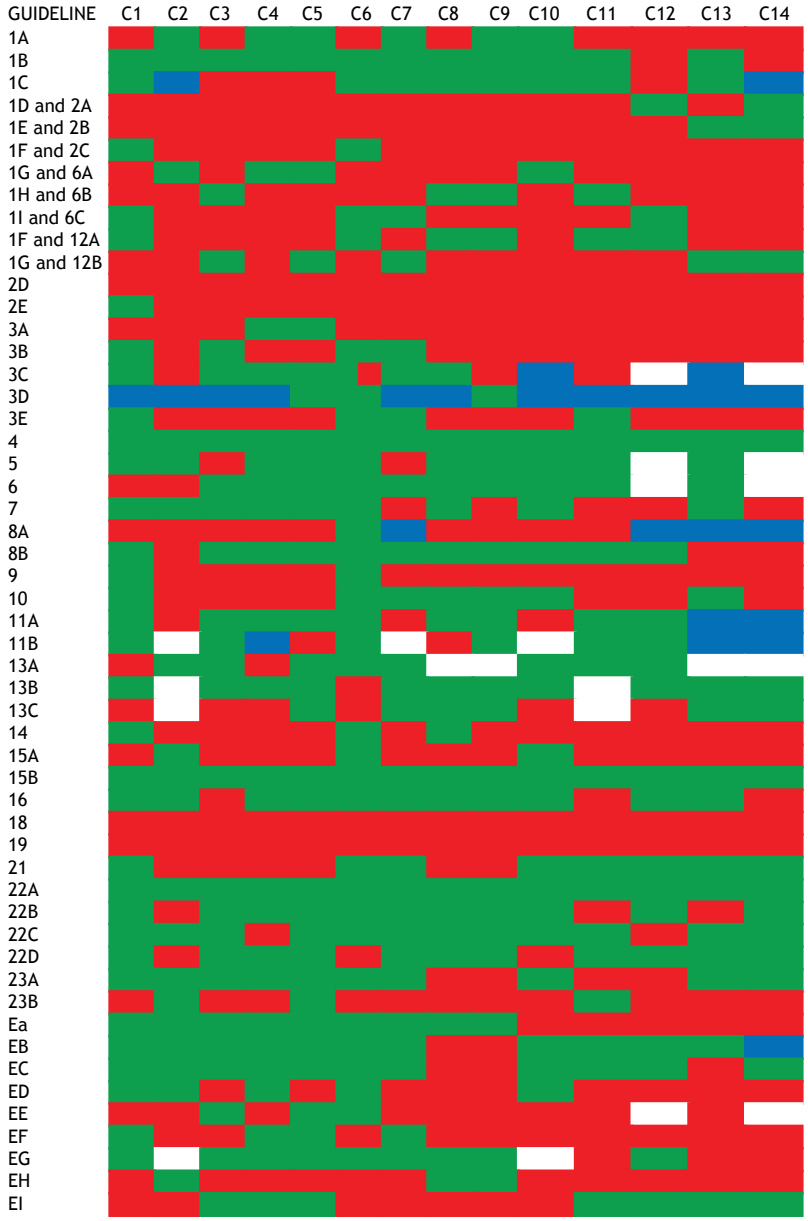

Figure 6. Compliance with the sweat test guidelines by LeGrys et al.[13] per center. 1A: Macroduct® coils available; 1B: Stimulation of sweat using pilocarpine iontophoresis; 1C: Evaluation of the amount collected either in weight (mg) or volume (µL); 1D and 2A: without sweat stimulation; 1E and 2B: inadequate collection method (alternative methods); 1F and 2C: use of a helper method to increase sweat volume; 1G and 6: collection of sweat into Macroduct® coils; 1H and 6B: collection of sweat on filter paper; 1I and 6C: collection of sweat in gauze; 1F and 12A: chloride level determined by manual titration, using the Schales and Schales mercuric nitrate procedure; 1G and 12B: chloride level determined by coulometric titration, using a chloridometer; 2D: following the US National Committee for Clinical Laboratory Standards guidelines[17]; 2E: laboratory must have access to a copy of the guidelines[17] (paper copy or electronic file); 3A: iontophoresis equipment must be battery powered and regularly inspected; 3B: iontophoresis equipment powered by electrical network; 3C: iontophoresis performed with electrode lead; 3D: knowledge about the current applied; 3E: inspection for current control and leakage must be periodically performed by biomedical engineering according to the manufacturer's recommendations; 4: the minimum age for testing is 48 hours of life; 5: arms or legs were used as collection sites, and the iontophoresis current should not cross the heart; 6: iontophoresis should be carried out using pilocarpine for 5 min; 7: sweat collected for no more than 30 min; 8A: the incidence of insufficient samples was investigated and resolved if it exceeded 5% for patients older than three months of age; 8B: exclusion criteria were adopted; 9: collection and analysis were performed in duplicate; 10A: insufficient samples were not analyzed and were not pooled for analysis; 11A: collection and analytical procedures were designed to minimize evaporation or contamination; 11B: sweat collected in gauze, once reweighed, was stored with or without diluents in a tightly sealed container for up to 3 days at refrigerator temperature; 13A: performing and evaluating quality control in every sweat analysis run in order to determine quality control; 13B: a control sample was assayed with each patient run; 13C: a

positive and negative control (or more) were assayed with each patient run; 14: sweat tests are included in the overall evaluation of continuous quality improvement in the laboratory; 15A: reagents were appropriately labeled; 15B: sweat samples were appropriately labeled for patient identification throughout the process of sweat collection and analysis; 16: appropriate reference values for chloride in sweat were used; 18: laboratories document successful performance in the Brazilian National Health Oversight Agency proficiency testing survey for sweat test analysis; 19: the director of the center reviews all sweat test results by using procedures consistent with Health Insurance Portability and Accountability Act of 1996 regulations; and 21: all positive tests were confirmed with a repeat sweat chloride test. Red: noncompliant with the guidelines; green: compliant with the guidelines; white: not evaluated; and blue: no data.

by the manufacturer or a qualified company in order to ensure the safety of the procedure. Every center should also provide (or seek elsewhere) adequate training of the professionals responsible for handling the equipment.

(ii) Collection: most of the participating centers used methods for sweat collection that were in accordance with the established recommendations (use of filter paper, gauze, or MSCS). However, 2 centers used alternative, nonrecommended collection methods (use of a spoon and a watch glass), which affect the reliability of the ST. Although MSCS has been described as a suitable method for the collection of sweat by the US Health Department since 2013, it was not registered in Brazil during the period of study.[13] In September of 2014, the use of MSCS was properly licensed, as well as of the digital chloridometer, which enabled adequate, periodic maintenance of the equipment and uninterrupted acquisition of supplies. This fact will possibly change the present scenario: 7 centers were not using MSCS due to the lack of spare parts/supplies, difficulties in the maintenance of the equipment, or lack of trained professionals capable of using the system (how to perform sweat induction, sweat collection, and Cl^- level determination). Another factor to be considered is the high cost of supplies, which are imported, in comparison with the traditional method of stimulation and collection for the GC method, which uses pilocarpine and filter paper or gauze for sweat collection.

(iii) Quantification: The determination of the Cl^- level must be quantitative and performed by coulometry, flame photometry, or manual titration. Regardless of the procedure, there were no problems regarding this issue at the participating centers, except that conductivity, which is an unreliable procedure, was used for the diagnosis of CF at 2 centers. At another center, conductivity was used just for screening, which is an appropriate, correct approach.

CF is a progressive disease, which requires that patients be treated at referral centers so as to receive the best health care and adequate treatment. Having a safe, reliable diagnosis is the first step, and it is critical for the guidance of patients and their families by the medical staff.

The present study shows the real situation of STs in the state of SP, which may be representative of the overall situation for STs in Brazil. Altogether, our results show that STs largely deviate from internationally accepted guidelines at the participating centers. There is an urgent need for either domestic or imported equipment for sweat stimulation and for determining the level of Cl^- in sweat in accordance with international guidelines. Maintenance should be adequate, and spare parts and supplies should be always available so that the results obtained are reliable and appropriate.

From this unique moment, when we celebrate the introduction of NBS for CF in all states in Brazil, we must be prepared to overcome the challenges ahead. These challenges can only be overcome if they are first identified and objectively faced by the CF teams. In addition, we need to work together so as to change the current reality; we believe that we can only build a new reality if we first become aware of the limitations and difficulties inherent to each individual center.

The present study provides a warning regarding the need for standardization of STs in Brazil by means of the construction and adoption of guidelines for the diagnosis of CF. The issue has been in the discussion agenda of the Brazilian CF Study Group.

Directors of CF referral centers should review each current step in the performance of STs, working closely together with the laboratory staff, which will undoubtedly improve the quality of the results so as to provide a reliable CF diagnosis and minimize the possible bias of STs. The professionals who perform STs should be aware of the specificities of the disease and recognize the important role of a correctly performed ST to confirm or exclude a diagnosis of CF. Such training should be provided by the CF referral centers to its professionals, fostering their participation in internal or external training, scientific events, and other discussion forums. The proximity among the different professionals working in the area of CF, as well as the exchange of information among the different referral centers, will allow to increasing the knowledge regarding STs and, therefore, improve the procedures involved in it toward a more reliable diagnosis of CF.

In conclusion, we found no uniformity in the steps carried out in the performance of STs and large deviations from internationally accepted ST guidelines at the various participating centers in the state of SP. Major inadequate conditions included insufficient production of sweat, lack of stimulation equipment or clinical chemistry equipment, absence of written protocols, and use of obsolete noncertified measuring equipment. Even though we know that there are various difficulties and barriers to be overcome, we need to move towards meeting the 23 topics of the Cystic Fibrosis Foundation guidelines[13] so that STs are adequately carried out to this end.

There is an urgent need for standardization of STs, training of qualified personnel, suitable equipment, and certification. These are essential conditions for a reliable diagnosis of CF, especially with the increasing demand due to NBS nationwide, and for the assessment of a possible clinical benefit with the use of CFTR modulator drugs.

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Anatomic pulmonary resection via video-assisted thoracic surgery: analysis of 117 cases at a referral center in Brazil

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ABSTRACT

Objective: To describe our experience with video-assisted thoracic surgery (VATS) for anatomic pulmonary resection at a referral center for thoracic surgery in Brazil. **Methods:** All patients who underwent anatomic pulmonary resection by VATS between 2010 and 2015 were included. Clinical and pathological data, as well as postoperative complications, were analyzed. **Results:** A total of 117 pulmonary resections by VATS were performed, of which 98 were lobectomies and 19 were anatomic segmentectomies. The mean age of the patients was 63.6 years (range, 15-86 years). Females predominated (n = 69; 59%). The mean time to chest tube removal was 2.47 days, and the mean length of ICU stay was 1.88 days. The mean length of hospital stay was 4.48 days. Bleeding ≥ 400 mL occurred in 15 patients. Conversion to thoracotomy was required in 4 patients. **Conclusions:** Our results are similar to those published in major international studies, indicating that VATS is an important strategy for pulmonary resection. They also show that VATS can be safely performed with adequate training. This technique should be used more often for the treatment of lung diseases in Brazil.

Keywords: Lung neoplasms/therapy; Lung neoplasms/complications; Thoracic surgery, video-assisted.

INTRODUCTION

Lung cancer is the leading cause of cancer death in Brazil and around the world.[1,2] For 2014 in Brazil, 16,400 and 10,930 new cases of lung cancer were estimated to occur among men and women, respectively. These values correspond to an estimated risk of 16.79 new cases per 100,000 men and 10.75 new cases per 100,000 women. The latest global estimate was of an incidence of 1.82 million new cases of lung cancer in 2012, 1.24 million occurring in men and 583,000 occurring in women.[1] Surgical treatment is the gold standard for early-stage neoplasms. First described in the early 1990's, video-assisted thoracic surgery (VATS) lobectomy has been increasingly used in daily practice for the treatment of lung cancer. Data from a Society of Thoracic Surgeons demonstrate that 44.7% of pulmonary resections in 2010 were performed via VATS.[3]

In addition to malignant neoplasms, other lung diseases might require surgical treatment, such as those of benign neoplastic, inflammatory, and infectious etiology, which can also be treated by VATS resection. The potential documented benefits of VATS pulmonary resection include smaller incisions, lower pain intensity, a lower rate of ventilatory complications, minimal impact on the immune system, decreased release of inflammatory mediators, shorter hospital stays, etc.[3-6]

VATS should follow the sample principles as those of conventional surgery with anatomic pulmonary resection and mediastinal lymphadenectomy. VATS provides good oncologic results, and various studies have demonstrated that the number of lymph nodes resected by VATS is similar to that of those resected by conventional surgery,[7-9] without compromise of oncologic results.[10-12] Survival results for patients undergoing VATS lobectomy are similar to those for patients undergoing conventional lobectomy, and 5-year disease-free survival is up to 88% in stage IA patients.[10]

Although VATS is a well-established technique worldwide, it is not yet part of routine practice in many thoracic surgery centers in Brazil. The poor availability of materials and equipment essential for performing these procedures, both in the public and private health care systems, has delayed this technique's introduction to and consolidation in many health care facilities in the country.

METHODS

Patient selection and statistical analysis

The objective of the present study was to determine the clinical and epidemiological profile of patients who underwent anatomic pulmonary resection by VATS in the Department of Thoracic Surgery of the Santa Casa Sisters of Mercy Hospital *Pavilhão Pereira Filho*, located in the city of Porto Alegre, Brazil. All patients who underwent anatomic pulmonary resection by VATS from 2010, when the first such procedure was performed, to 2015 were

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analyzed. In the present study, the following variables were assessed: gender; clinical stage; histological type; tumor location; type of resection; and relevant postoperative data. All data were collected prospectively and analyzed.

Categorical variables were calculated as frequencies. Continuous numerical variables were calculated as means; however, medians and standard deviations were also calculated, because some parameters exhibited non-normal data distribution and a wide data range. All statistical analyses were performed with IBM SPSS Statistics, version 22 (IBM Corporation, Armonk, NY, USA).

Preoperative assessment

All patients with suspected or confirmed lung cancer who were candidates for VATS resection underwent CT scanning of the chest and upper abdomen before surgery. Positron emission tomography/CT was performed whenever available, because there is a directive regulating the use of this test in the public health care system, and private health insurance companies also have specific criteria for its use. Pulmonary function was assessed by spirometry. Staging was performed in accordance with the recommendations of major guidelines for preoperative assessment and management of lung cancer, especially those of American[13] and European[14] guidelines.

Surgical technique

Patients underwent general anesthesia with elective intubation and were placed in the lateral decubitus position. The surgical technique used was that described by a group from Duke University,[15] consisting of placement of a 10-mm trocar for placement of video optics in the 8th intercostal space, near the midaxillary line. A working port was placed in the 4th or 5th intercostal space, by means of a 4- to 6-cm incision crossing the anterior axillary line. In some cases, a third port was used for introducing auxiliary forceps and vascular staplers, being usually placed in the 8th intercostal space close to the posterior axillary line, as shown in Figure 1. Bronchial and vascular ligation was performed with a thoracoscopic linear stapler. Mediastinal lymphadenectomy was performed in all cases of neoplastic disease.

RESULTS

In the study period, a total of 117 VATS pulmonary resections were performed, of which 98 were lobectomies and 19 were anatomic segmentectomies. The study population was mostly composed of female patients (59%). The median age was 65 years (range, 15-86 years), and the mean age was 63.6 ± 13.2 years. Approximately one fourth (26.5%) of the patients had no history of smoking. Among smokers, the mean smoking history was 44.2 pack-years. The resection profile is shown in Table 1.

The median intraoperative bleeding was 100 mL (mean, 189 ± 260 mL), and bleeding less than or equal to 100 mL occurred in 69 patients (59%). Intraoperative bleeding greater than or equal to 400 mL occurred in 10 patients (8.5%), being mostly secondary to the dissection itself and the handling of small vessels, with smaller lesions being successfully managed by VATS. Arterial vascular injury requiring transfusion of blood components and conversion to thoracotomy occurred in 2 patients, but without any major hemodynamic instability.

The mean time to chest tube removal was 2.47 ± 2.18 days (median, 2 days), and the mean length of

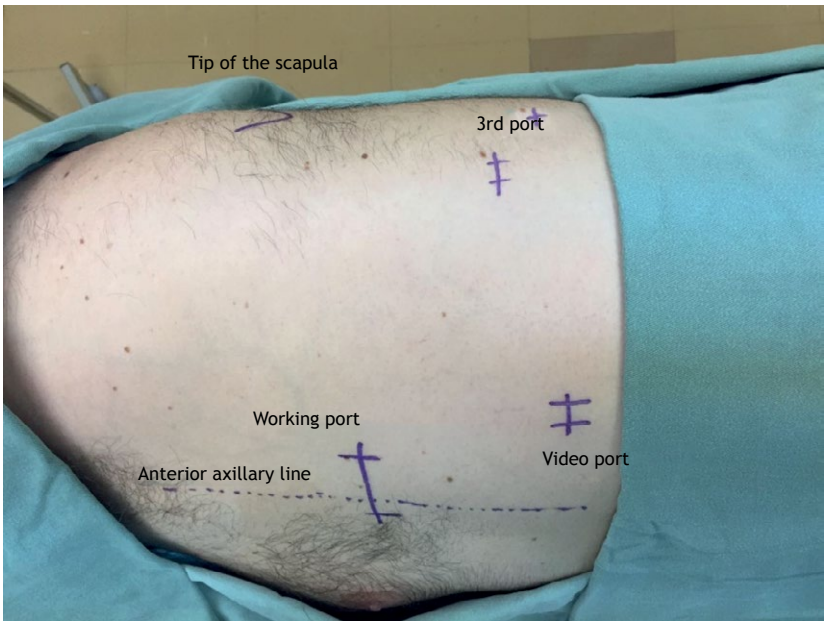

Figure 1. Anatomical representation of the surgical technique used.

ICU stay was 1.88 ± 1.88 days (median, 2 days). The mean length of hospital stay was 4.48 ± 3.54 days (median, 4 days). Some patients remained in the hospital after chest tube removal for clinical optimization. In this series, conversion to the open technique was required in 4 patients (3.4%), because of bleeding, in 2; because bronchoplasty was necessary, in 1; and because of a technical intraoperative decision, in 1. Although in these last two cases, imaging and endoscopic findings had shown that the lesions were central in location, VATS was performed, and the surgery proceeded as far as feasible. Postoperative complications included 6 cases of complicated pleural effusion and empyema, all of which were treated by pleuroscopy; 1 case of middle lobe torsion, which was treated by VATS middle lobectomy; and 1 case of prolonged air leak, in which a small thoracotomy was performed to treat the air fistula. There was 1 case of death within the first 30 days after surgery, resulting from complications from empyema and sepsis. There were no cases of intraoperative death.

Perioperative morbidity included 5 cases of empyema; 4 cases of prolonged chest tube air leak (defined as an air leak lasting more than 7 days); 4 cases of postoperative delirium; 2 cases of acute renal failure requiring dialytic therapy; 2 cases of atrial fibrillation with rapid ventricular response; 2 cases of pneumonia; and 1 case of pneumothorax and delayed subcutaneous emphysema.

As shown in Table 2, the etiology of most of the lesions treated in our study sample was malignant neoplasm (83.7% of the cases), with 87 resections for primary lung cancer, in which the predominant histological type was adenocarcinoma, and 11 cases of lung metastasis, 6 of which resulted from lesions that were colonic in origin, and with the remaining cases being of metastasis of sarcoma, melanoma, and clear cell renal carcinoma. Nineteen patients underwent anatomic pulmonary resection for the treatment of non-neoplastic diseases, the vast majority of whom had bronchiectasis, and 1 of those patients underwent the procedure for the treatment of fungal disease sequelae.

Table 1. Resection by lobectomy (n = 98) or by segmentectomy (n = 19).

Lobectomy	n (%)
Right upper	19 (19.4)
Middle	6 (6.1)
Right lower	20 (20.4)
Left upper	26 (26.5)
Left lower	26 (26.5)
Bilobectomy	1 (1.0)
Segmentectomy	
Culmen	5 (26.3)
Lingula	4 (21.1)
Basal pyramid	2 (10.5)
Upper segment	5 (26.3)
Lower segment	2 (10.5)
Bisegmentectomy	1 (5.3)

Analysis of pathological staging as per the 7th edition of the tumor-node-metastasis (TNM) classification[16] revealed that, in our sample, the vast majority of the malignant neoplastic lesions were stage I. Four patients had mediastinal lymph nodes that were affected by cancer and required adjuvant therapy. Table 3 specifies the number of lesions secondary to non-small cell tumors, according to the TNM pathological staging classification.

DISCUSSION

VATS pulmonary resection has increasingly become a reality in the treatment of patients in major centers for thoracic surgery in Brazil. In most of the 117 cases presented here, the procedures were performed in the last 2 years of the study period, after VATS was included by the Brazilian National Health Insurance Agency in the list of operations covered by health insurance plans. The growing experience in performing VATS and mastering the technique has made it possible to expand its use into the routine surgical treatment of lung diseases. Between January and September of 2015, approximately 30% of lobectomies at the *Pavilhão Pereira Filho* were performed via VATS.

One of the major concerns regarding VATS, especially in the stages of method introduction and at resident training centers, is the occurrence of bleeding and the forms of controlling it once it has occurred. We have observed that proper and careful handling of vessels and fissures makes it possible to perform these operations with low bleeding volume, even at resident training centers. In the present series, there were only 10 procedures in which intraoperative bleeding was estimated at more than 400 mL and

Table 2. Etiology (histological type) of the 117 cases included in the study.

Etiology (histological type)	n (%)
Adenocarcinoma	73 (62.4)
Epidermoid carcinoma	09 (7.7)
Large cell neuroendocrine tumor	01 (0.9)
Small cell neuroendocrine tumor	01 (0.9)
Carcinoid tumor	03 (2.6)
Metastases	11 (9.4)
Inflammatory lesions	19 (16.3)

Table 3. Stage of malignant lesions (non-small cell tumors; N = 86).

TNM classification	n (%)	Pathological stage	n (%)
T1aN0M0	21 (24.4)	IA	30 (34.9)
T1bN0M0	9 (10.5)	IB	41 (47.7)
T2aN0M0	41 (47.7)	IIA	10 (11.6)
T2bN0M0	3 (3.5)	IIB	1 (1.2)
T1bN1M0	1 (1.2)	IIIA	4 (4.7)
T2aN1M0	6 (7.0)		
T3N0M0	1 (1.2)		
T2aN2M0	4 (4.7)		

TNM: tumor-node-metastasis.

two conversions to thoracotomy for bleeding control, without that implying any technical compromise or affecting patient treatment.

The morbidity and mortality results obtained in our initial 5-year experience were found to be comparable to those reported in major international series. McKenna et al. published a large series of 1,100 cases in 2006,[6] reporting low rates of postoperative complications and demonstrating the feasibility and effectiveness of VATS lobectomy at a center experienced in this method. In their series, they found a conversion rate of 2.5% and a postoperative mortality rate of 0.8%. In 2008, Nicastri et al.[5] also reported a postoperative mortality rate of 0.7%, although their reported rate of conversion to thoracotomy was slightly higher (9.2%). In a literature review of more than 6,000 cases, Whitson et al.[11] found shorter time to chest tube removal, shorter hospital stays, and lower rates of postoperative complications in patients who underwent VATS resection than in those who underwent thoracotomy resection.

One of the objectives of VATS is to reduce the need for invasive management of patients, avoiding the use of neuraxial catheters for analgesia and the use of probes, which also reduces the need for ICU admission. The *Pavilhão Pereira Filho* has a dedicated surgical ICU. Although most of our patients did not require epidural analgesia, the routine of a 24-hour postoperative recovery period in the ICU was maintained for all patients. This explains, in part, the mean length of ICU stay of 1.88 days. In the present series, the median length of hospital stay was 4 days, with a mean of 4.48 days. In the future, with increased experience, we intend to reduce the length of patient stay in the ICU.

Although assessment of the amount of analgesia used was not one of our objectives, we found that there was a clear reduction in pain reporting by patients, which is much more evident at the first outpatient follow-up visit, when most patients return to their usual activities. Although we did not use a pain score, the continuity of the experience in the present sample allowed us to dispense with placing epidural catheters in patients, which were used in some of the first cases but were not longer used in the last half of the series, translating to an important objective datum on pain reduction.

When analyzing the group of sublobar resections (19 cases) only, we observed that 36.8% were performed for the treatment of primary neoplasms, 26.4% for the treatment of metastases, and 36.8% for the treatment of diseases with an inflammatory etiology. Although lobar resection remains the gold standard in the treatment of lung carcinoma, recent studies have demonstrated that anatomic segmentectomy with attention to adequate surgical margins and lymph node dissection may have results equivalent to those reported for lobectomy,[17] being considered a reasonable oncologic option particularly in patients with impaired pulmonary function who may not tolerate a lobectomy.

The present study lacks the power to estimate patient survival accurately, given that most resections were performed in the last 2 years. We intend to publish such data when the follow-up period is longer.

VATS pulmonary resection is being introduced in many centers in Brazil and is already part of routine practice in some. The present study sought to demonstrate that this technique can be safely performed and can provide good results, even at resident training centers. In the future, more studies will demonstrate the impact of VATS on the medium- and long-term oncologic results in the population undergoing such procedures in Brazil.

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Effects that passive cycling exercise have on muscle strength, duration of mechanical ventilation, and length of hospital stay in critically ill patients: a randomized clinical trial

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ABSTRACT

Objective: To evaluate the effects that passive cycling exercise, in combination with conventional physical therapy, have on peripheral muscle strength, duration of mechanical ventilation, and length of hospital stay in critically ill patients admitted to the ICU of a tertiary care university hospital. **Methods:** This was a randomized clinical trial involving 38 patients (≥ 18 years of age) on mechanical ventilation who were randomly divided into two groups: control (n = 16), receiving conventional physical therapy; and intervention (n = 22), receiving conventional physical therapy and engaging in passive cycling exercise five days per week. The mean age of the patients was 46.42 ± 16.25 years, and 23 were male. The outcomes studied were peripheral muscle strength, as measured by the Medical Research Council scale, duration of mechanical ventilation, and length of hospital stay. **Results:** There was a significant increase in peripheral muscle strength (baseline vs. final) in both groups (control: 40.81 ± 7.68 vs. 45.00 ± 6.89; and intervention: 38.73 ± 11.11 vs. 47.18 ± 8.75; $p < 0.001$ for both). However, the range of increase in strength was higher in the intervention group than in the control group (8.45 ± 5.20 vs. 4.18 ± 2.63; $p = 0.005$). There were no significant differences between the groups in terms of duration of mechanical ventilation or length of hospital stay. **Conclusions:** The results suggest that the performance of continuous passive mobilization on a cyclical basis helps to recover peripheral muscle strength in ICU patients.

(ClinicalTrials.gov Identifier: NCT01769846 [http://www.clinicaltrials.gov/])

Descriptors: Physical therapy modalities; Intensive care units; Early ambulation; Muscle strength.

INTRODUCTION

Currently, as a result of increasing technological advances, critically ill patients have prolonged ICU stays, which predisposes to the incidence of complications arising from immobility.[1] Prolonged immobility is harmful, with rapid reduction in muscle mass and bone mineral density, as well as impairment in other body systems; these manifestations are evident within the first week of bed rest,[2] which can contribute to functional decline and reduced quality of life.[3] Among immobility-related complications are malnutrition, increased rates of nosocomial infection,[4] changes in sleep quality,[5] and prolonged hospital stay.[6]

Development of generalized muscle weakness is a complication that affects 30% to 60% of ICU patients[6] and can persist for six months to as long as two years after ICU discharge,[7,8] consequently impacting physical functioning in such patients.[8] In addition, patients with reduced peripheral muscle strength have a longer duration of mechanical ventilation (MV).[9] However, these deleterious effects of immobility can be reversed or mitigated by physical therapy,[10,11] which contributes to decreased length of stay in the ICU and hospital.[12] Studies demonstrate that early mobilization of critically ill patients is considered a safe approach[13] that is aimed at preserving muscle mass and reducing muscle weakness after hospital discharge and that facilitates resumption of activities of daily living.[14,15] According to Hodgson et al.,[16] early mobilization is defined as the intensification and early application (within the first 2 to 5 days of critical illness) of the physical therapy that is administered to critically ill patients. However, the major reported

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barrier to performing early mobilization continues to be sedation, which, despite being necessary in some cases, limits the work of the physical therapist in the functional recovery of patients.[17,18]

In this context, passive mobilization is a strategy that the physical therapist has to prevent functional decline in critically ill patients. Although it has been widely used by professionals,[19,20] its effects in terms of the clinical recovery of patients have yet to be well established.

To date, cycle ergometers have been one of the most widely studied adjuvant tools in the treatment provided by physical therapists to ICU patients.[21-23] The use of early passive cycling exercise (< 72 h on MV) is safe and is associated with few hemodynamic changes even in more critically ill patients.[21] However, as already stated, little is known about the effects that passive mobilization (performed with a cycle ergometer or with a therapist) have on the clinical recovery of patients. Therefore, the objective of the present study was to evaluate the effects that passive cycling exercise, in combination with conventional physical therapy, have on the recovery of peripheral muscle strength, duration of MV, and length of hospital stay in ICU patients.

METHODS

This was a randomized clinical trial, with blinding of outcome assessment, conducted in the ICU of the Santa Maria University Hospital of the Federal University of Santa Maria, in the city of Santa Maria, Brazil, between January and July of 2015. The study was approved by the local research ethics committee (Protocol no. CAAE 07201712.8.0000.5346). All participants or their family members gave written informed consent before inclusion in the study.

This ICU has 16 beds, of which 10 are general intensive care beds and 6 are cardiac unit beds; it predominantly admits neurological, clinical, and surgical patients. Physical therapy is made available 12 h/day in the cardiac unit and 18 h/day in the general ICU. The physical therapist-to-patient ratio in the ICU as a whole is 1:8, whereas the nurse-to-patient ratio is 1:5 and the nursing technician-to-patient ratio is 1:2.

Our study included 49 patients (≥ 18 years of age; convenience sample) who were on MV; were maintained at a light level of sedation, as assessed by the Richmond Agitation-Sedation Scale[24] (score −2); and were hemodynamically stable. We excluded patients who were receiving palliative care, amputees, patients with leg fractures, and patients with neuromuscular disease, neurological disease, and/or ICU-acquired muscle weakness, as well as patients who were unable to use a cycle ergometer because of preexisting joint and/or musculoskeletal disorders.

The patients recruited for the study were assessed by clinical records, demographic information, clinical history, primary reason for ICU admission, and the Acute Physiology and Chronic Health Evaluation II (APACHE II) score.[25]

Patients were allocated from a computer-generated table of random numbers, and a randomization sequence was generated using Random Number Generator Pro 2.00 software (Segobit; Issaquah, WA, USA). All participants received the intervention by two physical therapists. Blinded assessments were performed by a single physical therapist, who was also responsible for the randomization.

Peripheral muscle strength in arms and legs was measured by the score on the Medical Research Council (MRC) scale,[26] before and after the implementation of the study protocol, by a single, previously trained rater. Muscle strength was initially assessed on the first day the patient was cooperative and responsive (Richmond Agitation and Sedation Scale score = −1) and then on the last day of ICU stay.

The patients who met the inclusion criteria were allocated to the intervention group (IG) or the control group (CG). The CG patients received conventional physical therapy, whereas the IG patients received conventional physical therapy and engaged in passive exercise on a leg cycle ergometer (MOTOmed letto 2; RECK-Technik GmbH & Co.KG, Betzenweiler, Germany). This device offers the possibility of performing the exercise passively, in the supine position, even if the patient is under sedation. Therefore, 20-min sessions of passive cycling exercise at a fixed rate of 20 cycles/min were performed 5 days per week, until the last day of ICU stay. In order to ensure that true passive exercise was performed, the device screen, which allows the visualization/analysis of the training session and detects active movements, was constantly monitored during the protocol.

Conventional physical and respiratory therapy were provided by the ICU physical therapists twice daily, for approximately 30 min, 7 days per week. The protocol included vibrocompression maneuvers; lung hyperinflation by the mechanical ventilator; and tracheal aspiration, when necessary; as well as passive and active-assisted motor exercises for arms and legs, depending on the clinical course of patients.

In order to ensure the clinical stability of the patients during and after the protocol, cardiovascular parameters, such as SpO_2, HR, mean arterial pressure, systolic blood pressure, and diastolic blood pressure, were continuously monitored noninvasively with a multiparameter monitor (DX 2022; Dixtal Biomédica, Manaus, Brazil).

The following parameters were used as the criteria for discontinuing the protocol: hemodynamic instability (mean arterial pressure < 60 or > 125 mmHg); SpO_2 < 88%; HR > 130 bpm or < 40 bpm; and signs of respiratory distress.

The statistical analysis was performed with the IBM SPSS Statistics software package, version 20.0 (IBM Corporation, Armonk, NY, USA). Variables were tested for normality with the Shapiro-Wilk test. Continuous variables were expressed as mean and standard deviation or as median and interquartile range, whereas

categorical variables were expressed as absolute and relative frequencies. The paired Student's t-test or the Wilcoxon test was used for intragroup comparisons between the pre- and post-implementation periods. The unpaired Student's t-test or the Mann-Whitney U test was used for intergroup comparisons. The level of statistical significance was set at $p < 0.05$.

RESULTS

In the study period, 58 patients were admitted to the adult ICU of the institution. Of those, 49 met the inclusion criteria and were randomized to the CG (n = 23) or the IG (n = 26). Subsequently, 7 and 4 patients in the CG and the IG, respectively, died. Therefore, the final sample consisted of 38 patients, of whom 16 were in the CG and 22 were in the IG (Figure 1). Table 1 shows the general characteristics of the sample. We found that the primary reason for ICU admission was respiratory-related. Duration of sedation, time to first treatment, and time to first muscle strength assessment were similar in the two groups. The median number of sessions (interquartile range) in the CG and the IG was 30.0 (26.5-53.0) and 36.0 (30.0-59.0), respectively. During the study period, there was no need to discontinue the protocol, nor were there any adverse events during or after its administration.

Table 2 presents the duration of MV, length of ICU stay, and length of hospital stay in the two groups studied. There were no significant differences between the groups in terms of length of ICU stay ($p = 0.824$), duration of MV ($p = 0.715$), or length of hospital stay ($p = 0.794$).

Figure 2 shows the MRC scale scores obtained before and after the implementation of the study protocol. There was a significant increase in peripheral muscle strength, as assessed by the MRC scale, in both groups (control: 40.81 ± 7.68 vs. 45.00 ± 6.89; and intervention: 38.73 ± 11.11 vs. 47.18 ± 8.75; $p < 0.001$ for both) after the implementation of the protocol. In the comparison of the differences shown by the groups between the pre- and post-implementation periods, the IG showed a significantly greater increase in the MRC scale scores than did the CG (8.45 ± 5.20 vs. 4.18 ± 2.63; $p = 0.005$).

DISCUSSION

The present study is the first randomized clinical trial to analyze the effects that a passive cycling exercise program, in combination with conventional physical therapy, have on peripheral muscle strength, duration of MV, and length of hospital stay in critically ill ICU patients. An increase in peripheral muscle strength, as assessed by the MRC scale, occurred in both groups (CG and IG); however, the increase in strength was greater in the IG. There were no differences between the groups in terms of length of ICU stay, duration of MV, or length of hospital stay.

Our results corroborate those of a study by Dantas et al.,[27] who also found no differences in duration of MV or length of hospital stay between a control group receiving conventional physical therapy and a group receiving early mobilization, which was based on a systematic mobility protocol but did not include leg cycling exercise.

Recently, Witcher et al.,[28] in a retrospective study conducted in a neurological ICU, demonstrated that the implementation of an early mobilization program did not change duration of MV, length of ICU stay, or length of hospital stay, a finding that is similar to that of the present study. Schweickert et al.,[14] in a

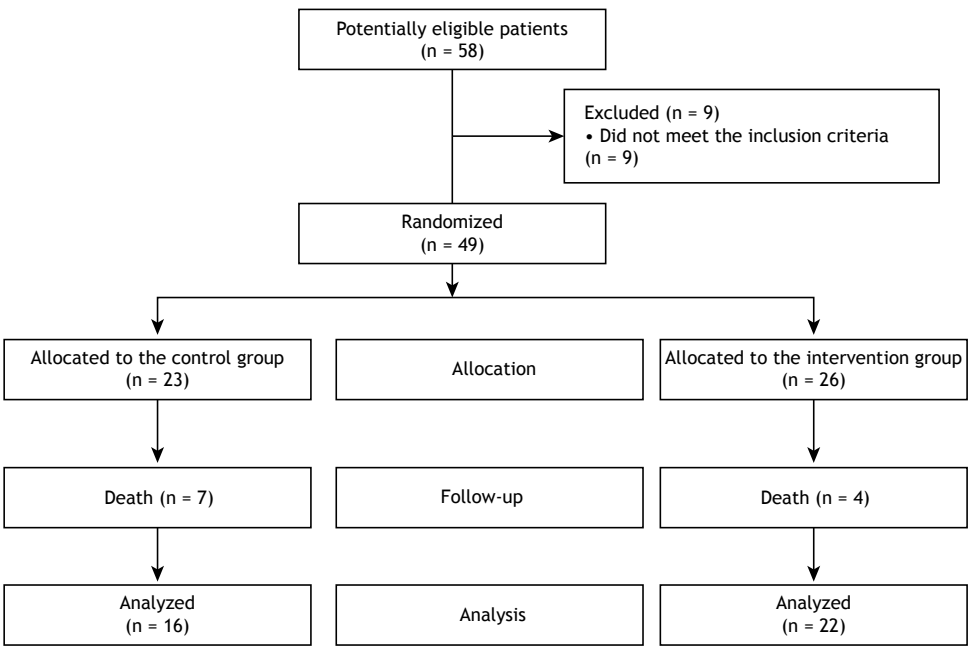

Figure 1. Flowchart of the study.

Table 1. Patient clinical and demographic characteristics.[a]

Variable	Control group (n = 16)	Intervention group (n = 22)
Age, years	45.13 ± 18.91	44.64 ± 19.23
Male gender, n (%)	7 (43)	16 (72)
Glasgow Coma Scale score	13. 33 ± 2.91	14.21± 3.62
APACHE II score	18.12 ± 6.36	17.34 ± 6.72
Duration of sedation, days	4 (3-7)	4 (2-7)
Primary reason for ICU admission, n (%)*		
Neurological	3 (18.75)	2 (9.09)
Respiratory	5 (31.25)	6 (27.27)
Abdominal	3 (18.75)	3 (13.64)
Cardiac	0 (0.00)	4 (18.18)
Other	5 (31.25)	7 (31.82)
Time to first session, days	2 (1-3)	3 (2-5)
Time to first assessment by the MRC scale, days	2.5 (2.5-2.5)	2.5 (2.0-2.5)
Duration of the protocol, days	15 (12-30)	12 (7-25)

APACHE II: Acute Physiology and Chronic Health Evaluation II; and MRC: Medical Research Council (scale). [a]Values expressed as mean ± SD or as median (interquartile range), except where otherwise indicated. *All comparisons were performed by using the Student's t-test, except where otherwise indicated (Mann-Whitney U test).

Table 2. Length of hospital stay, length of ICU stay, and duration of mechanical ventilation in the control and intervention groups.[a]

Variable	Control group (n = 16)	Intervention group (n = 22)	p
Length of hospital stay, days	46 (25-75)	38 (17-73)	0.794*
Duration of mechanical ventilation, days	15 (10-44)	18 (8.5-37)	0.824*
Length of ICU stay, days	18 (12-35)	22 (10-28)	0.715**

[a]Values expressed as median (interquartile range). *Student's t-test. **Mann-Whitney U test.

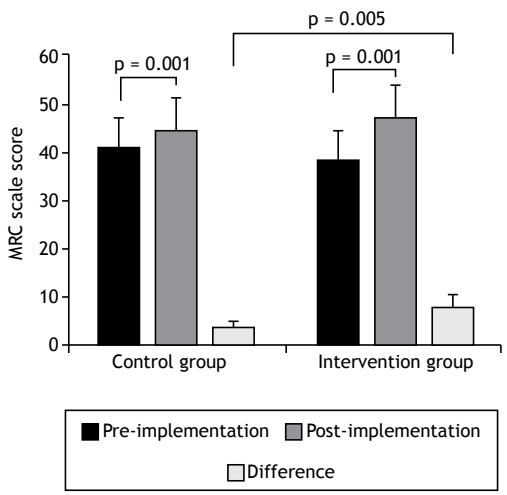

Figure 2. Peripheral muscle strength, as measured by the Medical Research Council (MRC) scale, before and after the implementation of the study protocol. Student's t-test.

pioneering, prospective randomized controlled trial, submitted 49 ICU patients on MV to an early active and passive mobilization program for 28 days. Those authors demonstrated that, at hospital discharge, the intervention group had achieved earlier functional independence, as well as having required 2.4 fewer days of ventilatory support, than had the control group, an outcome that did not occur in our study. However, it is important to emphasize that, in the study by Schweickert et al.,[14] the control group did not receive any physical therapy intervention, whereas, in our study, the CG engaged in respiratory and motor exercises, and passive cycling exercise was the only difference between the CG and the IG.

A recent systematic review[29] concluded that there is evidence that ICU early mobilization programs are safe and improve the clinical outcomes of ICU patients. Our findings are consistent with those of this review, in which no significant adverse effects were found during physical therapy in the critically ill patients, and an increase in muscle strength was found in both groups.

Regarding our finding of a significantly greater increase in peripheral muscle strength in the IG than in the CG, it is important to mention a pioneering randomized study by Burtin et al.,[23] who also found increased quadriceps strength after active and passive mobilization combined with early cycling exercise. However, that study differs from ours in the following aspects: eligibility criteria (those authors included patients who had been on MV for more than 7 days, whereas, in our study, we included patients with a mean duration of MV of 2.5 days); and isometric strength assessment of a single muscle group (quadriceps) using a dynamometer.

Patients exposed to a period of immobilization in the ICU are predisposed to morphological muscle changes, which can lead to reduced muscle strength

and hypotrophy.[30] Koukourikos et al.[31] mentioned that muscle atrophy is one the most common and most important problems observed in critically ill patients, its prevention being the major focus in the ICU. The risk factors for this outcome include corticosteroid use, immobility, sepsis, and inadequate glycemic control. In this sense, those authors point to early mobilization as one of the strategies adopted to reduce the incidence of muscle weakness in the ICU. Increased peripheral muscle strength, which was demonstrated in our CG at ICU discharge, can be explained by the effectiveness of conventional physical therapy. One possible explanation for this finding is that, in our study, all patients received physical therapy during their ICU stay, which does not occur in centers in the United States.[12] The only difference between the groups in our study was the performance of passive cycling exercise. Regarding our finding of a significantly greater muscle strength increase in the IG, which was demonstrated by higher scores on the MRC scale, Llano-Diez et al.[32] and Renaud et al.[33] state that passive exercise has a positive effect on the ability to generate muscle force, because it mitigates the deleterious effects of immobility by maintaining the architecture and intrinsic contractility properties of the muscle.

There are some limitations to our study that should be mentioned. First, our assessment was restricted to peripheral muscle strength in the ICU. Therefore, we cannot state whether the difference in muscle strength observed between our two groups would remain at hospital discharge. Second, although the cycle ergometer was used for passive exercise, it was impossible to ensure the total absence of muscle contraction by the patient (at the end of sedation) during the cycle ergometer protocol. In fact, in approximately 20% of the sessions in the IG, the visual resource available on the cycle ergometer detected active contraction. In these cases, the physical therapist immediately instructed the patients neither to contract their muscles nor to perform any effort with their legs. Therefore, we believe that such contractions were small in magnitude and may have had minimal influence on our results. We also emphasize that, although this active activity was caught by the equipment, most of the session occurred passively. Finally, we did not use objective measures of muscle strength, such as handgrip strength testing, in our assessment. However, it is important to emphasize that previous studies have demonstrated a good correlation between objective measures of muscle strength and manual muscle testing.[34]

In conclusion, early mobilization in the ICU, by implementing a passive cycling exercise protocol in patients on MV, can significantly increase peripheral muscle strength in such patients; however, it does not change duration of MV or length of hospital stay. Future studies of larger populations are needed to arrive at conclusions that are more definitive about this issue.

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Diffuse cystic lung diseases: differential diagnosis

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ABSTRACT

Diffuse cystic lung diseases are characterized by cysts in more than one lung lobe, the cysts originating from various mechanisms, including the expansion of the distal airspaces due to airway obstruction, necrosis of the airway walls, and parenchymal destruction. The progression of these diseases is variable. One essential tool in the evaluation of these diseases is HRCT, because it improves the characterization of pulmonary cysts (including their distribution, size, and length) and the evaluation of the regularity of the cyst wall, as well as the identification of associated pulmonary and extrapulmonary lesions. When combined with clinical and laboratory findings, HRCT is often sufficient for the etiological definition of diffuse lung cysts, avoiding the need for lung biopsy. The differential diagnoses of diffuse cystic lung diseases are myriad, including neoplastic, inflammatory, and infectious etiologies. Pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, lymphocytic interstitial pneumonia, and follicular bronchiolitis are the most common diseases that produce this CT pattern. However, new diseases have been included as potential determinants of this pattern.

Keywords: Cysts; Diagnosis, differential; Lung diseases, interstitial; Tomography, X-ray computed.

INTRODUCTION

A cyst is defined as a round circumscribed area that is surrounded by an epithelial or fibrous wall of variable thickness. On chest CT, a cyst is seen as an area with a low attenuation coefficient in the lung parenchyma, having a well-defined interface with the adjacent normal lung and usually containing air, although it can occasionally have a liquid or solid content.[1] A lung cyst can originate from various mechanisms, such as airway obstruction with distal airspace dilatation (check-valve mechanism), necrosis of the airway walls, and lung parenchymal destruction by proteases.[2] Diffuse cystic lung diseases are characterized by cysts in more than one lung lobe, the cysts usually being bilateral.

HRCT has broadened the understanding of diffuse cystic lung diseases, because it enables improved identification of cyst characteristics (including their distribution) and associated lesions (including assessment of the presence of extrapulmonary changes), narrowing the differential diagnosis and often avoiding the need for diagnostic confirmation by lung biopsy.[3]

The differential diagnoses of diffuse cystic lung diseases are myriad, including neoplastic, inflammatory, and infectious diseases, which have variable prognoses. Recently, other potential etiologies of this CT pattern have been proposed including constrictive bronchiolitis and paracoccidioidomycosis.[4,5]

The objective of the present pictorial essay was to describe the main diseases that can lead to the formation of diffuse cysts in the lung parenchyma, with an emphasis on CT findings (Table 1).

PULMONARY LANGERHANS CELL HISTIOCYTOSIS

Pulmonary Langerhans cell histiocytosis (PLCH) is characterized by the infiltration of Langerhans cells mainly in the lungs and less commonly in other organs, leading to the activation of an inflammatory process with potential dysfunction in the affected sites. It remains controversial whether PLCH is a polyclonal neoplastic or inflammatory disease. The mean age of patients ranges from 20 to 40 years, and, in more than 90% of cases, the disease is associated with a current or previous smoking history, including passive smoking. The lung is the most commonly involved site, and the most common symptom is progressive dyspnea on exertion; however, patients can be asymptomatic. There can be fever, sweating, weight loss, and, less commonly, extrapulmonary manifestations, such as diabetes insipidus, and bone and skin lesions.[6]

The initial HRCT findings of PLCH are centrilobular or peribronchiolar nodules, which usually measure 1-10 mm in diameter and are irregularly marginated. As the disease progresses, the nodules undergo cavitation and produce cystic lesions. A combination of nodules and cysts is often

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Table 1. Major etiologies of diffuse lung cysts.

Disease	Lung cyst distribution and characteristics	Other possible radiological findings
Pulmonary Langerhans cell histiocytosis	- Cysts are irregular and thick- or thin-walled, later becoming bizarre in shape, and can coalesce - Vary in number and size - Predominate in the upper lung zones, sparing the region of the costophrenic sinuses	- Irregularly marginated centrilobular or peribronchiolar nodules measuring 1-10 mm in diameter - Enlargement of the pulmonary trunk and of the right and left pulmonary arteries
Lymphangioleiomyomatosis	- Cysts are regular and thin-walled and usually measure 2-10 mm in diameter - Are diffusely distributed - Vary in number	- Small regular centrilobular nodules - Areas of ground-glass opacity - Pleural effusion - Ascites - Renal angiomyolipoma - Abdominal and pelvic lymphangioleiomyomas
Lymphocytic interstitial pneumonia	- Cysts vary in shape and are thin-walled - Measure up to 30 mm in diameter - Are diffusely distributed, predominating in the lower lobes and along the peribronchovascular bundle	- Ground-glass opacities and focal consolidations - Peribronchovascular bundle thickening - Poorly defined centrilobular nodules - Interlobular septal thickening - Reticular opacities - Mediastinal and hilar lymph node enlargement
Follicular bronchiolitis	- Cysts vary in shape and are thin-walled - Measure up to 30 mm in diameter - Are diffusely distributed, predominating in the lower lobes and along the peribronchovascular bundle	- Centrilobular nodules or ground-glass opacities
Birt-Hogg-Dubé syndrome	- Cysts are multiple and irregular - Predominate in the lower medial and subpleural regions of the lung	
Light-chain deposition disease	- Cysts are diffuse and thin-walled, without a predominant distribution - Measure up to 20 mm in diameter.	- Nodules - Mediastinal lymph node enlargement
Amyloidosis	- Cysts are thin-walled - Vary in size - Predominate peripherally	- Nodules or masses - Interlobular septal thickening - Ground-glass opacities - Lymph node enlargement
Cystic pulmonary metastatic disease	- Cysts are diffuse - Are thick- or thin-walled	- Nodules or masses
Paracoccidioidomycosis	- Cysts are diffuse and thin-walled, without a predominant distribution - Are few in number	- Reticular and linear opacities, consolidations, areas of “reversed halo” sign, bronchiectasis, and cavitated lesions - Paracicatricial emphysema
Pneumocystosis	- Cysts vary in size, shape, and wall thickness - Predominate in the upper lobes	- Extensive areas of ground-glass opacity, predominating in the central and perihilar regions - Septal thickening
Infection with *Staphylococcus aureus*	- Pneumatoceles	
Constrictive bronchiolitis	- Cysts are thin-walled - Are few in number and randomly distributed	- Areas of mosaic attenuation - Bronchiectasis and bronchiolectasis - Bronchial wall thickening
Hypersensitivity pneumonitis	- Cysts are sparse, few in number, and randomly distributed	- Centrilobular ground-glass micronodules - Areas of mosaic attenuation - Usual interstitial pneumonia or nonspecific interstitial pneumonia pattern
Desquamative interstitial pneumonia	- Cysts are regular and measure up to 20 mm in diameter - Predominate in the lower lung zones	- Diffuse ground-glass opacities predominating in the lower lung zones - Mild distortion of the lung architecture

observed (Figure 1A), which is sufficient for diagnostic confirmation. In later stages of the disease, cysts predominate, vary in number and size, are irregular and often bizarre-shaped, and can coalesce (Figure 1B). Initially, the walls of the cysts are thick, and, later, they become thinner. Cystic lesions predominate in the upper lobes, sparing the region of the costophrenic sinuses (Figure 1C). Pneumothorax can occur in up to 15% of cases (Figure 1D).[3,6] It is speculated that the cysts are formed by airway dilatation due to bronchiolar wall inflammation, nodule cavitation, or air space enlargement secondary to traction from fibrosing lesions. CT changes secondary to pulmonary hypertension, such as enlargement of the pulmonary trunk and of the right and left pulmonary arteries, can also be identified.[3]

The diagnosis of PLCH is confirmed when young individuals who are smokers present with a combination of nodules and cysts in the upper lung zones, sparing the region of the costophrenic sinuses. In cases of cysts without nodules, the diagnosis can be confirmed by bronchoscopy, despite its low sensitivity, when more than 5% of CD1a-positive cells are identified in the bronchoalveolar lavage fluid, or by transbronchial biopsy. In this context, surgical lung biopsy provides a higher diagnostic yield. Biopsy of skin or bone lesions can also establish the diagnosis of PLCH.[6]

LYMPHANGIOLEIOMYOMATOSIS

Lymphangioleiomyomatosis (LAM) is a low-grade neoplasm that most commonly affects women of reproductive age; LAM is characterized by a proliferation of atypical smooth muscle cells (LAM cells) around the airways, blood vessels, and lymphatic vessels; LAM occurs as an isolated disorder or in association with tuberous sclerosis complex, being caused by mutations in the *tuberous sclerosis complex 1* or *2* genes.[7,8] The most common respiratory manifestations of LAM include progressive dyspnea on exertion and recurrent pneumothorax (in up to 70% of cases) and, less commonly, cough, hemoptysis, and chylothorax.[8] Cysts in LAM are usually regular and thin-walled; typically measure 2-10 mm in diameter, are diffusely distributed, and vary in number; and are surrounded by normal lung parenchyma (Figures 2A and 2B).[9] Cyst formation in LAM is hypothesized to result from obstruction of terminal bronchioles by LAM cells with distal airspace dilatation and/or from degradation of the lung parenchyma due to an imbalance between proteases and protease inhibitors.[3,9] On CT, other changes can be found, such as pneumothorax, renal angiomyolipoma, chylothorax, chylous ascites, and abdominal and pelvic lymphangioleiomyomas (Figures 2C and 2D). In addition, there can be regular centrilobular nodules, usually due to multifocal micronodular pneumocyte hyperplasia and, less commonly, due to areas of ground-glass opacity secondary to alveolar hemorrhage or lymphatic congestion.[3,9]

The diagnosis of LAM can be confirmed by an HRCT finding of cysts characteristic of LAM, in association with the presence of at least one of the following clinical manifestations: tuberous sclerosis complex;

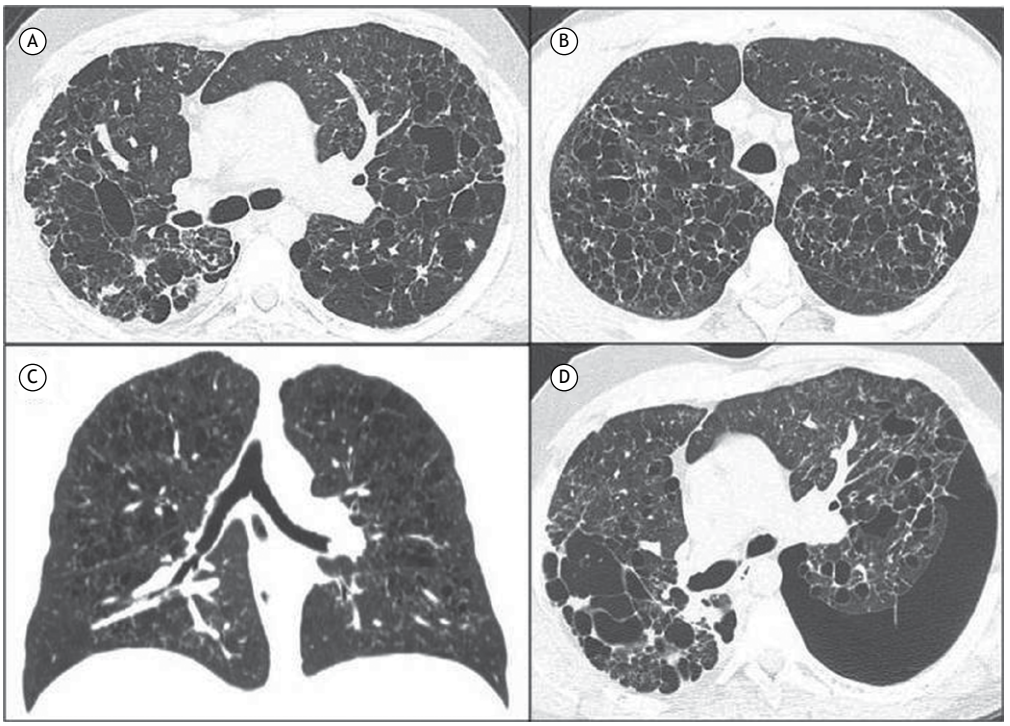

Figure 1. CT scans of patients with pulmonary Langerhans cell histiocytosis. In A, irregular cysts and irregularly marginated centrilobular nodules in the upper lobes (axial reconstruction). In B, irregular thin-walled cysts (axial reconstruction). In C, irregular cysts predominating in the upper lobes and sparing the region of the costophrenic sinuses (coronal reconstruction). In D, irregular cysts, some centrilobular nodules, and a left pneumothorax (axial reconstruction).

renal angiomyolipoma; lymphangioleiomyoma; chylothorax; or chylous ascites. However, if one of the characteristics described above is missing, the diagnosis can be established by the identification of an increase in serum VEGF-D levels, especially if these levels are above 800 pg/mL. If quantification of serum VEGF-D levels is not available or if serum VEGF-D levels are not increased, it is recommended that lung biopsy (preferably surgical) be performed.[7]

LYMPHOCYTIC INTERSTITIAL PNEUMONIA

Lymphocytic interstitial pneumonia (LIP) is a rare, benign, lymphoproliferative disease characterized histologically by a lymphocytic and plasmacytic infiltrate that affects alveoli and interlobular septa and can possibly form nodular lymphoid aggregates with reactive germinal centers.[10] The incidence of LIP is higher in women, usually between the fourth and sixth decades of life. LIP is usually associated with other systemic diseases, especially connective tissue diseases, such as Sjögren's syndrome and systemic lupus erythematosus; HIV infection; Epstein-Barr virus infection; and acquired immunodeficiencies, such as common variable immunodeficiency. The idiopathic form of LIP is rare. Patients can be asymptomatic, and the major clinical manifestations of LIP include dyspnea, cough, fatigue, and chest pain.[10,11] The most commonly observed pattern on pulmonary function testing is a restrictive pattern.[3]

Cysts are common in LIP, being present in up to 2 thirds of patients, and it is speculated that they result from ischemia due to vascular obstruction, postobstructive alveolar dilatation, or compression of bronchioles by lymphoid tissue, leading to a check-valve mechanism.[2] The cysts usually measure up to 30 mm in diameter, are thin-walled, vary in shape, and are diffusely distributed, predominating in the lower lobes and along the peribronchovascular bundle (Figure 3). Other CT changes that aid in the diagnosis of LIP include ground-glass opacities and focal consolidations, peribronchovascular bundle thickening, and poorly defined centrilobular nodules. Less commonly, interlobular septal thickening, reticular opacities, pleural thickening due to subpleural nodules, and mediastinal/hilar lymph node enlargement can be found.[2] In the absence of a clearly diagnosed systemic disease, it is

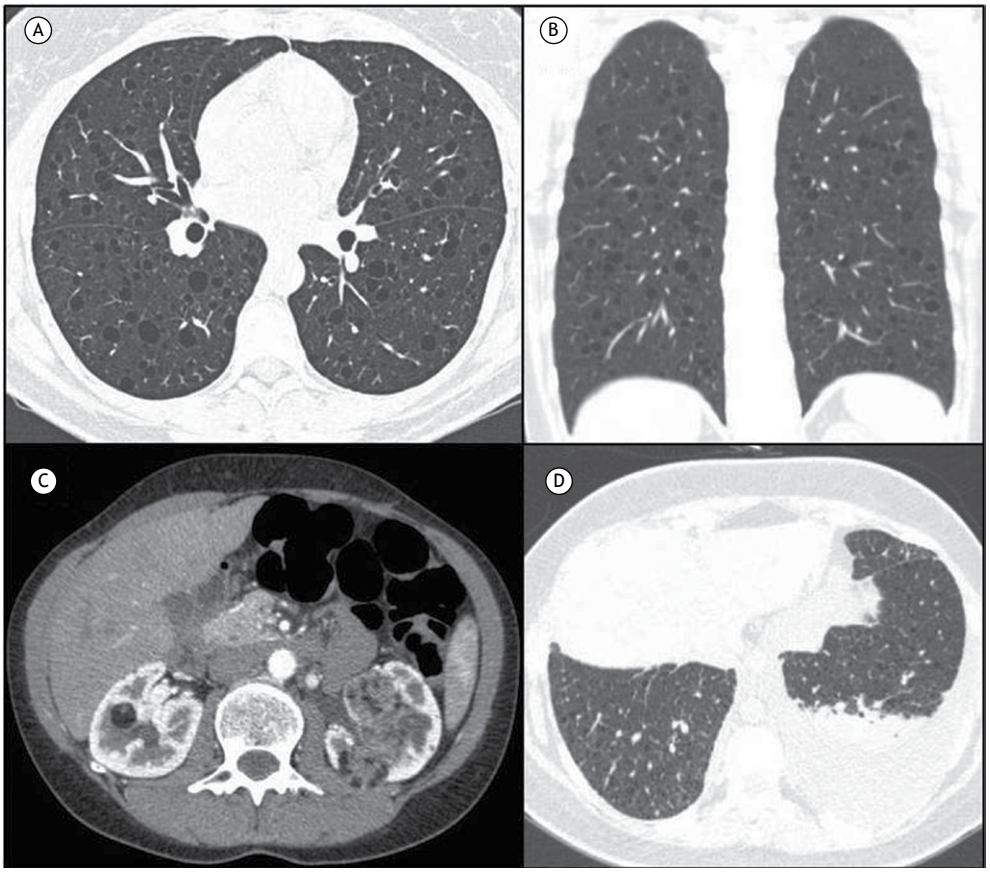

Figure 2. In A, axial reconstruction and, in B, coronal reconstruction of chest CT scans of a female patient with lymphangioleiomyomatosis, showing diffuse lung cysts with regular walls. In C, axial reconstruction of an abdominal CT scan of a female patient with lymphangioleiomyomatosis, showing bilateral, heterogeneous renal masses, consistent with angiomyolipoma. In D, axial reconstruction of a CT scan of a female patient with lymphangioleiomyomatosis, showing diffuse lung cysts and a left chylothorax.

recommended that the diagnosis of LIP be confirmed histologically.[11]

FOLLICULAR BRONCHIOLITIS

Follicular bronchiolitis is also part of the spectrum of lymphoproliferative disorders with lung involvement—the main finding that differentiates it from LIP is bronchiolocentric lymphocytic infiltration, which does not extend into other lung interstitial compartments; in addition, an obstructive pattern with air trapping is the most common pattern in follicular bronchiolitis.[11] The major mechanism responsible for cyst formation involves extrinsic compression of the bronchus-associated lymphoid tissue, causing a check-valve phenomenon, but it may also be related to bronchiolar ischemia due to vascular obstruction. The cysts are similar to those found in LIP, being predominantly peribronchovascular in distribution and thin-walled (Figure 4). There can be centrilobular nodules or ground-glass opacities.[2]

BIRT-HOGG-DUBÉ SYNDROME

Birt-Hogg-Dubé syndrome (BHDS) is a rare autosomal dominant disorder characterized by the development of follicular tumors, renal tumors, and lung cysts. BHDS is caused by heterozygous mutations in the gene encoding folliculin (*FLCN*) and located on chromosome 17, which encodes a tumor suppressor protein. Although treatment of renal tumors of low malignant potential is the primary focus of longitudinal care, pulmonary manifestations, especially cyst formation and spontaneous pneumothorax, are common.

Lung cysts develop in adults around the age of 30-40 years; however, lung cysts have been described in patients between 20 and 85 years of age and occur with nearly complete penetrance in BHDS.[12,13] Toro et al. identified that 89% of 198 patients with BHDS had lung cysts.[12] Lung cysts in BHDS are multiple, irregular, and thin-walled; predominate in lower medial and subpleural regions of the lung; and are often mislabeled as bullae (Figure 5). A family history of pneumothorax is present in 35% of cases.[12,13]

The diagnosis of BHDS should be suspected in young patients presenting with spontaneous pneumothorax, especially those with a personal or family history of pneumothorax, skin lesions, or renal tumors. Menko et al.[14] described criteria for the diagnosis of BHDS. These criteria are divided into major and minor criteria. The major criteria include: (1) at least five fibrofolliculomas or trichodiscomas, at least one of which being histologically confirmed, of adult onset; and (2) pathogenic *FLCN* germline mutation. The minor criteria include: (1) multiple bilateral lung cysts, with no other apparent cause, with or without spontaneous pneumothorax; (2) early-onset (< 50 years) renal cancer, multifocal or bilateral renal cancer, or chromophobe renal cell carcinoma (mixed variant) and oncocytic cell histology; and (3) a first-degree relative with BHDS. The diagnosis of BHDS requires the presence of one major criterion or two minor criteria.

LIGHT-CHAIN DEPOSITION DISEASE

Non-amyloid light-chain deposition disease (LCDD) is characterized by monoclonal protein deposition in several tissues and organs. Unlike in amyloidosis, these deposits do not stain with Congo red and are seen electron microscopically as amorphous nodular deposits. Renal involvement, determined by proteinuria and renal failure, is the most common manifestation, followed by cardiac and hepatic involvement. Of all cases of LCDD, 75% occur in association with multiple myeloma or macroglobulinemia.

Light chains are secreted by plasmocytes and are deposited in the alveolar walls, small airways, and vessels. The most common CT findings include nodules, lymph node enlargement, and diffuse thin-walled cysts measuring up to 2 cm in diameter (Figure 6). Cysts are

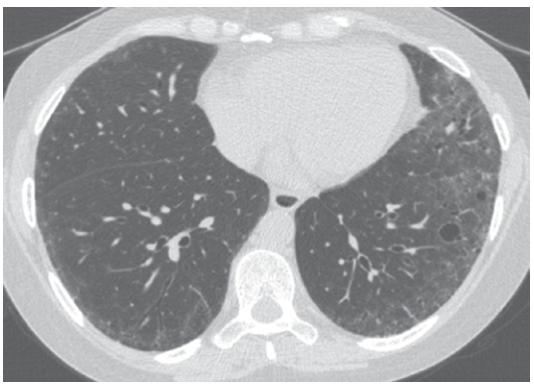

Figure 3. Axial reconstruction of a chest CT scan demonstrating lymphocytic interstitial pneumonia in a female patient with Sjögren's syndrome. Note the areas of ground-glass opacity, the reticular pattern, and the cysts predominating in the lower lung fields.

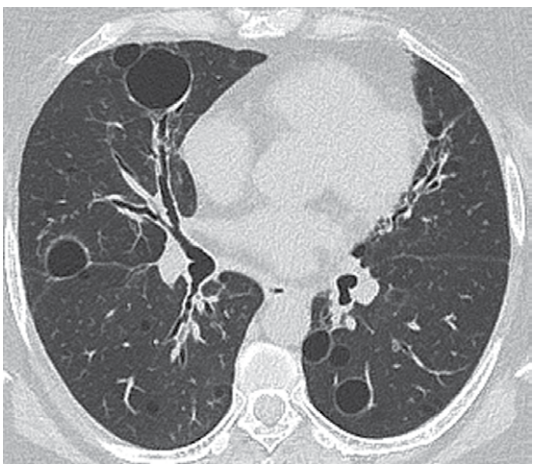

Figure 4. Axial reconstruction of a CT scan of a female patient with follicular bronchiolitis. Note the thin-walled cysts of various diameters throughout the lung parenchyma, especially along the peribronchovascular bundle.

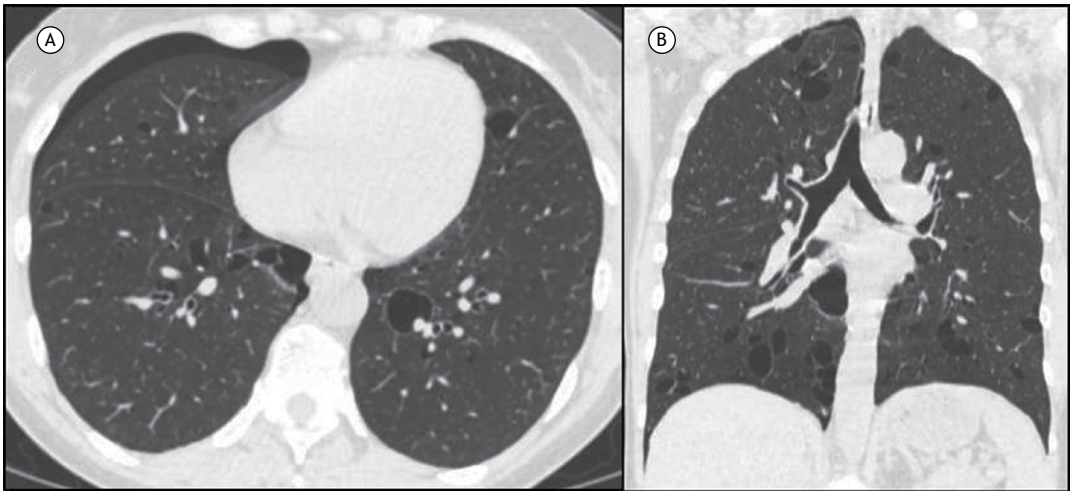

Figure 5. In A, axial reconstruction of a CT scan demonstrating thin-walled lung cysts and a right pneumothorax. In B, coronal reconstruction of a CT scan showing the distribution of the cysts in the lower lobes, a predominantly medial distribution. The patient in question was a 49-year-old female, had sudden dyspnea, and was diagnosed with Birt-Hogg-Dubé syndrome. The diagnosis was confirmed by the presence of characteristic lung cysts and a spontaneous pneumothorax and by a history of a first-degree relative with the disease.

believed to form as a result of small airway dilatation due to parietal deposits of protein.[15]

AMYLOIDOSIS

Amyloidosis is due to deposition of soluble plasma proteins within the extracellular space in an abnormal insoluble fibrillar form. The clinical manifestations and prognosis of amyloid deposits depend on their etiology and anatomical distribution. Amyloidosis is extremely heterogeneous and can be benign or potentially fatal, being classified as primary (i.e., associated with multiple myeloma or macroglobulinemia) or secondary (i.e., associated with rheumatoid arthritis, tuberculosis, Crohn's disease, cystic fibrosis, or Mediterranean fever).

CT findings of pulmonary amyloidosis include nodules, interlobular septal thickening, ground-glass opacities, and lymph node enlargement. Lung cysts are rare and are most often described with localized amyloidosis in association with Sjögren's syndrome. Proposed mechanisms of cyst formation include narrowing of the airway due to inflammatory cells, leading to a check-valve mechanism, and disruption of fragile alveolar walls due to amyloid deposition or due to ischemia from vascular infiltration by amyloid. The cysts are thin-walled, are predominantly peripheral, and are often accompanied by nodules or masses (Figure 7). The diagnosis of amyloidosis is based on histological confirmation through Congo red staining, which produces a greenish birefringence under cross-polarized light.[16,17]

CYSTIC PULMONARY METASTATIC DISEASE

Cystic pulmonary metastases occur most often in tumors of epithelial origin. The frequency of cavitation in metastatic nodules detected on X-ray is approximately 4%.[18] Squamous cell carcinomas, especially of the head and neck (Figure 8), are the ones that most commonly lead to cavitated pulmonary metastases on X-ray (69% of cases).[18,19] However, cavitation in metastatic adenocarcinomas is also often found.[18-20] Metastatic sarcomas and benign metastatic leiomyomas can also cause cavitation, and pneumothorax can be a complication. There can be nodules and masses. It should be borne in mind that chemotherapy can induce cavitation. The mechanism of cavitation is believed to be tumor necrosis or distal airspace dilatation secondary to bronchial infiltration by the tumor. Cavitated nodules with a thick wall are the most common, although cysts can be found especially in metastases from sarcomas and adenocarcinomas, as well as in benign metastatic leiomyoma.[20]

INFECTIONS

Paracoccidioidomycosis

Paracoccidioidomycosis, which is caused by the dimorphic fungus *Paracoccidioides brasiliensis*, is the most common systemic mycosis in Latin America. It predominates in males and in rural workers. Paracoccidioidomycosis is acquired by inhalation of infectious fungal particles that, upon reaching the lungs, cause the primary infection. Mucocutaneous lesions and lymph node enlargement are also common findings, and other less commonly affected organs include the kidneys, liver, bones, adrenal glands, central nervous system, and airways, with the formation of epithelioid granulomas, abscesses, and necrosis.[21]

Several radiological patterns have been described, including reticular opacities, consolidations, areas of "reversed halo" sign, bronchiectasis, pulmonary cavitations, and paracicatricial emphysema.[22] In a CT review of 50 cases,[4] lung cysts were found in 10%

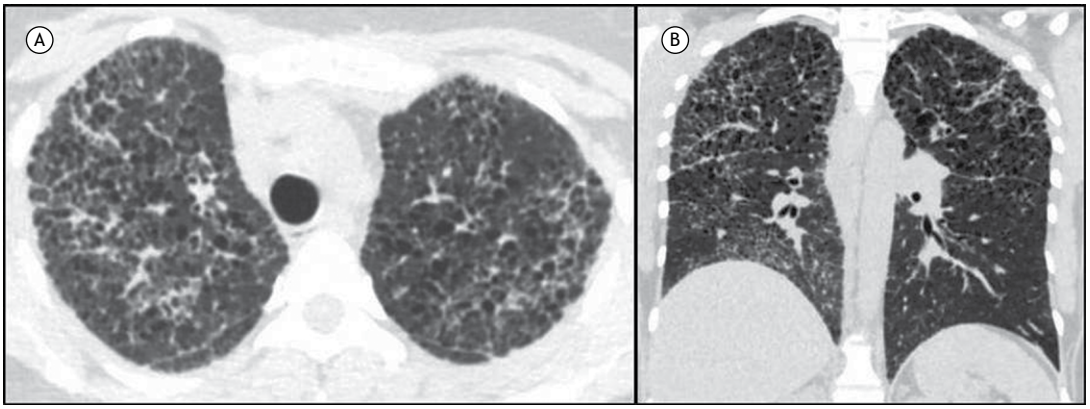

Figure 6. Chest CT scans. In A, axial reconstruction demonstrating several thin-walled, cystic structures associated with interlobular septal thickening and pulmonary micronodules. In B, coronal reconstruction showing the cranial distribution of the lung cysts. The patient in question was a 38-year-old female and was diagnosed with multiple myeloma, renal failure, and lung involvement associated with light-chain deposition disease.

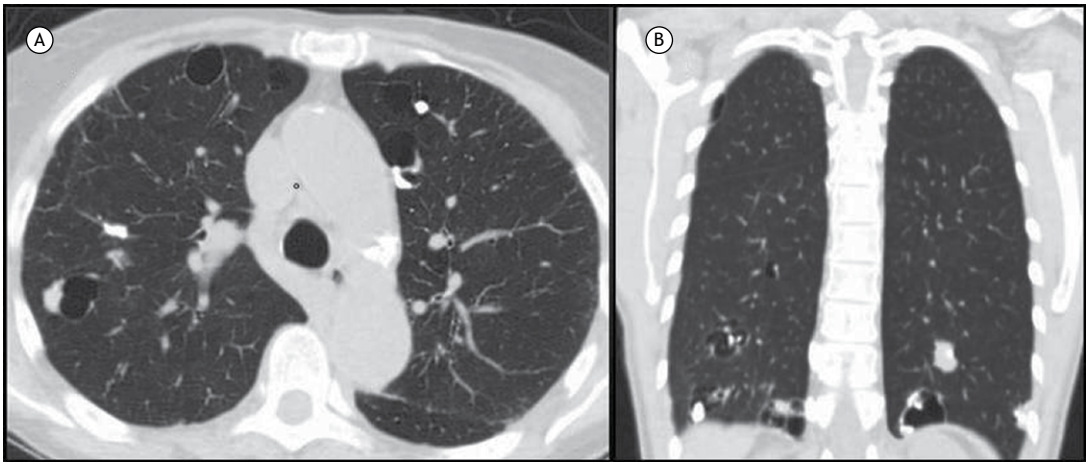

Figure 7. In A, axial reconstruction of a CT scan demonstrating several thin-walled, cystic structures associated with adjacent nodules, some of which were calcified. In B, coronal reconstruction of a CT scan showing randomly distributed lung cysts and associated nodules. The patient in question was a 56-year-old female and was diagnosed with Sjögren's syndrome and amyloidosis-related lung involvement.

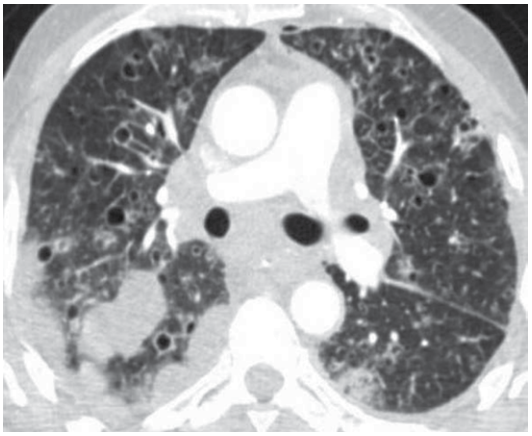

Figure 8. Axial reconstruction of a CT scan of a 66-year-old male patient with laryngeal squamous neoplasia. The scan demonstrates several cavitated nodules with a thick wall and cysts associated with loculated pleural effusion, also etiologically secondary to neoplasia.

of cases, and, in most cases, the cysts were diffuse and thin-walled, showing no preferential distribution, and few in number. Postulated mechanisms of cyst formation include bronchial obstruction caused by centrilobular fibrosis, peribronchial granuloma formation leading to airway dilatation or central necrosis and lesion elastic recoil.[4]

Pneumocystosis

Pneumocystosis, which is caused by the fungus *Pneumocystis jiroveci*, occurs in immunocompromised patients, such as HIV-infected patients with CD4 lymphocyte counts below 200 cells/mm^3, bone marrow transplant recipients, and patients on immunosuppressants. Symptoms, such as nonproductive cough, low fever, and dyspnea, are insidious, and spontaneous pneumothorax can occur—if left untreated, patients can progress to respiratory failure and death. Lymphopenia and high serum levels of lactate dehydrogenase aid in the diagnosis.[23]

CT findings include extensive areas of ground-glass opacity, preferentially located in the central and perihilar regions; septal thickening; and, possibly, pleural effusion and lymph node enlargement. Intralobular septal thickening associated with ground-glass opacities can result in a "crazy-paving" pattern. Cysts are relatively common, especially in HIV-infected patients, varying in size, shape, and wall thickness and tending to have a predilection for the upper lobes (Figure 9).[24,25] Cyst rupture can cause pneumothorax and pneumomediastinum.[24]

Infection with Staphylococcus aureus

Staphylococcal pneumonias can lead to the formation of pneumatoceles, which consist of gaseous airspaces resulting from airway dilatation due to a check-valve mechanism and occurring secondary to inflammation and parenchymal necrosis.[1] Pneumatoceles are most common in patients under one year of age and in intravenous drug users, and lesions can resolve with treatment of the infection.[1,26]

CONSTRICTIVE BRONCHIOLITIS

Constrictive bronchiolitis consists of bronchiolar narrowing due to fibrosis. Its most common etiologies are viral infections; autoimmune diseases, such as rheumatoid arthritis; and graft-vs.-host disease after solid organ or bone marrow transplant. The most common symptoms of constrictive bronchiolitis are progressive dyspnea on exertion and dry cough, and, functionally, it is characterized by an obstructive pattern and air trapping.[27]

On HRCT, the most common changes of constrictive bronchiolitis include areas of mosaic attenuation, bronchiolectasis, bronchiectasis, and bronchial wall thickening. Cysts are rare, few in number, thin-walled, and randomly distributed. A check-valve mechanism due to airway obstruction, with air trapping and distal airspace dilatation, has been suggested as a factor in cyst formation in this condition.[5]

HYPERSENSITIVITY PNEUMONITIS

Hypersensitivity pneumonitis (HP) is an interstitial disease with variable clinical presentation, characterized by inflammation of the lung parenchyma secondary to inhalation of specific organic antigens, such as fungus and birds derivatives, or chemical substances, such as isocyanate. Progressive dyspnea and dry cough are the most common symptoms. Histologically, the subacute and chronic forms are characterized mainly by bronchiolocentric interstitial inflammation and poorly formed granulomas; in addition, there can be fibrosing forms, including the usual interstitial pneumonia pattern and nonspecific interstitial pneumonia.[28]

An HRCT finding of cysts in HP is unusual, the cysts occurring mainly in the subacute and chronic forms and being sparse, few in number, and randomly distributed (Figure 10).[29] The presence of cysts in association with classic CT findings of HP, such as centrilobular ground-glass nodules and areas of mosaic attenuation, aids in the diagnosis.[25,28] It is speculated that airway obstruction, with air trapping and distal airspace dilatation, is responsible for cyst formation in HP.

DESQUAMATIVE INTERSTITIAL PNEUMONIA

Desquamative interstitial pneumonia (DIP) is characterized by extensive intra-alveolar accumulation of macrophages with anthracotic pigment. Symptoms are nonspecific and include cough and dyspnea. The incidence of DIP in men is twice as high as that in women, being highest around the fifth decade of life. Most patients (> 90%) are smokers, although DIP is found in other contexts, such as inhalation of inorganic particles and connective tissue diseases, especially rheumatoid arthritis and progressive systemic sclerosis.

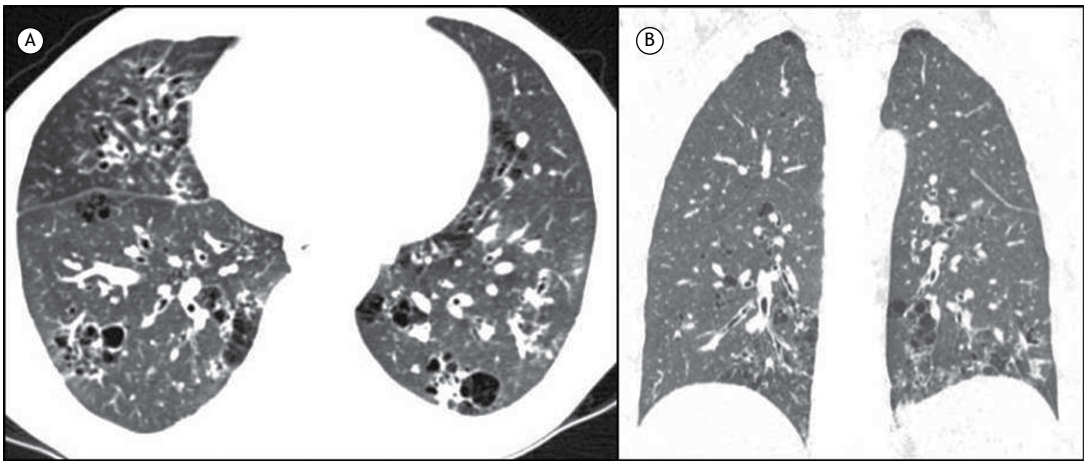

Figure 9. CT scans of a 33-year-old male patient who had been HIV-positive for three years and was poorly compliant with treatment. He had dyspnea and lung involvement secondary to pneumocystosis. In A, axial reconstruction demonstrating diffuse areas of ground-glass density, interspersed with bronchial wall thickening and several peribronchiolar cystic structures of various sizes. In B, coronal reconstruction showing lung cysts with a peribronchiolar distribution.

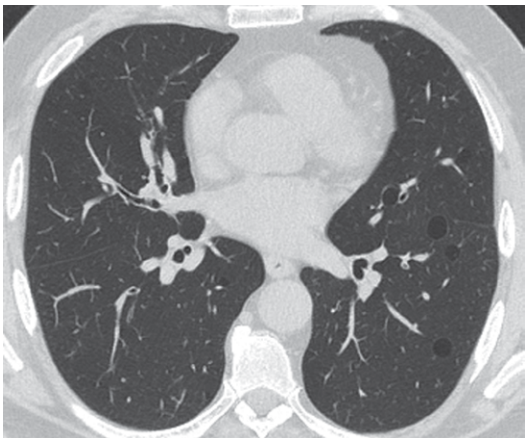

Figure 10. Axial reconstruction of a CT scan of a male patient with a diagnosis of hypersensitivity pneumonitis due to exposure to birds: after the subacute phase, there remained scattered, randomly distributed cysts in the lung parenchyma.

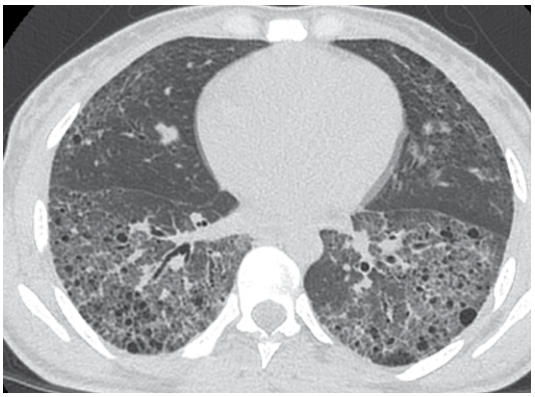

Figure 11. Axial reconstruction of a CT scan of a female patient with limited systemic sclerosis and a desquamative interstitial pneumonitis pattern, which was confirmed by open lung biopsy. The scan shows small-diameter lung cysts interspersed with areas of ground-glass opacity and traction bronchiolectasis, especially in the lower lung fields.

CT findings include small-diameter (up to 2 cm), round cysts interspersed with diffuse ground-glass opacities, especially in the lower lobes, usually with mild distortion of the lung architecture (Figure 11).[25,30]

FINAL CONSIDERATIONS

Many diseases with a variable course, of neoplastic, inflammatory, or infectious origin, can lead to the formation of diffuse lung cysts, and other potential etiologies of this radiological pattern have been proposed. HRCT has become an indispensable tool in the analysis of patients with diffuse lung cysts, because the analysis of the characteristics and distribution of the cysts, as well as the identification of other pulmonary and extrapulmonary manifestations, makes it possible to arrive at a definitive diagnosis or to narrow the differential diagnoses, optimizing clinical assessment.

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Bloodstained sputum of unknown etiology

Filipa Fernandes[1], Rita Gomes[1], Filomena Luís[1]

A 72-year-old male, former smoker presented to his physician, reporting cough and bloodstained sputum. The patient reported no asthenia, appetite loss, or significant weight loss. He was transferred to an emergency room and was involved in a traffic accident during interhospital transfer, resulting in polytrauma (including thoracic trauma). At admission, the patient presented with hemodynamic stability, dyspnea, amnesia, and an injury to the scalp. Lung auscultation revealed breath sounds and bilateral rhonchi.

An X-ray of the chest (Figure 1) showed an alveolar-interstitial pattern in the right lung, and a CT scan of the chest (Figure 2) revealed thickening of the posterior wall of the main right bronchus and a decrease in the caliber of its emergence as well as in the distal caliber of the right upper lobe bronchus.

Given the context of thoracic trauma and the imaging findings, bronchoscopy was performed in order to collect bronchial secretions, BAL fluid, and biopsy samples. The bronchoscopy revealed violaceous, edematous mucosa, together with infiltrate showing spur cells, in the right upper lobe bronchus; lumen reduction of segmental bronchi; and caseous necrosis resembling "candle wax drippings" (Figure 3). The bronchoscopy results (no evidence of active bleeding) allowed us to exclude bronchial rupture due to the trauma. Direct microscopy and bacterial culture of bronchial secretions led to a diagnosis of endobronchial tuberculosis, the etiological agent being identified as *Mycobacterium tuberculosis* complex.

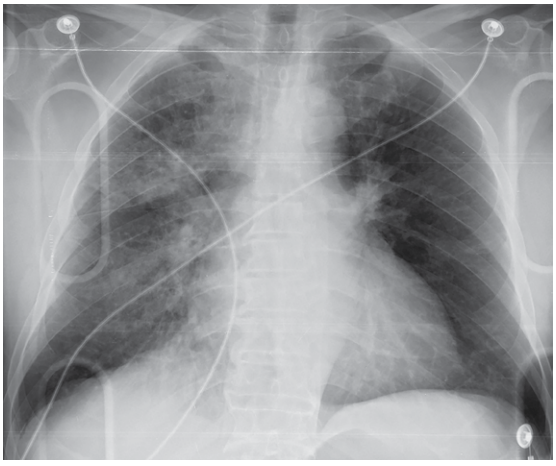

Figure 1. Posteroanterior chest X-ray revealing an alveolar-interstitial pattern in the right lung, with signs of ipsilateral volume loss.

Despite advances in the diagnostic modalities, the diagnosis of endobronchial tuberculosis continues to represent a challenge. Chest CT and bronchoscopy are valuable tools for obtaining the pathological diagnosis.

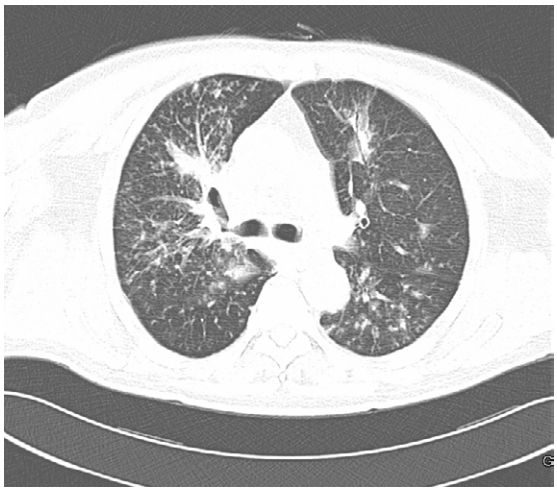

Figure 2. An axial CT scan of the chest, showing posterior wall thickening in the right main bronchus and a decrease in its caliber, as well as irregularities at the emergence of the right upper lobe bronchus.

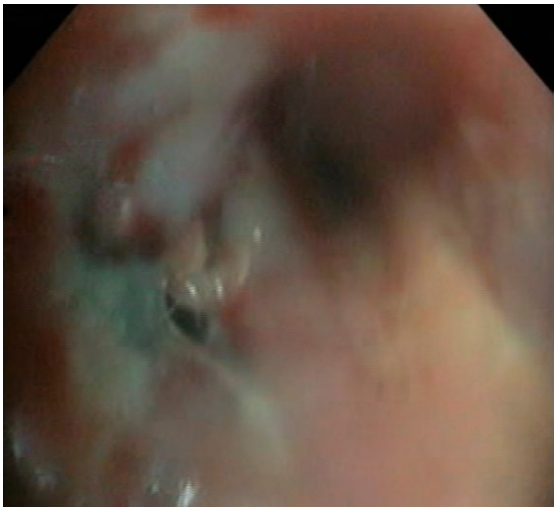

Figure 3. Bronchoscopic image showing the aspect of the lesion prior to biopsy: infiltrate showing spur cells; lumen reduction of segmental bronchi; and caseous necrosis resembling "candle wax drippings".

RECOMMENDED READING

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CASE REPORT

Tracheobronchopathia osteochondroplastica

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Study carried out at the Serviço de Doenças do Aparelho Respiratório, Hospital do Servidor Público Estadual de São Paulo, São Paulo (SP) Brasil.

ABSTRACT

Tracheobronchopathia osteochondroplastica is a rare benign disease, of unknown cause, characterized by numerous sessile, cartilaginous, or bony submucosal nodules distributed throughout the anterolateral walls, projecting into the laryngotracheobronchial lumen. In general, tracheobronchopathia osteochondroplastica is diagnosed incidentally during bronchoscopy or autopsy and is not associated with a specific disease. We report the case of a male patient who was diagnosed with tracheobronchopathia osteochondroplastica via bronchoscopy and biopsy.

Keywords: Dyspnea; Tracheal diseases; Bronchoscopy.

INTRODUCTION

Tracheobronchopathia osteochondroplastica (TO) is a rare benign disease, of unknown cause, characterized by numerous sessile, cartilaginous, or bony submucosal nodules distributed throughout the anterolateral walls of the trachea, projecting into the laryngotracheobronchial lumen. TO presents as round or polypoid osteocartilaginous projections covering the corrugated portion of the tracheobronchial mucosal surface and the narrow, rigid area in the respiratory tree.[1-3] The nodular lesions are sessile and calcified and vary from 1 to 10 mm in diameter. They are characterized by slow, progressive growth, being focal or diffuse, covered by metaplastic or normal epithelium, and extend from the perichondrium to the tracheal lumen, along the ring path, with active hematopoietic inclusion in nodular neoformations. TO can cause stenosis of the laryngotracheobronchial lumen, but without involvement of the posterior wall, with the possibility of progression to the main bronchi.[4]

The first case of TO was described by Wilks, as early as in the 19th century, in a 38-year-old male patient with tuberculosis. Since then, hundreds of cases have been reported worldwide.[5] However, many patients go undiagnosed because of a lack of knowledge about TO on the part of physicians. The etiology and pathogenesis of TO remain unknown. In general, it is diagnosed incidentally during bronchoscopy or autopsy and is not associated with a specific disease. TO predominantly affects males in the fifth to seventh decade of life[1,2] and is usually asymptomatic.[6]

In the present study, we report a case of TO found incidentally on a male patient's CT scan performed to investigate dyspnea.

CASE REPORT

A 59-year-old male patient presented with a 1-month history of dyspnea on severe exertion, associated with a progressive cough and throat clearing. The patient had hepatitis B and chronic atrial fibrillation. He reported being a nonsmoker. His physical examination yielded normal findings. A chest X-ray revealed no significant changes. Pulmonary function testing indicated mild obstructive lung disease with a response to bronchodilator use. Echocardiography showed an ejection fraction of 49% and mild, diffuse left ventricular hypocontractility. Chest CT images are shown in Figure 1. At bronchoscopy, multiple granular lesions were seen in the trachea and bronchi (Figure 2). Biopsy revealed nodular areas consisting of ossified cartilaginous tissue in the subepithelial regions, with the underlying respiratory epithelium exhibiting a characteristic pattern and no atypia (Figure 3).

DISCUSSION

TO is a rare benign disease of unknown cause. It was described macroscopically by Rokitansk in 1855 and microscopically by Wilks in 1857. Some etiopathogenic theories have been postulated. In 1863, Virchow postulated that echondrosis and exostosis lead to calcium deposition in and ossification of the tracheal rings. In 1947, Dalgaard postulated that the elastic tissue undergoes metaplasia to form cartilage and calcium deposition. In 1910, Aschoff-Freiburg attributed TO to changes in the elastic tissue in the trachea, introducing the term tracheopathia osteoplastica; and, in 1964, Secrest et al. labeled the disease as tracheobronchopathia osteoplastica.[7]

TO is usually asymptomatic. The most common symptoms are dyspnea; chronic cough; expectoration,

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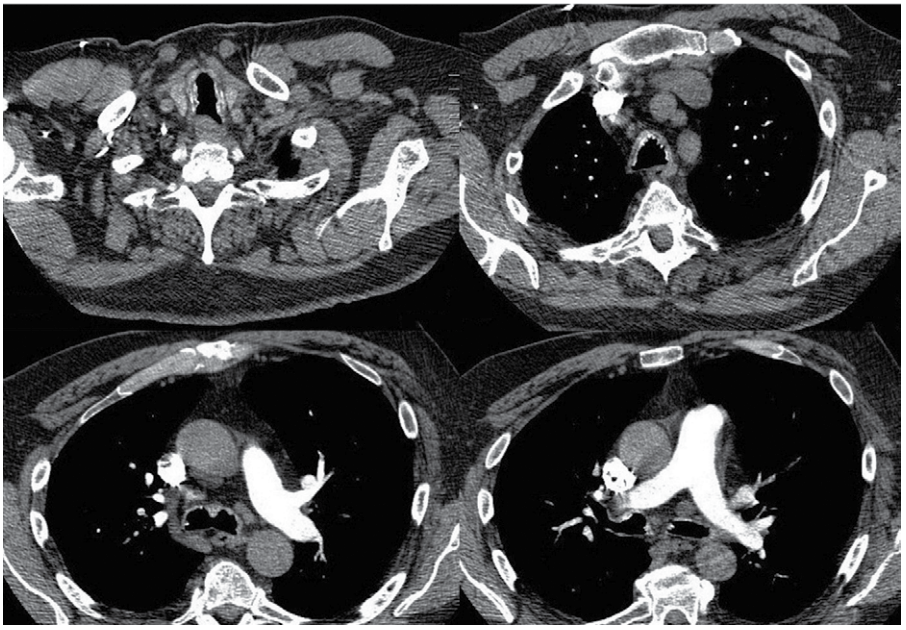

Figure 1. Chest CT scan showing multiple parietal calcifications and intraluminal nodular protrusions in the trachea and main bronchi, sparing the posterior membrane.

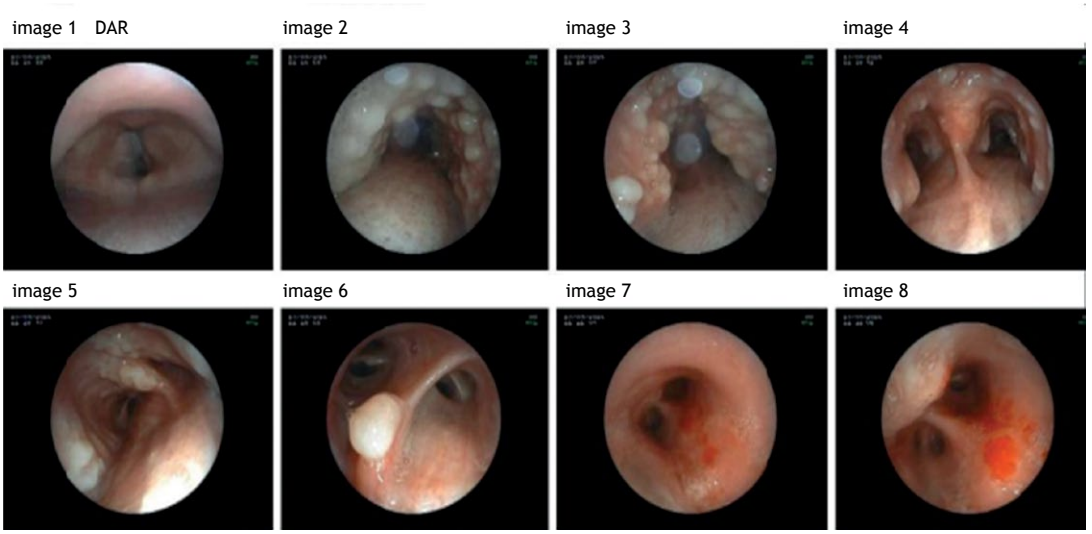

Figure 2. Bronchoscopic images showing that the tracheal caliber was preserved; the mucosa had a diffuse, coarse, granular whitish aspect, but without causing stenosis; and the main carina was thinner and mobile and had granular lesions. The ostia of the subsegmental bronchi were patent and covered by intact mucosa.

which is often abundant; and occasionally hemoptysis. Pulmonary function testing generally does not show airflow limitation. Only a small fraction of patients have ventilation anomalies, most commonly bronchial obstruction. CT and bronchoscopy remain the gold standard for identifying TO.

The clinical incidence of TO is estimated to range from 2 to 7 cases per 1,000 population, and its onset occurs between 25 and 85 years of age, most commonly in the fifth decade of life. There is no gender predominance. The interval between the first symptoms and diagnosis is approximately 4 years in 45% of cases; however, it may be longer than 25 years.[7] Incidental findings on bronchoscopy occur at a ratio of approximately 3:2,000-5,000 population. According to Secrest et al., it is estimated that only 51% of cases will be diagnosed during the patient's lifetime.[7] No correlation has been found between TO and smoking; however, some studies indicate an association between TO and chronic tracheal inflammation, arguing that this is possibly a factor of disease progression.[8,9]

Histologically, the mucosal bed may appear normal, with alternating areas of inflammation and necrosis and proliferative abnormal cartilage or bone formation in the submucosa, and there may be squamous metaplasia of the columnar epithelium, calcium deposits,

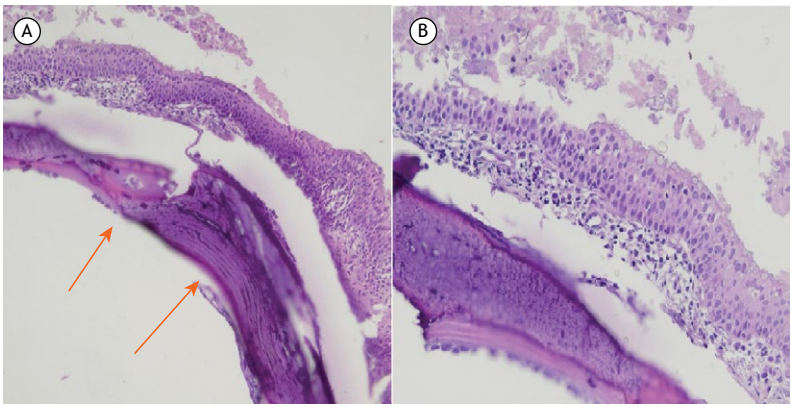

Figure 3. In A, abnormal cartilaginous tissue in the submucosal region, with metaplastic ossification (arrows; H&E; magnification, ×40). In B, same section at greater magnification showing metaplastic squamous epithelium covering the metaplastic bone tissue (H&E; magnification, ×100).

fragments of adipocytes, and active hematopoietic bone marrow tissue.[9,10] There is bony tissue, which is often cartilaginous, adjacent to the cartilaginous rings. Microscopically, the benign bony-cartilaginous tissue grows and replaces the bronchial submucosa and compresses the mucous glands. Bone marrow may be present. The epithelium covering these nodules is usually intact, metaplastic, sometimes dysplastic, or ulcerated. In the case presented here, transbronchial biopsy revealed the presence of cartilaginous tissue, with foci of metaplastic ossification, in the submucosal region. Metaplastic squamous epithelium, which was intact and exhibited no atypia, covered the osteocartilaginous nodule.

The differential diagnosis of TO consists mainly of papillomatoses, sarcoidosis, chondrosarcoma, hamartomas, amyloidoses, tuberculoid calcifications, dermatomyositis, scleroderma, Wegener's granulomatosis, and paratracheal calcified lymph nodes.[11,12]

To date, there is no definitive therapy for eradicating TO. Treatment is nonspecific; antibiotics are used to treat respiratory tract infections, and antitussives and inhaled corticosteroids are used to treat cough. Surgical treatment is indicated when the symptoms do not respond to clinical treatment; tracheal segmental resection, anterior laryngofissure, partial laryngectomy, and bronchoscopic removal of lesions can be performed.[8] Neodymium:yttrium-aluminum-garnet (Nd:YAG) laser photocoagulation, as well as placement of a silicone mold, can be a treatment option.[13-16]

The prognosis of patients with TO is favorable. Many cases in the literature have reported little progression over the years. However, it has been demonstrated that some patients died from severe respiratory infections.[17]

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Pulmonary talcosis caused by intravenous methadone injection

Dante Luiz Escuissato[1], Rimarcs Gomes Ferreira[2], João Adriano de Barros[1], Edson Marchiori[3]

TO THE EDITOR:

A 38-year-old woman presented to our pulmonology clinic with complaints of progressive dyspnea and dry cough for more than three months. She denied fever or weight loss. On physical examination, she presented as hypoxemic, with a room air oxygen saturation of 92% and an RR of 24 breaths/min. Pulmonary function tests showed that spirometric values were within normal limits, but there was a slight increase in residual volume (127% of predicted), as well as a reduction in DLCO (70% of predicted). Other laboratory test results were normal. A CT of the chest showed bilateral centrilobular nodules, most of them showing tree-in-bud appearance, scattered diffusely in the lung parenchyma (Figures 1A and 1B). After the CT examination, flexible bronchoscopy was then performed. Cultures of BALF were negative. Transbronchial biopsy performed in the left lower lobe showed multinucleated giant cell granulomas with birefringent foreign material, compatible with talc (Figures 1C and 1D). The centrilobular nodules were determined histopathologically to be tiny foreign body particles lodged in the centrilobular arterioles and perivascular space.

Upon further discussion, the patient remembered that approximately one month before the onset of symptoms, she had self-administered an i.v. injection of a crushed methadone pill diluted in water, due to strong pain caused by trigeminal neuralgia. Based on the clinical history, CT findings, and pulmonary biopsy results, the diagnosis of pulmonary talcosis secondary to i.v. drug injection was made. Echocardiogram results were normal. No signs of pulmonary hypertension were seen. During 3 years of follow-up, the patient showed clinical stability with the persistence of dyspnea on exertion and dry cough. Findings of control CT examinations were unchanged.

Pulmonary talcosis is most commonly observed after inhalation of talc due to occupational exposure

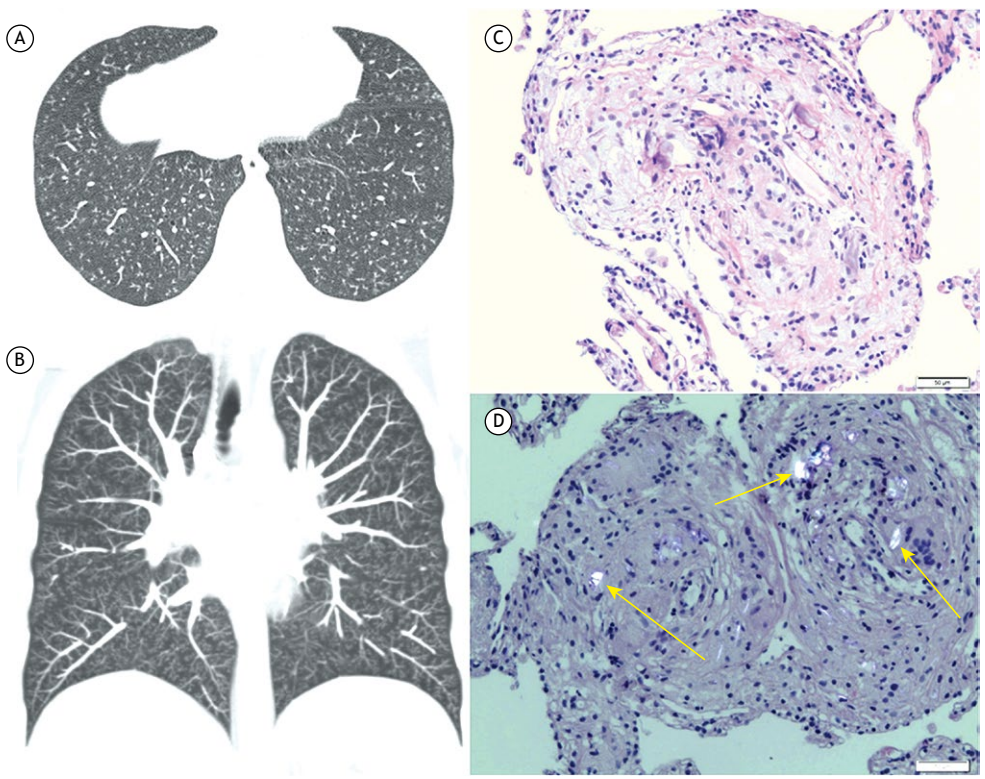

Figure 1. Axial (in A) and coronal (in B) reformatted CT images showing numerous small bilateral centrilobular nodules, associated with the tree-in-bud pattern. In C, lung tissue biopsy demonstrating an interstitial granulomatous reaction to the talc particles with a giant-cell reaction (H&E; magnification, ×100), whereas, in D, under polarized light, birefringent crystals (arrows) are visible (H&E; magnification, ×100).

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(talc-induced pneumoconiosis), i.v. drug abuse (intravascular talcosis), and, occasionally, excessive use of cosmetic talc. Clinical symptoms, imaging findings, and histological presentations of pulmonary talcosis are essentially identical in these different etiologies.[1-4]

The most common form of pulmonary talcosis is caused by i.v. talc administration. Illegal street drugs commonly contain adulterants to increase their mass, and these adulterants commonly contain microscopic insoluble material. Another common source of such material is the injection of medications intended for oral use. The medications are typically crushed, mixed with water, heated, and then injected i.v. The filler materials (excipients) used in oral tablets include not only talc, but also other insoluble particles, such as cellulose, crospovidone, and starch, which can induce a foreign-body reaction in pulmonary arterioles. Heroin, cocaine, and methadone are the most commonly injected drugs.[1-5] However, other medications, particularly analgesics and stimulants, are also used. Some authors[2] have suggested that the term "intravascular talcosis" is a misnomer, since talc is only one of various possible materials used as excipients, and have proposed the term "excipient lung disease" to identify this condition.

Patients with talcosis can be asymptomatic or present with respiratory failure. The symptoms are usually nonspecific and can include dyspnea, cough, fever, weight loss, chronic respiratory failure due to emphysema, and conditions related to pulmonary hypertension or fibrosis. Other complications of i.v. drug abuse resulting from the lack of a sterile technique include infections, such as endocarditis, septic embolism, HIV, and HCV. Physical examination and laboratory test findings are usually unremarkable in patients with talcosis. A characteristic finding of fundoscopy is the presence of crystals in retinal vessels. A history of i.v. drug abuse is an important clue to making the diagnosis; however, most i.v. drug abusers are reluctant to provide histories of exposure, and most diagnoses are made after lung biopsy.[1-4] The i.v. administration of talc or other excipients results in acute embolization of small vessels. Numerous tiny particles become lodged in the pulmonary vessels and migrate to the pulmonary interstitium, where they cause a granulomatous foreign-body reaction, with or without fibrosis. The granulomas can be visualized under polarized light as birefringent needle-shaped talc crystals in multinucleated giant cells.[1-3]

The earlier CT findings of talcosis consist of a diffuse fine nodular pattern, which corresponds basically to small centrilobular nodules and areas of ground-glass attenuation in all lung zones. The centrilobular nodules were determined histopathologically by tiny foreign body particles lodged in the centrilobular arterioles, and also in the perivascular space. The ground glass opacities may represent the confluence of these micronodules and/or microscopic granulomas below the resolution of HRCT.[1-3]

Periarteriolar, centrilobular micronodules can create a tree-in-bud pattern, mimicking bronchiolar disease. Centrilobular and panacinar emphysema patterns have been reported in i.v. drug users, with the lower-lobe panacinar pattern being predominant. Over time, talc micronodules may coalesce into perihilar conglomerate masses, resembling progressive massive fibrosis from silicosis or coal workers' pneumoconiosis. The conglomerate masses in talcosis may contain high-attenuation material.[1,2,4,5] The differential diagnosis for our patient (considering the presence of small bilateral centrilobular nodules, most with a tree-in-bud appearance) included arteriolar and bronchiolar diseases. The main conditions considered were infectious diseases (fungal, viral, and bacterial, particularly tuberculosis), noninfectious bronchiolitis, cystic fibrosis, aspiration/inhalation diseases, and peripheral pulmonary vascular diseases, such as pulmonary intravascular tumor embolism. There is no established treatment for talc granulomatosis. Patients must stop exposure and all tobacco use. Most authors believe that the use of steroids and immunosuppressants has no benefit. Associated pulmonary hypertension should be treated with vasodilators. Lung transplantation is considered to be a viable option for the treatment of talcosis. It is reserved as a last resort for patients with end-stage disease.[1] In our case, it was agreed that no treatment was required due to the stable nature of the disease. In conclusion, the CT manifestations of intravascular talcosis consist of diffuse centrilobular nodules associated with a tree-in-bud pattern and ground-glass opacities, heterogeneous conglomerate masses containing areas of high attenuation, and panlobular emphysema in the lower lobes. The diagnosis should be considered in the setting of a history of i.v. drug abuse, but the final diagnosis is made after lung biopsy in most cases.

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NACIONAIS

XI Curso Nacional de Doenças Intersticiais (DIP) e V Curso Nacional de Circulação Pulmonar
Data: 10 e 11 de março de 2017
Local: Centro de Convenções Rebouças, São Paulo/SP
Informações: 0800616218 ou eventos@sbpt.org.br

XVII Curso Nacional de Atualização em Pneumologia
Data: 20 a 22 de abril de 2017
Local: Othon Palace Copacabana - Rio de Janeiro/RJ Informações: 0800616218 ou eventos@sbpt.org.br

XX Congresso da Sociedade Brasileira de Cirurgia Torácica
Data: 03 a 06 de maio de 2017
Local: Windsor Barra – Rio de Janeiro/RJ
Organização: Método Eventos
Informações: Beatriz Lemgruber
(21) 25485141

INTERNACIONAIS

ATS 2017
Data: 19-24 de Maio de 2017
Local: Washington, D.C/USA
Informações: www.thoracic.org

SEPAR 2017
Data: 2-5 de junho de 2017
Local: Madrid Marriott Auditorium Hotel & Conference Center, Madrid/Espanha
Informações: www.separ.es

ERS 2017
Data: 09-13 de Setembro de 2017
Local: Milão, Itália
Informações: www.ersnet.org

CHEST 2017
Data: 28/10 a 01 de novembro de 2017
Local: Toronto/Canadá
Informações: www.chestnet.org

REGIONAIS

II Simpósio Nacional de Diagnóstico em Câncer de Pulmão Oncologia D'Or Neotórax
Data: 16 de março
Local: Rio de Janeiro – RJ

VI Congresso Brasileiro de Fibrose Cística
Data: 05 a 08 de abril
Local: Curitiba – PR

2° Simpósio de Imuno-Oncologia do Câncer – Hospital do Câncer Mãe de Deus
Data: 27 a 29 de abril
Local: Gramado – RS

XX Congresso da Sociedade Brasileira de Cirurgia Torácica
Data: 03 a 06 de maio
Local: Rio de Janeiro – RJ

9º Congresso do Centro-Oeste de Pneumologia e Tisiologia
Data: 08 a 10 de junho
Local: Cuiabá – MT

VIII Congresso Gaúcho de Pneumologia e II Congresso Gaúcho de Pneumologia Pediátrica
Data: 29 de junho a 01 de julho
Local: Centro de Eventos do Hotel Plaza São Rafael

IX Congresso Mineiro de Pneumologia e Cirurgia de Torácica
IV Congresso Mineiro de Pneumologia Pediátrica
Data: 29 de junho a 01 de Julho
Local:Belo Horizonte – MG

XVI Congresso de Pneumologia e Tisiologia do Estado do Rio de Janeiro
27 a 30 de setembro
Rio de Janeiro – RJ

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