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How can anemia negatively influence gas exchange?

Roberta Pulcheri Ramos[1]

Tissues obtain energy primarily from oxygen. Adequate oxygen levels in the inhaled air and a preserved ventilation/perfusion ratio ($\dot{V}$/Q) are the major determinants of oxygen supply to the blood. However, peripheral supply depends on effective oxygen transport to the tissue mitochondria, a critical task that is performed by hemoglobin. Without hemoglobin, cardiac output would have to increase up to 20 times in order to meet resting metabolic demands, and this would certainly be incompatible with life.[1]

Arterial oxyhemoglobin saturation (SaO_2) represents the percentage of occupied oxygen binding sites on hemoglobin. In patients with chronic anemia, SaO_2 is usually within the reference range, as is the amount of oxygen dissolved in the blood. However, the arterial oxygen content (which essentially depends on oxygen saturation levels and hemoglobin concentration) is reduced. This results in inadequate tissue supply, particularly when oxygen demand is increased, as occurs during exercise. Compensatory mechanisms include a hyperkinetic cardiovascular response and increased peripheral oxygen extraction.[2] A reduction in mixed venous oxygen tension might contribute to arterial oxyhemoglobin desaturation during exercise, especially in patients with chronic cardiopulmonary disease.

In addition to the aforementioned mechanisms, the hemoglobin dissociation curve plays an important role in changes in gas exchange. Patients with sickle cell disease are of note in this context; it has been demonstrated that the hemoglobin dissociation curve shifts to the right in such patients.[3,4] Although this constitutes a "protective" mechanism—given that it promotes the release of oxygen to the tissues—it can contribute to decreasing arterial oxyhemoglobin levels in such patients, particularly during exercise, because hemoglobin S has low affinity for oxygen. In addition, the negative impact that lung parenchymal changes secondary to vaso-occlusive crises have on pulmonary gas exchange, particularly in adults with sickle cell disease, cannot be ignored.[5,6] However, to date, few studies have examined lung function abnormalities in the early stages of the disease.

In the previous issue of the JBP, Vieira et al.[7] evaluated children and adolescents with sickle cell disease using spirometry and the six-minute walk test. It is of note that changes in gas exchange during exercise were common in the study sample: 52% had a significant decrease in SaO_2 as assessed by pulse oximetry (SpO_2) at the end of the six-minute walk test. This finding was common even in those with normal spirometry results.

In patients with sickle cell disease, the possibility of impairment in the pulmonary circulation is also of note. In a recent study conducted in Brazil, it was demonstrated that pulmonary hypertension (PH) is a major complication of sickle cell disease.[8] It was also demonstrated that patients with PH (including those with postcapillary PH) have reduced exercise tolerance, despite having preserved or even increased cardiac output. In the study conducted by Vieira et al.,[7] the lack of echocardiographic evaluation constitutes a limitation that precludes the identification of other factors associated with desaturation. In patients with high-output PH, increased pulmonary flow can lead to diffusion/perfusion mismatch enhanced by a rightward shift of the hemoglobin dissociation curve and associated $\dot{V}$/Q mismatch (Figure 1).

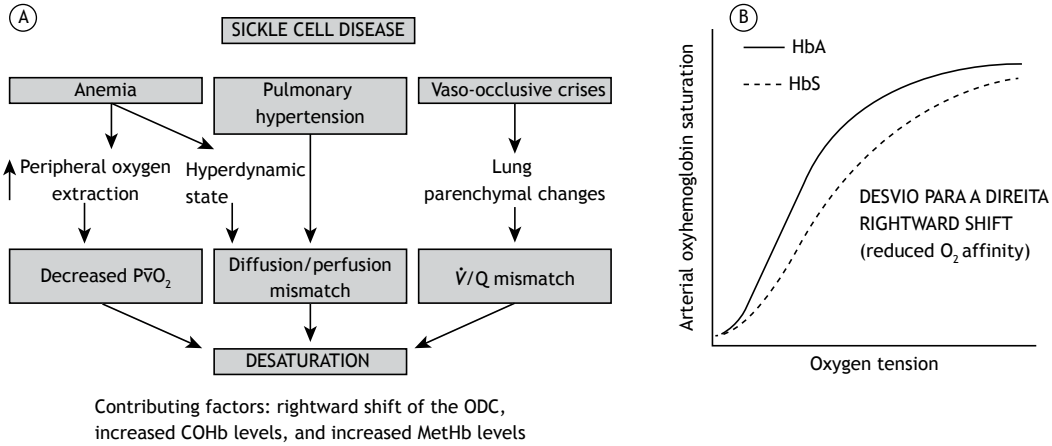

Figure 1. In A, factors potentially associated with desaturation in patients with sickle cell disease. In such patients, pulmonary hypertension generally presents as a hemodynamic state characterized by low pulmonary vascular resistance and high cardiac output, and is unlikely to contribute to decreasing $P\bar{v}O_2$. In B, graphical representation of the dissociation curves of hemoglobin (Hb) A and HbS. The rightward shift reflects reduced oxygen affinity. $P\bar{v}O_2$: mixed venous oxygen tension; $\dot{V}$/Q: ventilation/perfusion; ODC: oxyhemoglobin dissociation curve; COHb: carboxyhemoglobin; and MetHb: methemoglobin.

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In addition to the lack of echocardiographic evaluation, the aforementioned study has limitations such as the lack of lung volume measurements, DLCO measurement, and arterial blood gas analysis. However, the study is important because it shows the characteristics of sickle cell disease in a sample of patients in Brazil. It is of note that some of the results were inconsistent with the literature, the proportion of patients in whom SpO_2 decreased during exercise being higher than those reported in previous studies.[9,10] According to the authors, patients with sickle cell disease should be evaluated for lung function from childhood onward. Prospective cohort studies involving sickle cell disease patients are needed in order to identify possible prognostic implications.

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The search for individualized smoking cessation therapy

Ilka Lopes Santoro[1]

"Giving up smoking is the easiest thing in the world. I know it because I've done it thousands of times."

Mark Twain

Although the prevalence of smoking in Brazil has been decreasing in recent decades,[1] tobacco is a drug classified as licit; therefore, the epidemic of this neurobehavioral disease, caused by nicotine dependence, will probably endure for many decades to come.[2] As with any epidemic, it is necessary to understand the disease behavior for different population groups in order to devise effective treatment and control strategies.

In this sense, it is important to emphasize that we are in the era of individualized therapies, it being essential to establish a risk classification for each subgroup of patients in order to outline the therapeutic strategies to be implemented for each of them. First, there is strong evidence that women are affected differently by tobacco compared to men, because women adhere more strongly to their smoking addiction. This occurs especially among those who are more vulnerable and those disadvantaged by low income or a low level of education.[3-5] A second aspect that needs to be highlighted is that smoking addiction in women can be potentiated more by the sensorial and social context than by nicotine dependence, which means to say that, unlike males, females use tobacco to cope with negative emotions and situations or in an attempt to reduce stress or control weight.[6]

In order to make such an epidemiological assessment, the article entitled "Smoking among female sex workers: prevalence and associated variables",[7] published in the current issue of the JBP, focuses on a specific subgroup of the Brazilian population that fits perfectly among the women most vulnerable to addiction. The authors were very happy in their choice of this object of study to describe the characteristics and prevalence of smoking in this population subgroup, a prevalence that was found to be much higher than the mean prevalence reported for the general Brazilian population (71.1% vs. 10.4%).

In addition, the authors sought to understand the pattern of tobacco use, reporting early age at smoking initiation, high daily tobacco consumption, with a high level of nicotine dependence, and low motivation for smoking cessation. They also investigated whether there were associations between smoking and mood disorders (anxiety, depression, and perceived stress).

Furthermore, although governmental interventions—such as increasing the prices of cigarette packs by increasing taxes—reduced cigarette sales by 32%, the authors found that consumption of illicit cigarettes from Paraguay is a common practice in the subgroup in question.

In conclusion, it is important to note that, by establishing the behavior of female sex workers regarding tobacco use, the study by Devóglio et al.[7] raises a fundamental issue, which is that of structured planning developed specifically to address this highest risk subgroup. Therefore, not only should a cognitive behavioral approach and the use of pharmacotherapy be considered to improve the quality of life of these women but also the use of a harm reduction strategy. In addition, certain particularities of this subgroup should be taken into account, such as the need to reduce modifiable risk factors (use of alcohol and illicit drugs), which are also very prevalent, as well as the need to establish cigarette smuggling control policies.

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The halo sign

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

A 49-year-old male smoker (with a smoking history of 90 pack-years) presented with vague complaints of dyspnea. Laboratory test results were normal. Serology for HIV was negative. A CT scan of the chest showed a nodule with the halo sign in the left lower lobe (Figure 1). Fungal serology was negative.

The halo sign is a nonspecific CT finding consisting of a halo of ground-glass opacity surrounding a nodule or, less commonly, a mass or a rounded area of consolidation.

In most cases, a halo of ground-glass opacity represents perinodular hemorrhage. In cases of angioinvasive aspergillosis (AIA), for example, a nodule represents pulmonary infarction secondary to fungal angioinvasion and a surrounding halo of ground-glass opacity represents perinodular alveolar hemorrhage. In other infectious processes, the halo sign represents perilesional inflammatory infiltration. In cases of adenocarcinoma, the halo sign represents tumor cell proliferation along the alveolar septa, the pulmonary architecture being preserved (lepidic growth). The same features can be seen in some cases of metastatic adenocarcinoma (particularly in cases of adenocarcinoma originating from the gastrointestinal tract or pancreas).

As an initial diagnostic approach, it is useful to determine patient immune status. In immunocompromised patients, the halo sign is most commonly due to infectious diseases, the most common being invasive fungal diseases, such as AIA. Therefore, in the presence of febrile neutropenia, especially in patients with hematological malignancies and in bone marrow transplant recipients, AIA is the major cause of the halo sign. In such cases, the halo sign is considered to constitute early evidence of AIA, warranting initiation of antifungal therapy before serologic test results are known. Early diagnosis is essential because the disease is associated with high mortality rates. In immunocompetent patients, especially asymptomatic patients and smokers, bronchial carcinoma, particularly lepidic adenocarcinoma (formerly known as bronchioloalveolar carcinoma), is the major cause of the halo sign. The differential diagnosis should also include the following: hemorrhagic metastases, particularly those related to angiosarcomas and choriocarcinomas; lymphomas; Kaposi's sarcoma; bacterial infections (including tuberculosis and actinomycosis); fungal infections (including candidiasis, mucormycosis, cryptococcosis, histoplasmosis, and paracoccidioidomycosis); viral infections (including infection with cytomegalovirus, herpes simplex virus, and varicella-zoster virus); sarcoidosis; granulomatosis with polyangiitis (Wegener's granulomatosis); and organizing pneumonia.

Although the halo sign is a nonspecific finding with a broad differential diagnosis, the differential diagnosis can be considerably narrowed by correlating clinical data, laboratory test results, and associated CT findings. However, in many cases, a final diagnosis requires histopathological examination. In our patient, a biopsy revealed adenocarcinoma with a lepidic growth pattern.

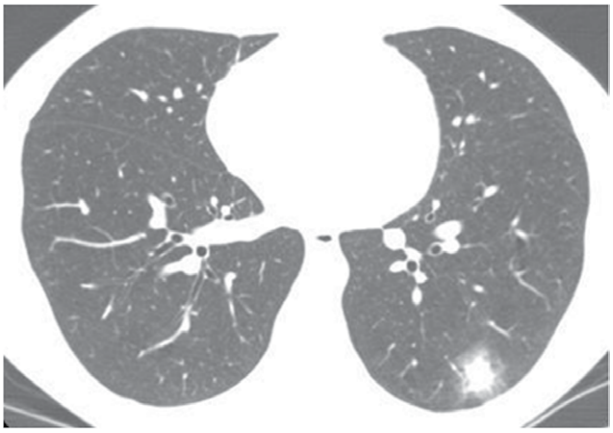

Figure 1. CT scan of the chest with lung window settings at the level of the lower lobes, showing a soft-tissue density nodule located in the left lower lobe and surrounded by a halo of ground-glass opacity (the halo sign).

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Types of outcomes in clinical research

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

PRACTICAL SCENARIO

In a randomized trial evaluating the efficacy of a new drug for pulmonary arterial hypertension (PAH), patients were randomly assigned to receive the new drug or a placebo. The primary composite outcome was the time to the first PAH-related event (worsening of symptoms, initiation of treatment with prostanoids, lung transplantation, or atrial septostomy) or to death. Secondary outcomes included changes in the 6-minute walk distance (6MWD) and adverse events.

DEFINITIONS

Outcomes (also called events or endpoints) are variables that are monitored during a study to document the impact that a given intervention or exposure has on the health of a given population. Typical examples of outcomes are cure, clinical worsening, and mortality. The primary outcome is the variable that is the most relevant to answer the research question. Ideally, it should be patient-centered (i.e., an outcome that matters to patients, such as quality of life and survival).

Secondary outcomes are additional outcomes monitored to help interpret the results of the primary outcome: in our example, an increase in the 6MWD is inversely associated with the need for lung transplantation. They can also provide preliminary data for a larger study. For example, a preliminary trial that uses 6MWD as the primary outcome may include mortality as a secondary outcome if the power of the study to detect a difference in mortality is low. Although investigators may be tempted to monitor several outcomes, the effort and cost to monitor various outcomes may be prohibitive. Therefore, it is essential to decide which outcome(s) to monitor (Table 1).

Surrogate outcomes are biomarkers intended to substitute for a clinical outcome, for example, 6MWD as a marker of disease severity in PAH. Surrogate outcomes are typically continuous variables and occur earlier than does the clinical outcome, reducing costs, study duration, and size. Surrogates are commonly used as the primary outcome in phase I and II clinical trials. However, they may lead to false interpretations of the efficacy of the intervention if the surrogate is not a very good predictor of the clinical outcome.

Composite outcomes are made up of multiple variables. In our practical scenario, the primary outcome was composed of several clinical outcomes related to disease progression. Using composite outcomes has the advantage of increasing the power of the study when each of the events is rare and when events are competitive (patients who die cannot have a lung transplant). However, the interpretation of results can be misleading: if the intervention reduces the occurrence of the composite outcome, it does not necessarily mean that it reduces the occurrence of all of its components.

IMPORTANT CONSIDERATIONS

- The study outcomes should be stated *a priori* (before the researcher looks at the results) in order to avoid the risk of drawing false conclusions by testing every possible variable until one is statistically significant.
- The sample size calculation should be carried out to detect a clinically relevant effect of the intervention on the primary outcome, although calculations can also be made for secondary outcome variables, which may increase the sample size but also increase trial validity.
- More importantly, the choice of the most suitable outcome should be based on the research question and the corresponding hypothesis.

Table 1. Types of outcomes.

Outcome	Patient-centered	Composite	Surrogate
Asthma	Asthma control (questionnaire)	Hospitalization or a > 20% decline in asthma control	FEV_1, peak flow, eosinophils
PAH	2-year survival	Lung transplantation or death	6MWD, PASP
ARDS	Hospital survival	Time to extubation or tracheotomy	PaO_2/FiO_2 ratio, ventilator-free days

PAH: pulmonary arterial hypertension; 6MWD: six-minute walk distance; and PASP: pulmonary artery systolic pressure.

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ORIGINAL ARTICLE

Smoking among female sex workers: prevalence and associated variables

Ligia Lopes Devóglio[1], José Eduardo Corrente[2], Maria Helena Borgato[3], Ilda de Godoy[3]

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Study carried out in the Departamento de Enfermagem, Faculdade de Medicina de Botucatu, Universidade Estadual Paulista, Botucatu (SP) Brasil.

ABSTRACT

Objective: To assess the prevalence of smoking and associated variables in female sex workers (FSWs). **Methods:** This was a quantitative cross-sectional study involving FSWs in the city of Botucatu, Brazil, who completed a sociodemographic questionnaire, including data regarding smoking status, motivational stage of change, and degree of nicotine dependence, as well as the Perceived Stress Scale and the Hospital Anxiety and Depression Scale. **Results:** We included 83 FSWs. The mean age was 26.8 years. Among the participants, 58 (69.8%) had at least a high school education, only 26 (31.3%) resided in the city of Botucatu, 59 (71.1%) were smokers, 5 (6.0%) were former smokers, 74 (89.2%) regularly consumed alcohol, and 43 (51.8%) used illicit drugs. The majority of the women were classified as having an intermediate stress level, and 51 (61.4%) were classified as having possible or probable anxiety, whereas depression was found to be improbable in 57 (68.7%). The level of nicotine dependence was high among the smokers, the majority of whom showed no intention to quit smoking. Smoking was associated with illicit drug use ($p = 0.0271$) and with alcohol consumption ($p = 0.0001$), although not with the levels of stress, anxiety, or depression; nor was the age at smoking initiation associated with the length of time as an FSW ($p = 0.4651$). **Conclusions:** The prevalence of smoking among the FSWs evaluated here was much higher than the 8.3% reported for the overall female population of Brazil. Our findings show that FSWs are exposed to various risk factors inherent to their profession. Therefore, harm reduction is an important strategy to be adopted.

Descriptors: Women, Smoking, Sex workers; Prevalence; Risk factors.

INTRODUCTION

According to the World Health Organization, smoking is no longer considered a habit but rather a disease, a true epidemic, which can be totally preventable. Currently, 5.4 million people die every year from tobacco-related diseases, and it is estimated that, if there are no significant changes, by 2030, this number will reach 8 million and that 80% of smokers will be in (low- and middle-income) developing countries.[1,2]

The current prevalence of smoking is higher among men than among women, given that the latter started smoking later than the former. However, in recent decades, there has been a small decline in the smoking curve for men, whereas, for women, there has been an increase, which contradicts the idea of smoking as a male epidemic.[2-4]

Data indicate that 22% of the world population smoke cigarettes, with approximately 820 million being male and 176 million being female. Tobacco use accounts for up to 34% of deaths among men and 22% of deaths among women; in Brazil, these rates are lower (12.8% and 9.4%, respectively).[2] The World Health Organization estimates that, if nothing is done, smoking among women will double worldwide from 2005 to 2025.[5]

Some developed countries, such as the USA and Australia, have monitored smoking trends by occupation in order to aid in the identification of occupational groups that need to be prioritized in interventions for smoking control and cessation. A study conducted in Brazil aimed to describe this relationship, and, as in the countries mentioned above, it was found that the prevalence of smoking is higher in subjects who occupy positions requiring a lower level of education and greater physical effort.[6]

Although the topic of prostitution is little discussed today, prostitution is a phenomenon that is still present in the Brazilian society and in various countries around the world.[7] There are various factors determining prostitution, whether economic, such as migration to urban centers, a lack of jobs, the large number of single mothers who have difficulty raising their children, subhuman living conditions, a low level of education, a lack of perspective, etc.; or psychological, such as affective issues, trauma exposure in childhood or adolescence, or a lack of family support.[8] These factors may often be associated with smoking and the use of other drugs in this population.

Studies have shown that female SWs are constantly exposed to various risk factors, such as social vulnerability, submission, and especially licit and illicit drug abuse, because they have difficulty maintaining quality of life, ending up adopting behaviors that are detrimental to

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their health; this shows the need for interventions that address multiple aspects of health.[7,9]

Profiling tobacco users, by collecting data such as the prevalence and level of smoking by age group, gender, income, etc., is also a very important factor, because it is based on these data that health care professionals will be able to plan prevention interventions that are more efficient in certain populations. For all these reasons, the prevalence of smoking, the profile of smokers, motivations for smoking cessation, and the consequences of smoking have been studied in several countries in the world, because these data provide us with a better understanding of the worldwide epidemic of smoking.[1,10]

Therefore, the objective of the present study was to assess the prevalence of smoking and to analyze the association between smoking and other variables in female sex workers (SWs).

METHODS

This was an exploratory, quantitative, analytical, cross-sectional study conducted in the city of Botucatu, which is located in the central region of the state of São Paulo, Brazil, and has an estimated population of 137,899 people.[11] The area served by the primary health care clinic in the Cecap district, an area characterized by being one of the main prostitution hubs in the city, was used as a reference. Site visits were conducted to two workplaces that are registered with the city.

Forms were administered to 83 female SWs. The sample was calculated on the basis of a study of 102 female SWs conducted in the city of Botucatu in 2008, which showed that the smoking rate in that population was high, corresponding to 68.6% (70 women).[12]

To find the prostitution hubs, we initially contacted the Municipal Sexually Transmitted Diseases/AIDS Program, which is active in the city and conducts site visits to various population groups that are vulnerable to these diseases, such as the group of female SWs. After this contact, and accompanied by the health care workers, we conducted the first site visits to the workplaces of the female SWs. Subsequently, we returned on our own to the prostitution hubs until the sample number was met.

Numerous site visits were conducted to the workplaces of the female SWs, and, since this is a hard-to-reach population, because they are afraid to participate in research, surveys, etc., the interviews were requested and conducted in their work environments. Some female SWs declined to participate in the study for fear of being discovered by their families, even when we explained that their names would not be disclosed.

Data were collected between February and November of 2014. Identification forms and smoking assessment forms were administered to all women who agreed to participate in the study; in addition, motivational stage of change was assessed as per the transtheoretical model of change developed by DiClemente & Prochaska,[13] which describes readiness to change according to the stages that the individual goes through and that are classified as follows: precontemplation—the smoker has no intention to quit in the next six months; contemplation—the smoker has an intention to quit in the next six months but has not set a quit date; preparation—the smoker intends to quit in the next thirty days; action—the individual has been smoke-free for up to six months; and maintenance—the individual has been smoke-free for more than six months. The Perceived Stress Scale[14] and the Hospital Anxiety and Depression Scale[15] were administered to assess the levels of stress, anxiety, and depression in these women.

The female SWs were assessed for smoking characteristics using a specific form, based in other studies, containing questions about smoking history, presence of tobacco-related diseases, social and family history, factors related to smoking initiation, and tobacco intake, in order to determine their smoking profile.[10] In addition, they were asked if they simultaneously used other drugs, whether licit (alcohol) or illicit, in order to avoid our having to interpret possible biases. Tobacco intake was measured in pack-years, calculated by dividing the number of cigarettes smoked per day by 20 (the number of cigarettes in one pack) and multiplying the result by the number of years of smoking. The degree of dependence was assessed by the Fagerström Test for Nicotine Dependence.[16,17]

For data analysis, first, a database was created using Microsoft Excel, and, subsequently, descriptive statistics were calculated for quantitative variables (mean and standard deviations) and qualitative variables (frequencies and proportions). Qualitative variables were tested for associations by the chi-square test or Fisher's exact test. For variables with more than two categories, means were compared by using ANOVA followed by Tukey's test.

In all tests, we used a 5% significance level or the corresponding p value. All analyses were performed with the Statistical Analysis System software, version 9.3 (SAS Institute, Cary, NC, USA), with the aid of the statistician in charge of the study.

The study was approved by the Botucatu Municipal Department of Health and the Research Ethics Committee of the São Paulo State University Botucatu School of Medicine, in accordance with Brazilian National Health Council Resolution no. 466/13 (Protocol no. 711.738).

RESULTS

A total of 83 female SWs participated in the study. The mean age was 26.8 ± 63 years (range, 18-48 years). The majority of the women (n = 58; 69.8%) had at least a high school education, 78 (94.0%) lived alone, and 49 (59.0%) had children (mean, 2.04 ± 1.3 children). The mean length of time as a SW was 3.7 ± 5.0 years. The mean monthly income was R$ 3,708.33 ± R$ 3,001.58 (range, R$ 500.00-R$ 17,000.00), and

some reported not knowing how much they earned because of their short time as a SW. This is a fluctuating population; only 26 (31.3%) were permanent residents of the city of Botucatu, Brazil.

The prevalence of smoking was 71.1% (n = 59), and 6.0% (n = 5) were former smokers. Licit and illicit drug use was found to be prevalent in the female SWs; 74 (89.2%) of the women consumed alcohol, and 43 (51.8%) used illicit drugs, such as marijuana (36.1%), cocaine (34.9%), and crack cocaine (3.6%). In addition, 65 (78.3%) did not engage in physical activity. The distribution of the general characteristics is shown in Table 1.

The mean age at smoking initiation was 16.0 ± 4.5 years among the smokers. Of the 59 smokers, 81.4% reported smoking every day and 88.1% always inhaled the smoke; the mean number of cigarettes smoked per day was 22.3 ± 20.0, corresponding to approximately 8.6 ± 8.2 packs per week, which resulted in a monthly expenditure of R$ 139.56 ± R$ 115.25. The mean tobacco intake in this group of women was 11.9 ± 14.1 pack-years. The prevalence of high or very high dependence, as measured by the Fagerström scale, was 47.4%.

In analyzing age at smoking initiation and length of time as a SW, we found that there was no association between the two (p = 0.4651); therefore, the majority of the women smoked even prior to starting working as a SW.

The most common motivational stage of change was precontemplation, in 40.6%, and all former smokers were in the maintenance stage. These data are shown in Table 2. In the preconception group, all women smoked regular cigarettes; in addition, 11 (18.6%) smoked flavored cigarettes, 5 (8.5%) smoked hand-rolled cigarettes, 5 (8.5%) smoked water-pipe tobacco, and 2 (3.4%) smoked electronic cigarettes.

Of the 32 women (54.2%) who had tried to quit smoking, 21 (65.6%) reported having felt more irritated during the abstinence period and 20 (62.5%) reported increased appetite. Of those 32 women, 30 (93.7%) did not use any smoking cessation aids.

Among the smokers, 43 (72.9%) started smoking because they chose to do so rather than because someone offered them a cigarette, and the influencing factors included parents (in 13.6%), friends (in 55.4%), and curiosity to try a cigarette (in 79.7%). Before buying cigarettes, some SWs reported that they got

Table 1. Distribution of the general characteristics of the female sex workers in the study (N = 83).[a]

General characteristic	Result
Age, years	26.8 ± 6.3 (18-48)
Length of time as a SW, years	3.7 ± 5.0 (0.0027-15.0000)
Monthly income, R$	3,708.33 ± 3,001.58 (500.00-17,000.00)
Number of children	2.04 ± 1.30 (1-7)
Level of education	
< 9 years of schooling	11 (13.3)
9 years of schooling	14 (16.9)
High school (incomplete)	24 (28.9)
High school (complete)	28 (33.7)
College (incomplete)	5 (6.0)
College (complete)	1 (1.2)
Marital status	
Living with a steady partner	4 (4.8)
Married	1 (1.2)
Divorced	3 (3.6)
Single	74 (89.2)
Widowed	1 (1.2)
Smoking status	
Smoker	59 (71.1)
Former smoker	5 (6.0)
Nonsmoker	19 (22.9)
Has children	49 (59.0)
Engages in physical activity	18 (21.7)
Consumes/uses	
Alcohol	74 (89.2)
Cocaine	29 (34.9)
Crack cocaine	3 (3.6)
Marijuana	30 (36.1)
Other drugs	43 (51.8)

SW: sex worker. [a]Values expressed as mean ± SD (range) or n (%).

Table 2. Smoking history of the female smokers in the study (N = 59).[a]

Smoking history	Result
Age at smoking initiation, years	16.1 ± 4.5 (8-30)
Cigarettes/day	22.3 ± 20.0 (2-120)
Packs/week	8.6 ± 8.2 (0.25-42.00)
Monthly expenditure, R$	139.56 ± 115.25 (2.00-675.00)
Number of successful quit attempts	1.6 ± 0.9 (1-3)
Longest time without smoking, years	0.6 ± 0.4 (0.0082-1.0000)
Tobacco intake, pack-years	11.9 ± 14.1 (0.25-27.0)
Type of smoker	
Daily	48 (81.4)
Weekend	0 (0.0)
Occasional	11 (18.6)
Inhales the smoke	
Always	52 (88.1)
Never	2 (3.4)
Sometimes	5 (8.5)
Level of dependence	
Very low	20 (33.9)
Low	5 (8.5)
Medium	6 (10.2)
High	16 (27.1)
Very high	12 (20.3)
Has tried to quit smoking	32 (54.2)
Withdrawal symptoms in those who tried to quit (n = 32)	
Irritation	21 (65.6)
Insomnia	5 (15.6)
Sadness	6 (18.8)
Agitation	12 (37.5)
Slowness	1 (3.1)
Loss of concentration	1 (3.1)
Increased appetite	20 (62.5)
Used smoking cessation aids	30 (6.3)
Motivational stage of change	
Precontemplation	26 (40.6)
Contemplation	15 (23.5)
Preparation	18 (28.1)

Values expressed as mean ± SD (range) or n (%).

Table 3. Smoking history of the female former smokers in the study (N = 5).[a]

Smoking history	Result
Age at smoking initiation, years	14.4 ± 2.5 (12-18)
Duration of smoking, years	11.4 ± 7.4 (0.25-17.0)
Age at smoking cessation, years	25.8 ± 8.0 (16-37)
Length of time as a former smoker, years	4.4 ± 2.7 (1-7)
Cigarettes/day	33.0 ± 29.1 (5-80)
Packs/week	11.6 ± 10.1 (2-15)
Tobacco intake, pack-years	25.0 ± 29.7 (0.25-36.00)

[a]Values expressed as mean ± SD (range).

cigarettes from family members (in 20.3%) or friends (in 42.4%).

The smoking history distribution of the female SWs who smoked is shown in Table 2. Regarding the smoking history of the former smokers, the mean age at smoking initiation was 14 ± 2.5 years, the mean duration of smoking was 11.4 ± 7.4 years, and the mean age at smoking cessation was 25.8 ± 8.0. The mean number of cigarettes smoked per day was 33.0 ± 29.1, corresponding to approximately 11.6 ± 10.1 per week. The mean tobacco intake in this group of women was 25.0 ± 29.7 pack-years. The smoking history distribution of the female SWs who were former smokers is shown in Table 3.

Table 4. Perceived Stress Scale score and Hospital Anxiety and Depression Scale classification in the study sample (N = 83).[a]

Score	Smoking status	Result				p
PSS	Smoker	23.4 ± 4.59				0.4301
	Nonsmoker	22.1 ± 4.34				
	Former smoker	24.8 ± 7.46				
HADS classification		**Improbable**	**Possible**	**Probable**	**TOTAL**	
Anxiety	Smoker	21 (25.3)	12 (14.5)	26 (31.3)	59 (71.1)	0.3715
	Nonsmoker	10 (12.1)	5 (6.0)	4 (4.8)	19 (22.9)	
	Former smoker	1 (1.2)	1 (1.2)	3 (3.6)	5 (6.0)	
	Total	32 (38.6)	18 (21.7)	33 (39.7)	83 (100)	
Depression	Smoker	43 (51.8)	8 (9.7)	8 (9.7)	59 (71.1)	0.4299
	Nonsmoker	12 (14.5)	5 (6.0)	2 (2.4)	19 (22.9)	
	Former smoker	2 (2.4)	2 (2.4)	1 (1.2)	5 (6.0)	
	Total	57 (68.7)	15 (18.1)	11 (13.2)	83 (100)	

PSS: Perceived Stress Scale; and HADS: Hospital Anxiety and Depression Scale. [a]Values expressed as mean ± SD or n (%).

Table 5. Frequency distribution of dyspnea in the study sample (N = 83).

Smoking status	Dyspnea			p
	Yes n (%)	No n (%)	Total n (%)	
Smoker	27 (32.5)	32 (38.6)	59 (71.1)	0.4515
Nonsmoker	2 (2.44)	17 (20.5)	19 (22.9)	< 0.0001
Former smoker	3 (3.6)	2 (2.4)	5 (6.0)	1.0000
Total	32 (38.5)	51 (61.5)	83 (100.0)	

The stress level, as measured by the Perceived Stress Scale,[14] which ranges from zero to 40 (the latter represents perceived stress), was defined as intermediate among the smokers, former smokers, and nonsmokers, and there were no significant differences among the three groups of women, as shown in Table 4. In addition, there were no statistically significant differences among the three groups of women regarding the Hospital Anxiety and Depression Scale classification[15]; 51 (61.4%) of the women had scores corresponding to possible or probable anxiety, whereas depression was found to be improbable in 57 (68.7%). The data are shown in Table 4.

At the time of the study, the most commonly reported respiratory symptom was dyspnea (in 38.5%), followed by cough (in 26.5%), palpitation (in 25.3%), chest pain (in 22.9%), dizziness (in 22.9%), expectoration (in 20.5%), and wheezing (in 14.5%). Among the women who did not have dyspnea, the associations were significantly different only for those who were nonsmokers ($p < 0.0001$); therefore, in the present study, smoking was not associated with this respiratory symptom, according to the results shown in Table 5.

The smokers reported higher illicit drug use ($p = 0.0271$), whereas cocaine non-use was significant among the nonsmokers ($p = 0.0094$) and former smokers ($p = 0.0114$), as was lower marijuana use among the nonsmokers ($p < 0.0001$). There was higher alcohol consumption among the smokers ($p < 0.0001$) and nonsmokers ($p < 0.0001$). The data are shown in Table 6.

We believe that, because this is a population that has to consume alcohol, given that nightclub owners impose this condition, alcohol consumption was not related only to the smokers but also to the nonsmokers.

DISCUSSION

The prevalence of smoking in our sample of female SWs (71.1%) was much higher than the 10.4% and 8.3% reported, respectively, for the general and the female population of Brazil in 2014.[18] However, it was equivalent to that reported in another study of female SWs (68.6% of smokers, 84.3% of alcohol users, and 42.2% of illicit drug users).[12] We conclude that, among the smokers, the level of nicotine dependence is high and that the majority of them have no intention to quit smoking.

In Brazil, the mean age at first trying a cigarette is 15.9 years and mean cigarette consumption is 14.1 cigarettes per day,[19] findings that corroborate those of the present study. Among our sample of female SWs who smoked, cigarette consumption was slightly higher, 22.3 cigarettes per day. A study conducted in five countries in Europe found a higher mean age at first trying a cigarette, 18.2 years, among women,[20] showing that, currently, there has been a shift in the smoking epidemic from developed to developing countries.

Dyspnea was the most commonly reported respiratory symptom in our study, but it was not associated with the smokers. A study of smokers and nonsmokers also found a higher prevalence of respiratory symptoms

Table 6. Use of illicit drugs, cocaine, marijuana, and alcohol in the study sample (N = 83).

Illicit drug use				
Smoking status	Yes n (%)	No n (%)	Total n (%)	p
Smoker	36 (43.3)	23 (27.7)	59 (71.1)	0.0271
Nonsmoker	6 (7.2)	13 (15.8)	19 (22.9)	0.0515
Former smoker	1 (1.2)	4 (4.8)	5 (6.0)	0.2019
Total	43 (51.7)	40 (48.3)	83 (100.0)	
Cocaine use				
Smoking status	Yes n (%)	No n (%)	Total n (%)	p
Smoker	24 (28.9)	35 (42.2)	59 (71.1)	0.0656
Nonsmoker	5 (6.0)	14 (16.9)	19 (22.9)	0.0094
Former smoker	0	5 (6.0)	5 (6.0)	0.0114
Total	29 (34.9)	54 (65.1)	83 (100.0)	
Marijuana use				
Smoking status	Yes n (%)	No n (%)	Total n (%)	p
Smoker	27 (32.5)	32 (38.6)	59 (71.1)	0.4615
Nonsmoker	2 (2.4)	17 (20.5)	19 (22.9)	< 0.0001
Former smoker	1 (1.2)	4 (4.8)	5 (6.0)	0.2059
Total	30 (36.1)	53 (63.9)	83 (100.0)	
Alcohol use				
Smoking status	Yes n (%)	No n (%)	Total n (%)	p
Smoker	54 (65.1)	5 (6.0)	59 (71.1)	< 0.0001
Former smoker	16 (19.3)	3 (3.6)	19 (22.9)	< 0.0001
Nonsmoker	4 (4.8)	1 (1.2)	5 (6.0)	0.2059
Total	74 (89.2)	9 (10.8)	83 (100.0)	

among the smokers; however, there were no significant differences between the groups regarding dyspnea.[21]

The most commonly consumed cigarette brand among the female SWs (in 41.4%) is produced in Paraguay and is sold illegally; therefore, this cigarette brand is not taxed and has a price far below the market price, being sold for up to R$ 2.50. This can lead to an increase in consumption in this population: low cost and easy access. As a result of the tobacco control policy in Brazil, taxes on cigarettes increased by 116% between 2006 and 2013, and, as a direct consequence, there was a 32% decrease in cigarette sales.[22] Brazil has currently proposed a protocol for tobacco monitoring in the member countries of the Southern Common Market; the idea is to have control over the amount of cigarettes produced and the places where they are sold, in order to combat the Illegal cigarette trade, which has been flourishing.[23]

Women have experienced several withdrawal symptoms, two of which are irritability and increased appetite; other studies have shown that, in addition to increasing the chances of relapse, these symptoms make smoking cessation difficult in women.[24,25]

Studies have also confirmed the influence of family members and friends as a determinant of cigarette smoking initiation, which usually occurs during adolescence; curiosity also appears as a motivator of smoking initiation.[19,24-26]

We found high consumption of alcohol and illicit drugs in our sample of female SWs. Alcohol consumption was higher among the smokers and former smokers, and, regarding illicit drug use (cocaine, crack cocaine, and marijuana), there was significance in these two groups as compared with the nonsmokers; therefore, we can suggest that smoking is associated with illicit drug use.

Smoking is classified as a risk factor for involvement with other drugs and is seen as a predecessor to involvement with illicit drugs, such as marijuana, cocaine, and crack cocaine. In a review of the literature, we found it possible to identify a positive relationship between cigarette smoking and cocaine use. In smokers, the number of cigarettes smoked is greater when under the influence of cocaine, making it essential that smoking cessation treatment be initiated concomitantly with treatment of dependence on other substances.[27,28]

Studies have been inconclusive regarding the association between smoking and alcohol consumption; some quantitative studies have shown a positive association between the two, reporting that alcohol consumers are more likely to smoke cigarettes and to develop dependence on them in the future, whereas other studies have not shown a correlation between the two.[29-31]

We found no significant differences among the three groups of women regarding anxiety, depression, or perceived stress; therefore, being a smoker was not

associated with any of these symptoms. However, we found that anxiety was a prevalent symptom in the majority of the female SWs and that it may be linked to their profession and work environment, since it is not associated only with the smokers. The association of stress, anxiety, and depression with smoking is quite complex; studies have indicated that smoking is a risk factor for anxiety disorders[32] and that the association between smoking and anxiety disorders is stronger than that between smoking and depression; however, it has been hypothesized that these emotional problems arose even prior to cigarette smoking initiation.[33]

Since female SWs are exposed to various risk factors, such as licit and illicit drug use, we conclude that harm reduction is an important strategy to be adopted in this group of women living in a situation of vulnerability. We conceive harm reduction as a late intervention strategy, at the level of tertiary prevention, that requires little effort, because the initial goal is not abstinence from drug use but rather the minimization of its consequences.[34] Harm reduction consists of individualized interventions aimed at providing information, education, and counseling regarding possible risks and harms related to licit and illicit drug use, prioritizing the quality of life of users,[35] such as the study population.

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ORIGINAL ARTICLE

Use of indwelling pleural catheters for the definitive treatment of malignant pleural effusion

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Study carried out in the Departamento de Cirurgia Torácica, Hospital Santa Marcelina and at the Centro de Oncologia, Hospital Alemão Oswaldo Cruz, São Paulo (SP) Brasil.

ABSTRACT

Objective: To evaluate the safety and feasibility of the use of indwelling pleural catheters (IPCs) in patients with malignant pleural effusion (MPE). **Methods:** We prospectively collected data from patients with MPE undergoing IPC placement between January of 2014 and July of 2015. All patients submitted to IPC placement had a life expectancy > 30 days, in accordance with the MPE treatment guidelines established by the British Thoracic Society. The data collected included gender, age, body mass index, primary cancer site, duration of IPC drainage, IPC-related complications, length of hospital stay, pleural effusion recurrence, and occurrence of spontaneous pleurodesis. **Results:** A total of 19 patients underwent IPC placement during the study period. Median overall survival after IPC insertion was 145 days. The median follow-up among the surviving patients was 125 days (range, 53-485 days), and the median time between catheter insertion and removal was 31 days (range, 2-126 days). There were IPC-related complications in 5 patients (26.2%), and spontaneous pleurodesis was achieved in 8 (42.0%). Among those 8 patients, the IPC was removed between days 30 and 126 in 4, and spontaneous pleurodesis occurred within the first 30 days in 4. **Conclusions:** The use of IPCs seems to be feasible and safe in patients with MPE.

Keywords: Pleural effusion, malignant; Survival; Palliative care.

INTRODUCTION

The best way to prevent pleural fluid accumulation in malignant pleural effusion (MPE) has yet to be clarified. The two major procedures available are pleurodesis and the placement of an indwelling pleural catheter (IPC).[1] Various studies, including two randomized trials,[2-5] have demonstrated that those two techniques provide similar benefits, showing reduced length of hospital stay and prevention of new pleural procedures. In addition, the British Thoracic Society recommends the use of IPC for patients with trapped lung.[1] Thus, IPC has been widely used in the United States, Canada, and Europe.[2-5]

Although there have been no reports on the use of IPCs in Brazil, it would increase the definitive treatment options for MPE in the country, reducing the length of hospital stay for some patients, which would have a significant positive impact on the Brazilian Unified Health Care System, as well as providing an option for patients who prefer not to undergo pleurodesis. This is particularly important when we consider that most such patients have a limited life expectancy, and their quality of life can therefore be preserved by keeping them in an outpatient setting. However, the use of IPC implies at-home drainage. It is therefore necessary that patients and caregivers understand the technical guidelines and identify signs of infectious complications. Faced with this challenge, we opted to offer pleurodesis to patients with complete lung reexpansion. The aim of the present study was to evaluate the safety and feasibility of the use of IPC, including only patients with trapped lung.

METHODS

We prospectively collected data from patients with MPE undergoing IPC placement between January of 2014 and July of 2015. The study was approved by the institutional review board, and all patients gave written informed consent.

We defined MPE as the presence of malignant cells in the pleural fluid or of neoplastic pleural infiltration identified by pathological assessment. All patients submitted to IPC placement had symptomatic MPE and trapped lung, and their life expectancy was greater than 30 days, in accordance with the British Thoracic Society guidelines for the treatment of MPE.[1] The life expectancy criterion and patient selection were guided by the Eastern Cooperative Oncology Group scale[3] and defined after a multidisciplinary discussion involving the oncology and the palliative care teams. Patients receiving chemotherapy, inpatients, and outpatients were included in the study. Patients in whom thoracoscopy was the only reasonable approach to making a diagnosis were excluded, as were those with volume on lateral decubitus thoracic ultrasound that was insufficient for safely performing local anesthesia and those with pleural empyema.

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The placement of IPCs followed the routine Seldinger technique,[2] guided by ultrasonography. The first drainage was performed with a vacuum collector and was carried out by the patient and his or her caregivers after the medical staff had trained them. This training and the first drainage were carried out immediately after the procedure in our postoperative unit.

Pleural drainage with a vacuum collector was performed every three days (maximum 1 L/day of drainage). The IPC was removed when the output was less than 250 mL in three consecutive drainages and chest X-rays showed no signs of fluid reaccumulation in the pleural cavity. No sclerosing agent was used in those patients. If an X-ray showed signs of fluid reaccumulation in the pleural cavity, symptomatic patients were submitted to pleural drainage with a small-gauge drain (14 French) and the IPC was removed.

Patient follow-up was carried out during outpatient visits on the seventh postoperative day, and, after that consultation, the following visits were monthly until the removal of IPC or the death of the patient. The collected data included gender, age, body mass index, primary cancer site, duration of IPC drainage, IPC-related complications, length of hospital stay, pleural effusion recurrence, and occurrence of spontaneous pleurodesis (SP).

Recurrence was defined as the need for a new approach: thoracentesis, pleural drainage, or drainage with pleurodesis. We defined SP as the removal of the catheter without the need for further effusion-directed intervention during the lifespan of the patient. IPC-related complications were graded in accordance with the classification of surgical complications devised by Dindo et al.[6]: grade I—minor risk events, not requiring therapy; grade II—need for pharmacological intervention; grade III—need for surgical or radiological intervention; grade IV—life-threatening complication; and grade V—death.

RESULTS

A total of 19 patients underwent IPC placement during the study period. The characteristics of the patients and the catheters are shown in Table 1; a flowchart of the outcomes of the patients in the study is shown in Figure 1. The median overall survival time from IPC insertion was 145 days in our series. The median follow-up time among the surviving patients was 125 days (range, 53-485 days), and the median time between catheter insertion and removal was 31 days (range, 2-126 days).

Of the 19 catheters inserted, 2 were removed by the fourth postoperative day because of pneumothorax and drain displacement, respectively. Of the remaining 17 patients, only 2 (10.5%) presented with recurrence of pleural effusion. One of the patients was submitted to thoracentesis, and another underwent drainage, at 162 days and 76 days after catheter insertion, respectively.

Of the 19 patients, 8 (42%) achieved SP, including the 2 patients in whom the IPC was removed by the fourth postoperative day. Of those 8 patients, 4 underwent catheter removal between days 30 and 126, and 4 achieved SP within the first 30 days. Six of the 8 patients achieving SP had breast cancer. Of the 7 patients with lung cancer, only 1 achieved SP.

There were IPC-related complications in 5 patients (26.2%). Using the classification of surgical complications,[6] we classified the complications as grade II and grade III in 1 and 4 patients, respectively. No major (grades IV or V) complications occurred. One patient had empyema and was treated with antibiotics, the IPC being left in place until the infection had been resolved. There were two cases of ipsilateral pneumothorax related to lung perforation due to the IPC, one of which was treated with oxygen supplementation and negative pressure suction applied to the IPC drainage system. However, the other patient required replacement of the IPC with a pigtail drainage catheter on the second day after IPC insertion. Drain displacement occurred in 2 patients. In one of those two cases, IPC removal and pleural drainage with a small-gauge drain were necessary. In the other case, the displacement occurred at the time when the criteria for IPC removal had been met. There were no mechanical complications, such as IPC obstruction, and none of the IPCs had to be removed because of pain.

DISCUSSION

The increasing use of IPC over the last decade demonstrates the desire of clinicians and patients to use minimally-invasive, palliative techniques in

Table 1. Characteristics of the patients (N = 19) and variables regarding the indwelling pleural catheters used in the study.[a]

Variable	Result
Patient	
Age, years	60 [27-84]
Gender	
Female	14 (73.6)
Male	5 (26.3)
Primary cancer site	
Breast	8 (42.1)
Lung	7 (37.0)
Lymphoma	2 (10.5)
Prostate	1 (5.2)
Sarcoma	1 (5.2)
IPC	
Time for IPC removal, days	31 [2-126]
Spontaneous pleurodesis	6 (31.5)
Complications	
Catheter displacement	2 (10.5)
Pneumothorax	2 (10.5)
Empyema	1 (5.2)

IPC: indwelling pleural catheter. [a]Values expressed as n (%) or median [range].

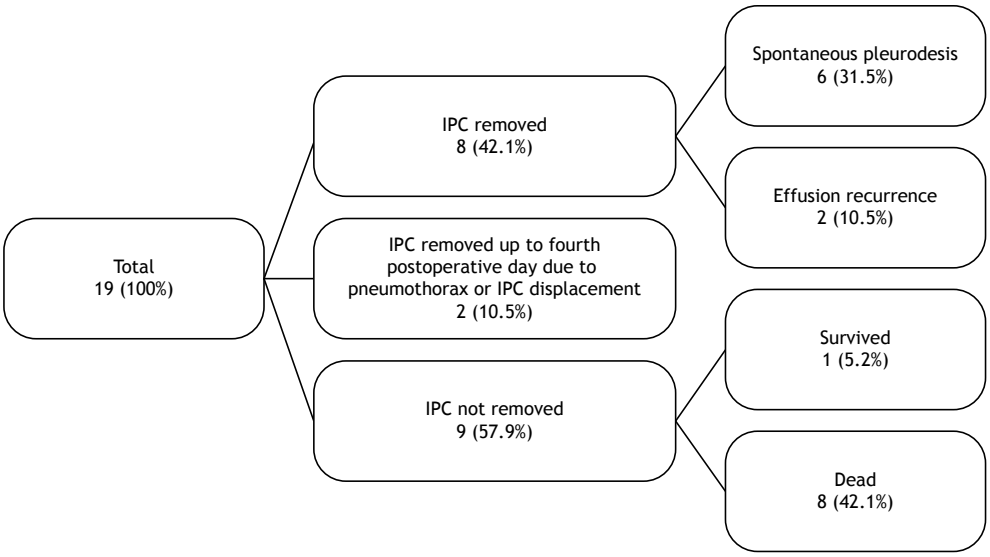

Figure 1. Flowchart of patient outcomes (N = 19). IPC: indwelling pleural catheter.

MPE management. This has also been shown in the literature.[2,3] Current guidelines advocate talc slurry pleurodesis as the first-line therapy for MPE, reserving the use of an IPC as a second-line treatment or for those patients who have incomplete lung reexpansion.[1] However, in 2012, the results of a study suggested that both talc pleurodesis and IPC placement are effective initial treatments for symptom relief in MPE.[3] Therefore, the use of an IPC has been shown to be an alternative that favors home treatment for patients with MPE who prefer not to undergo more invasive procedures, such as pleurodesis. To our knowledge, this is the first report of the definitive MPE treatment with IPC placement in Brazil. Our initial results suggest that, within the context of the Brazilian Unified Health Care System, the use of an IPC can be a safe therapeutic option for the definitive treatment of MPE and, at the same time, can reduce the length of hospital stays.

Effective palliation is one of the most important outcome measures in MPE. Unfortunately, we do not have the data to show the degree of palliation. Nevertheless, of the 17 patients in our sample who did not undergo early drain removal due to complications, 15 (88.3%) did not require new pleural procedures, suggesting a reasonable correlation with symptom control. Four studies also found that few patients submitted to IPC placement required subsequent pleural drainage procedures, with a pooled failure rate of only 8.9%, failure occurring in 21 of the 236 patients treated with IPC placement.[2,3,7,8] However, Davies et al. identified a higher frequency of IPC failure; in a sample of 51 patients, 12 (23%) were readmitted to the hospital in order to repeat drainage or because of drain-related complications, although those patients spent a median of only 1 day (interquartile range, 0-3 days) in the hospital for drainage or drain-related complications.[3]

In the literature, the reported rate of complications related to IPC use varies from 6% to 22%.[9-18] Many such complications are minor (e.g., cellulitis and catheter obstruction). In the present study, the complication rate was 26.2%, all of the complications were treated through simple procedures, and there were no severe complications. Another important observation is that none of the IPCs had to be removed because of pain.

In contrast with the apparently high rate of palliation, the rate of SP was 42% in our series. Our initial result is in agreement with data in the literature; a recent systematic review of the use of IPC in patients with MPE reported a rate of SP of 45.6%,[19] whereas another study reported that that rate was 26%.[20] Regarding predictors of SP, Warren et al.[15] reported that patients with breast or gynecological malignancies had higher rates of SP, whereas Suzuki et al.[20] reported that the type of cancer was not a significant predictor of SP. In our study, patients with breast cancer showed the highest rate of SP (75%). However, because of the small size of our sample, it was not possible to confirm the influence that the primary cancer site or any other variable had on SP.

The present study has some limitations. We did not perform a cost analysis, which is important regarding public health care systems. Penz et al. reported that the use of IPCs becomes less costly when compared with talc pleurodesis for patients with an expected survival of ≤ 14 weeks.[21] In addition, we did not perform an objective quality of life assessment using questionnaires. However, as mentioned above, the degree of palliation seemed appropriate, given that 88.3% of the patients required no new therapeutic procedure for MPE. Finally, although we analyzed a small sample of patients, our true goal was to analyze our initial experience. Based on our results, more robust studies on the use of IPCs should be carried out.

We conclude that the use of IPCs seems to be feasible and safe in patients with MPE.

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Family caregiver burden: the burden of caring for lung cancer patients according to the cancer stage and patient quality of life

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ABSTRACT

Objective: Patients with lung cancer experience different feelings and reactions, based on their family, social, cultural, and religious backgrounds, which are a source of great distress, not only for the patients but also for their family caregivers. This study aimed to evaluate the impact that lung cancer stage and quality of life (QoL) of lung cancer patients have on caregiver burden. **Methods:** This was a prospective cross-sectional study. Consecutive patient-caregiver dyads were selected and asked to complete the Hospital Anxiety and Depression Scale and the Medical Outcomes Study 36-item Short-Form Health Survey (SF-36). Family caregivers also completed the Caregiver Burden Scale. Group-based modeling was used in order to identify patients with early- or advanced-stage cancer (IA to IIIA vs. IIIB to IV) plus non-impaired or impaired QoL (SF-36 total score > 50 vs. ≤ 50). Patient-caregiver dyads were stratified into four groups: early-stage cancer+non-impaired QoL; advanced-stage cancer+non-impaired QoL; early-stage cancer+impaired QoL; and advanced-stage cancer+impaired QoL. **Results:** We included 91 patient-caregiver dyads. The majority of the patients were male and heavy smokers. Family caregivers were younger and predominantly female. The burden, QoL, level of anxiety, and level of depression of caregivers were more affected by the QoL of the patients than by their lung cancer stage. The family caregivers of the patients with impaired QoL showed a higher median burden than did those of the patients with non-impaired QoL, regardless of disease stage. **Conclusions:** Caregiver burden is more affected by patient QoL than by lung cancer stage.

Keywords: Lung neoplasms; Quality of life; Caregivers; Anxiety; Depression; Cost of illness.

INTRODUCTION

Advances in diagnostic and treatment strategies for lung cancer (LC), together with an increasing, aging population have resulted in a shift from impatient to outpatient treatment, underscoring the importance of family caregivers.[1-3] Despite the advances in treatment, patients faced with a diagnosis of LC experience different feelings and reactions, based on their family backgrounds, which are undoubtedly a source of great distress not only for the patient but also for family caregivers.[3]

Family caregivers are usually relatives, partners, or close friends who have a significant personal relationship with the patient and provide a broad range of assistance for the person with a chronic or disabling condition, such as LC.[2] Family caregivers are expected to assist the patients in every aspect of their lives, which could range from helping with basic activities of daily living to providing emotional, social, and financial support.[4,5] In this setting, the burdens of family caregiving may include not only physical tasks but also emotional distress, since caregivers tend to neglect their own needs on behalf of the patient.[6]

Despite the increasing attention given to caregivers and families in the cancer literature, some health professionals still remain unaware of the fact that patients and caregivers have an interdependent relationship, in terms of their quality of life (QoL), and therefore fail to address the needs of caregivers as a part of the therapeutic strategy.[7,8] In addition, much of the current knowledge about the experience of family caregivers derives from clinical impressions rather than from research.

It has been suggested that the burden of family caregivers of cancer patients might vary according to the illness stage and could depend on factors related to the patient condition. Although some studies have addressed QoL and the burden of family caregivers of patients with LC, only a few studies have related those aspects to the perception that patients have of their own health-related QoL.[2,3,6] Therefore, the objective of the present study was to evaluate the impact that LC stage and LC patient QoL have on the family caregiver burden.

METHODS

Subjects and study design

We performed a prospective cross-sectional study in order to identify the features of family caregiver burden.

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Consecutive patient-caregiver dyads were selected from the Oncology Outpatient Clinic at the University Hospital of the *Universidade Federal de São Paulo*, located in the city of São Paulo, Brazil, when they came for their routine evaluation prior to starting treatment. We included only those patient-caregiver dyads in which the patient and the family caregiver both agreed to participate. The study was approved by the local institutional review board, and all participants gave written informed consent.

Eligible patients had a clinical and histological diagnosis of LC and a Mini-Mental State Examination[9] score of 20 or higher. In addition, family caregivers were considered eligible if they were over 18 years of age, had a Mini-Mental State Examination score of 20 or higher,[9] and were regarded by the patient as his or her primary caregiver (the relative most involved with his or her current care).

Cancer stage/QoL grouping

In order to compare the variables of the patients and of their family caregivers, the sample was stratified. For this process, we used the disease stage and the QoL of the patients, the latter being assessed with the Medical Outcomes Study 36-item Short-Form Health Survey (SF-36).[10] Group-based modeling was used in order to identify patients with early- or advanced-stage cancer (IA to IIIA vs. IIIB to IV) plus non-impaired or impaired QoL (an SF-36 total score of > 50 vs. ≤ 50). Therefore, patient-caregiver dyads were stratified into four groups (Figure 1):

- Early-stage cancer plus non-impaired QoL
- Advanced-stage cancer plus non-impaired QoL
- Early-stage cancer plus impaired QoL
- Advanced-stage cancer plus impaired QoL

Data collection and procedures

A structured form was filled out regarding socio-demographic characteristics and the Karnofsky Performance Status (KPS) scale results of the patients. The characteristics and the disease-related variables studied included gender, age (in years), smoking status (never/ever-smoker), histological cancer type (squamous cell, adenocarcinoma, or other), LC stage,[11] and treatment status (yes/no). Characteristics of family caregivers included gender, age (in years), smoking status (never/ever-smoker), educational background, hours/day providing direct care, and relationship with the patient (child, spouse, or other). Patient-caregiver dyads were asked to complete the Hospital Anxiety and Depression Scale (HADS)[10] and the SF-36 in separate locations, so that information and responses would be neither shared nor influenced by the other subject. In addition, family caregivers also completed the Caregiver Burden Scale (CBS).[13]

Psychological distress was assessed by the HADS, which is a 14-item instrument with two dimensions (7 items each) that assesses anxiety and depression symptoms. Each item is scored on a 4-point scale from 0 (not present) to 3 (considerable), adding up to a maximum possible score of 21.[12] The HADS has been validated as a screening instrument for use in Brazil.[14] The probability of subjects experiencing anxiety or depression was established according to predetermined thresholds for each of the dimensions: a score < 8 was considered indicative of an improbable diagnosis; scores between 8 and 11 were considered indicative of a possible diagnosis; and scores > 11 were considered indicative of a highly likely diagnosis of depression, anxiety, or both.[15] For statistical analysis, the scores were transformed into a dichotomous variable: a likely (≥ 8) or an unlikely (< 8) diagnosis of anxiety or depression.

Health-related QoL was assessed by the SF-36, which has previously been translated into Portuguese and validated for use in Brazil.[10] It consists of 11 items with a total of 36 different possible answers, which are grouped into eight main domains: functional capacity, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health.[16] For each dimension, questions are coded, the scores are summed, and the overall score is transformed into a score from 0 (the worst QoL) to 100 points (the best QoL). Although there is no agreement about the optimal cut-off point to use, a review of the individual SF-36 total score accuracy found that the best trade-off between sensitivity and specificity was achieved using 50 as a cut-off point. Therefore, an SF-36 total score ≤ 50 would identify impaired QoL.

The CBS version validated for use in Brazil was applied in order to assess the family caregiver burden associated with the functional and behavioral disability of the patient.[13] It is a self-report 22-item scale with five dimensions: general tension, isolation, disappointment, emotional involvement, and environment. This tool is measured on a 4-point Likert scale that ranges from

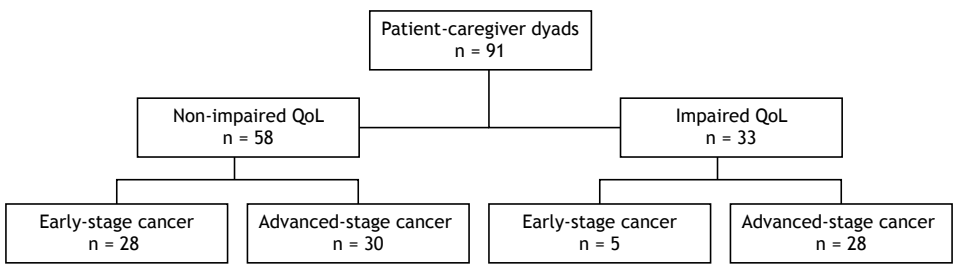

Figure 1. Algorithm for patient-caregiver dyads in the group-based modeling according to disease stage and patient quality of life (QoL) stratification.

1 (never) to 4 (nearly always), on which a high total score represents a high burden. The caregiver burden was stratified into two levels: minimal (from 0 to 20 points in the total score) and considerable (from 21 to 60 points).[17]

Statistical analysis

For the sample size calculation, we took into account the fact that one study reported that 16% of the caregivers for COPD patients had a CBS total score over 26 points.[18] Assuming that 36% of the caregivers for LC patients had similar results in the CBS, 82 patient-caregiver dyads would be required for a type I error of 5% and a power of 80%.

For statistical analyses, we stratified the patient-caregiver dyads into four groups according to LC stage and QoL of the patients. Descriptive analyses were conducted for each group in order to explore the relations among all demographic, psychological, and clinical variables. The chi-square test or Fisher's exact test was used for categorical variables. Continuous variables were analyzed using the Student's t-test, the Kruskal-Wallis test, or the Mann-Whitney test, depending on distribution of the variable.

Significance levels were set at $p < 0.05$, and data were analyzed using the IBM SPSS Statistics software package, version 19 (IBM Corporation, Armonk, NY, USA).

RESULTS

Participant characteristics

A total of 91 patient-caregiver dyads met the inclusion criteria. The majority of the patients (56%) were men, and a great majority (77%) were heavy smokers (median smoking history, 50 pack/years [interquartile range: 30-70]). Although 64% of the patients had locally advanced or metastatic disease, they showed a good level of performance status (median KPS score = 90). The predominant histological type (in 52%) was adenocarcinoma.

Overall, the family caregivers were younger than the patients (47.6 ± 13.2 years vs. 65.2 ± 11.1 years), predominantly female (84%), and never-smokers (61%). The majority (63%) had a high level of education (over 12 years of schooling). According to the family caregivers themselves, nearly half of them were daughters of their patients. The median (interquartile range) of the duration of daily caregiving was 4 h (2-10 h).

Analyses of patient and family caregiver characteristics by group-based modeling

Table 1 shows the characteristics of the patient-caregiver dyads, stratified into four groups: early-stage cancer+non-impaired QoL (n = 28); advanced-stage cancer+non-impaired QoL (n = 30); early-stage cancer+impaired QoL (n = 5); and advanced-stage cancer+impaired QoL (n = 28).

Among the patients, the proportion of men was significantly greater in the early-stage cancer+non-impaired QoL group than in the other groups. The KPS score changed according to QoL and disease stage; it was significantly higher in the early-stage cancer+non-impaired QoL group than in the advanced-stage cancer+impaired QoL group. No differences were found among the four groups of patients regarding level of education, smoking status, histological type, or treatment status. In addition, the time that family caregivers spent providing direct care to the patients was significantly greater in the advanced-stage cancer+impaired QoL group than in the early-stage cancer+non-impaired QoL group. No differences were found among the four groups of family caregivers regarding gender, age, level of education, smoking status, or type of relationship between caregiver and patient.

Among the family caregivers of patients with advanced-stage cancer, those who took care of the patients with impaired QoL had a significantly higher caregiver burden, worse symptoms of anxiety/depression, and worse QoL than did the caregivers of patients with non-impaired QoL (Figure 2). In addition, the caregivers of patients with early-stage cancer+non-impaired QoL had a lower level of caregiver burden than did those of patients with advanced-stage cancer+impaired QoL.

DISCUSSION

In this study, a multi-evaluation strategy was applied in order to measure caregiver burden by investigating QoL, anxiety, and depression from the perspectives of patients and family caregivers at the same time. The caregiver burden, as well as their QoL, anxiety, and depression, was more affected by the QoL of the patients than by the LC stage. In this sense, caregivers of patients with impaired QoL had a greater caregiver burden regardless of the disease stage. Therefore, the QoL of the patient has a significant impact on caregiver burden.[19,20] Another way of interpreting these results is to acknowledge that stratifying patients by cancer stage (early and advanced) is an overly simplistic way of defining the patient-caregiver dyad situations. In the present study, the most important predictor for family caregiver burden was the SF-36 score of the patient. The relationship between the QoL of the patient and the caregiver burden reflects a vicious cycle.[21,22] Although many patients with impaired QoL need uninterrupted daily care, family caregivers are facing issues and tasks for which they have no qualifications or training. In addition, family caregivers have to deal with their own physical limitations and medical problems. This overwhelms the caregiver, who ends up providing insufficient help, which leads to further impairment of the QoL of the patient and increases his or her dependence.[23,24] Furthermore, some authors have reported the presence of more intense anxiety symptoms in the caregivers of patients with advanced-stage cancer.[20,25] Although increased caregiver anxiety tends to be associated with caregiver

Table 1. Characteristics of the patients and caregivers according to the group-based modeling used in the study (disease stage and quality of life of the patients).[a]

Variable	Patient groups				p*
	ES + NI-QoL n = 28	AS + NI-QoL n = 30	ES + I-QoL n = 5	AS + I-QoL n = 28	
Patients					
Male	22 (78)	13 (43)	2 (40)	14 (50)	0.03
Age, years	68.0 ± 8.2	64.2 ± 11.8	62.6 ± 12.9	64.1 ± 12.6	NS
KPS score	91.4 ± 6.5	85.7 ± 7.3	80.0 ± 18.7	80.7 ± 11.2	< 0.001
Under treatment	23 (82)	23 (77)	3 (60)	15 (54)	0.09
Level of education, years					
≤ 9	22 (79)	19 (63)	4 (100)	24 (86)	NS
> 9	6 (21)	11 (37)	0 (0)	4 (14)	
Smoking status					
Never smoker	3 (11)	6 (20)	2 (40)	10 (36)	NS
Ever smoker	25 (89)	24 (80)	3 (60)	18 (64)	
Smoking history, pack-years	50.5 ± 36.3	35.6 ± 33.6	52.8 ± 61.2	29.9 ± 30.5	NS
Histological type					
Squamous cell	10 (36)	10 (33)	2 (40)	8 (28)	NS
Adenocarcinoma	14 (50)	16 (54)	1 (20)	16 (57)	
Others	4 (14)	4 (13)	2 (40)	4 (15)	
	Patient groups				
Caregivers	ES + NI-QoL	AS + NI-QoL	ES + I-QoL	AS + I-QoL	
Female	25 (89)	24 (80)	4 (80)	23 (82)	NS
Age, years	48.8 ± 9.5	45.3 ± 14.7	39.8 ± 10.8	50.4 ± 14.7	NS
Level of education, years					
≤ 9	10 (36)	10 (33)	0 (0)	13 (47)	NS
> 9	18 (64)	20 (67)	5 (100)	15 (53)	
Smoking status					
Never smoker	15 (54)	20 (67)	3 (60)	18 (64)	NS
Ever smoker	13 (46)	10 (33)	2 (40)	10 (36)	
Smoking history, pack-years	7.6 ± 15.4	9.4 ± 17.3	6.2 ± 3.3	4.9 ± 11.0	NS
Relationship between caregiver and patient					
Child	16 (57)	13 (43)	4 (80)	12 (44)	NS
Spouse	10 (36)	10 (33)	0 (0)	8 (28)	
Sibling	2 (7)	7 (24)	1 (20)	8 (28)	
Direct caregiving, h/day					
< 4	24 (86)	14 (47)	3 (60)	12 (43)	0.004
≥ 4	4 (14)	16 (53)	2 (40)	16 (57)	

ES: early-stage (cancer); NI: non-impaired; QoL: quality of life; AS: advanced-stage (cancer); I: impaired; KPS: Karnofsky Performance Status; and NS: not significant. [a]Values expressed in n (%) or mean ± SD. *Chi-square test and one-way ANOVA.

perception of the disease progression,[8] in the present study, the level of caregiver anxiety was not a risk factor for increased caregiver burden. This might be related to the tendency of caregivers to underestimate their perception of anxiety. It is worth noting the culture among Brazilian caregivers; we believe that their major concern is to meet the needs and expectations of the patient at the expense of their own needs.

It is also important to highlight the fact that the proportion of smokers and their smoking history among family caregivers of LC patients are almost 10 times smaller/lower than those observed among the patients in the dyads. This result may be related to the increasingly intensive antismoking policies implemented in the past 10 years in Brazil.

In the present study, nearly half of the family caregivers was taking care of the patients for over 4 h/day (28 h/week), which is higher than the 24.4 h/week reported by the National Alliance for Caregiving.[26] As discussed above, family caregivers reported a greater caregiving burden when the QoL of the patients worsened; conversely, the number of hours/day for providing direct caregiving was greater among caregivers whose patients had advanced-stage cancer, regardless of the QoL of the patient. Cancer treatment is known to be a arduous path, comprising frequent surgical or clinical interventions and multiple hospitalizations, as well as overwhelming physical and emotional stress.[19] Consequently, regardless of how fit and independent the patient is at the time of the

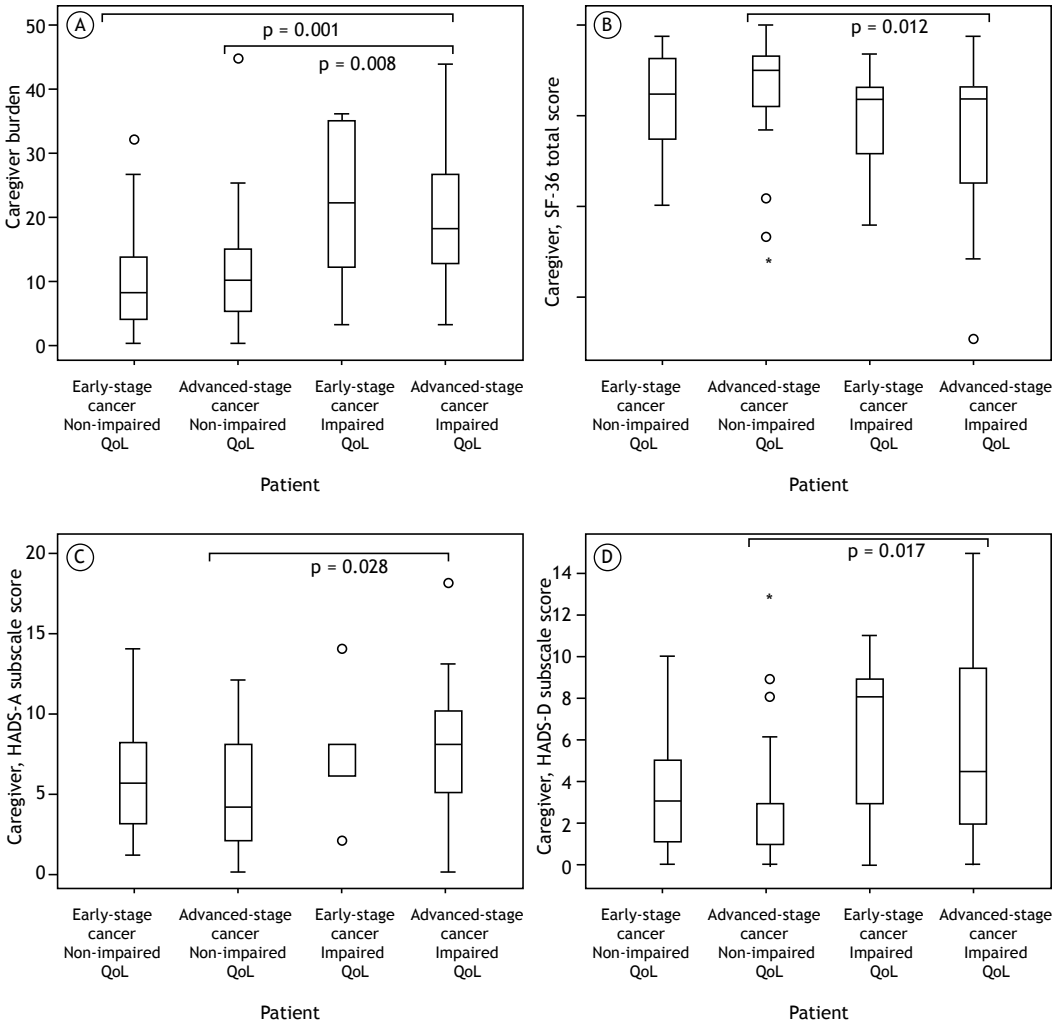

Figure 2. Distribution of caregiver burden (in A), SF-36 total score of caregivers (in B), HADS-A subscale score of caregivers (in C), and HADS-D subscale score of caregivers (in D) according to the group-based modeling adopted in the study. QoL: quality of life; SF-36: Medical Outcomes Study 36-item Short-Form Health Survey; HADS: Hospital Anxiety and Depression Scale; A: anxiety; and D: depression. *Kruskal-Wallis and post-hoc Dunn tests.

diagnosis, he or she will eventually need a caregiver to help him or her throughout the illness trajectory.[21,27,28]

A traditional Brazilian value has been that families take responsibility for the care of their elderly members. Although this situation implies lower costs, supportive policies and multidisciplinary palliative care services do not provide enough support for those families. In addition, the great majority of family caregivers are unprepared to provide care, having little knowledge about the disease and its course.[29]

Some limitations of our study should be noted. First, it was a cross-sectional study, and, consequently, caution should be used when interpreting the results. The study design prevented us from determining the stability of the family caregiver involvement over time. Further studies are needed in order to investigate the long-term effect that patient QoL has on family caregiver burden. Second, although a group of family members might be sharing tasks and making decisions regarding treatment, which might have some implications in caregiver burden, we did not consider multiple caregivers in the present analysis. Despite these limitations, our study has relevance for the clinical perspective that the family caregiver can assume more autonomy instead of being a passive participant in the caregiving process framework. Interaction among physicians, families, and patients, based on effective communication, is crucial in order to improve QoL and reduce the caregiver burden.

Future research regarding practical, behavioral, and self-care skills is encouraged so that patients and caregivers can successfully cope with LC in an easier way. It is crucial that efforts should be developed in order to relieve the caregiver burden by creating a framework to help promote supportive relationships in which the patient and the caregiver will both benefit. Therefore, we intend to design a supportive, personalized multidisciplinary approach in order to strengthen caregiver confidence in giving care, which will increase the quality of caregiving. Because there

is a dynamic relationship between the burden and the satisfaction of caregiving, this framework can provide caregivers with realistic expectations.

In summary, the results in our study suggest that caregiver burden is more affected by the QoL of the patients than by their LC stage.

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Trends in asthma mortality in the 0- to 4-year and 5- to 34-year age groups in Brazil

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ABSTRACT

Objective: To provide an update on trends in asthma mortality in Brazil for two age groups: 0-4 years and 5-34 years. **Methods:** Data on mortality from asthma, as defined in the International Classification of Diseases, were obtained for the 1980-2014 period from the Mortality Database maintained by the Information Technology Department of the Brazilian Unified Health Care System. To analyze time trends in standardized asthma mortality rates, we conducted an ecological time-series study, using regression models for the 0- to 4-year and 5- to 34-year age groups. **Results:** There was a linear trend toward a decrease in asthma mortality in both age groups, whereas there was a third-order polynomial fit in the general population. **Conclusions:** Although asthma mortality showed a consistent, linear decrease in individuals ≤ 34 years of age, the rate of decline was greater in the 0- to 4-year age group. The 5- to 34-year group also showed a linear decline in mortality, and the rate of that decline increased after the year 2004, when treatment with inhaled corticosteroids became more widely available. The linear decrease in asthma mortality found in both age groups contrasts with the nonlinear trend observed in the general population of Brazil. The introduction of inhaled corticosteroid use through public policies to control asthma coincided with a significant decrease in asthma mortality rates in both subsets of individuals over 5 years of age. The causes of this decline in asthma-related mortality in younger age groups continue to constitute a matter of debate.

Keywords: Asthma/epidemiology; Asthma/mortality; Asthma/drug therapy.

INTRODUCTION

Asthma is a chronic inflammatory disease characterized by lower airway hyperresponsiveness and variable airflow limitation that are reversible either spontaneously or with treatment. The typical clinical features of asthma include recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning.[1]

According to the Brazilian Thoracic Association Guidelines for Asthma Management,[2] there were 160,000 hospital admissions due to asthma exacerbations in 2011. The guidelines also state that asthma is the fourth leading cause of hospital admissions via the Brazilian Unified Health Care System as a whole, as well as being the third leading cause of hospital admissions among children and young adults.[2]

Although asthma-related deaths are relatively rare, they are considered to be of great importance because they are, in most cases, preventable through early diagnosis and appropriate treatment. According to the Global Initiative for Asthma,[1] appropriate asthma treatment can retard lung inflammation and the subsequent tissue damage, thereby decreasing the frequency and intensity of asthma attacks.[1]

Increases in asthma morbidity and mortality have frequently been reported in most industrialized countries and in Brazil, primarily during the 1980s and 1990s.[3-6] The Asthma Insights and Reality in Latin America survey showed that the asthma morbidity rate is high throughout Latin America.[7] The survey also showed that the vast majority of patients had not received an appropriate diagnosis, were not given appropriate therapy, were not adequately monitored, were failing to achieve the goals for asthma management set forth in international asthma guidelines, and were at risk for severe asthma attacks.[7]

Although the causes of the reported increase in the asthma burden are still largely unknown, the most relevant aspects are environmental, genetic, and behavioral factors, either alone or in combination.[8-10] Recent studies have demonstrated that other factors could influence asthma mortality, such factors including the widespread use of anti-inflammatory asthma drugs, influenza vaccination campaigns, and broader social inclusion in the health care system, together with other initiatives, all of which could rapidly change the trends in asthma mortality. In a recent meta-analysis of asthma-related deaths, Wijesinghe et al.[11] stressed the need to update the data and maintain surveillance on international asthma mortality trends, especially for the 5- to 34-year age group, because death certificate information (regarding the cause of death) is considered more accurate in that group.[11] Despite the increased difficulty in making an accurate diagnosis in

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children under 5 years of age, asthma-related deaths among such children have been included in analyses because of the reported increase in the prevalence of asthma and the historical importance of this age group to the overall rates of asthma morbidity and mortality.[12,13] Therefore, the aim of this study was to provide an update on asthma mortality trends in Brazil for the 0- to 4-year and 5- to 34-year age groups between 1980 and 2014.

METHODS

Study design

This was an ecological time-series study that analyzed the trends in mortality from asthma. Crude and age-adjusted asthma mortality rates were calculated.

Data collection

Death certificates were obtained from the Mortality Database maintained by the Information Technology Department of the Brazilian Unified Health Care System (http://www.datasus.gov.br), filtered for asthma listed as the underlying cause of death in the 1980-2014 period. This database is composed of death certificates, organized on the basis of the codes established in the International Classification of Diseases, 9th and 10th revisions (ICD-9 and ICD-10, respectively). To obtain the total number of deaths attributed to asthma, we used the ICD-9 code 493 (asthma) for the 1980-1995 period, whereas we used the ICD-10 codes J45 (asthma) and J46 (status asthmaticus; i.e., acute severe asthma) for the 1996-2014 period. Initially, we calculated asthma mortality rates for the general population, after which we calculated those rates for two specific age groups: 0-4 years and 5-34 years.

Asthma mortality rates

Asthma mortality rates for the 1980-2014 period were calculated from annual demographic data and population estimates obtained from the Brazilian Institute of Geography and Statistics. We calculated the crude asthma mortality rates (per 100,000 population) and the age-adjusted asthma mortality rates.

Statistical analysis

In the modeling process, the dependent variable (Y) was the polynomial coefficient for the asthma mortality rate and the independent variable (X) was the calendar year. The coefficient of determination (R^2) was used as a measure of the accuracy of the models. The models were tested for linear fitness ($Y = \beta0 + \beta1X$) quadratic fitness ($Y = \beta0 + \beta1X + \beta2X^2$), cubic fitness ($Y = \beta0 + \beta1X + \beta2X^2 + \beta3X^3$) and exponential fitness ($Y = e^{\beta0 + \beta1X}$). The statistical analysis was performed with the IBM SPSS Statistics software package, version 19.0 (IBM Corporation, Armonk, NY, USA). Values of $p < 0.05$ were considered statistically significant. In the models, β_0 was the mean annual rate, β_1 was the coefficient of linear effect (speed), and β_2 was the coefficient of quadratic effect (acceleration).

RESULTS

Descriptive analysis

In the general population of Brazil, the absolute number of asthma-related deaths dropped from 2,286 in 1980 to 2,096 in 2014. The crude asthma mortality rate dropped from 1.92 to 1.03 deaths per 100,000 population, corresponding to a 46.2% reduction, between 1980 and 2014 (Tables 1 and 2).

Death certificate data showed that the number of asthma-related deaths among individuals ≤ 34 years of age decreased by 67% over the period studied, dropping from 803 (35.1% of all asthma-related deaths) in 1980 to 262 (12.5% of all asthma-related deaths) in 2014 (Table 1). Asthma-related deaths in the 0- to 4-year age group accounted for 26.1% of all such deaths in 1980, a figure that decreased to 3.8% in 2014. In that same age group, the age-adjusted asthma mortality rate decreased by 85.2% over the study period, from 3.63/100,000 population in 1980 to 0.54/100,000 population in 2014 (Table 2). There was less variation in the absolute number of deaths and its representativeness in the 5- to 34-year age group than in the 0- to 4-year age group. In the former group, the number of asthma-related deaths decreased from 207 (9.1% of all such deaths) in 1980 to 182 (8.7% of all such deaths) in 2014. It is of note that the age-adjusted asthma mortality rate for the 5- to 34-year age group decreased by 81.3% over the study period—from 0.95/100,000 population in 1980 to 0.18/100,000 population in 2014 (Tables 1 and 2).

Trend analysis

The curve estimation model best representing the age-adjusted trends in asthma mortality for the 0- to 4-year and 5- to 34-year age groups showed a linear and constant trend toward a decrease during the period analyzed. The general mortality trend in Brazil (crude asthma mortality rate) showed a polynomial fit during the period analyzed, an initial decrease being followed by an increase that was then followed by another decrease (Figure 1).

In the 0- to 4-year age group, there was a constant downward trend, with a mean annual decrease (β_1) of 0.091 deaths/100,000 population and an adjusted R^2 of 0.953. In the 5- to 34-year age group, there was a mean annual decrease of 0.019 deaths/100,000 population and an adjusted R^2 of 0.866. Despite differences concerning the speed of the decline, similar trends were observed in the two age groups evaluated (Table 3).

After 2004, governmental asthma control policies increased the availability of inhaled corticosteroids in Brazil, thus reversing the annual trend in overall asthma mortality rates, which shifted from an increase of 0.018 deaths/100,000 population before 2004 to a decrease of 0.05 deaths/100,000 population after 2004. A similar shift was observed in the 5- to 34-year age group, in which there was a linear, downward polynomial fit, the annual asthma mortality rates decreasing by

Table 1. Asthma-related deaths, by age group, in Brazil—1980-2014.

Year of death	0-4 years (% total)	5-34 years (% total)	0-34 years (% total)	Total asthma-related deaths in Brazil
1980	596 (26.07)	207 (9.06)	803 (35.13)	2286
1981	529 (25.84)	194 (9.48)	723 (35.32)	2047
1982	591 (27.72)	200 (9.38)	791 (37.10)	2132
1983	556 (25.35)	202 (9.21)	758 (34.56)	2193
1984	502 (25.23)	215 (10.80)	717 (36.03)	1990
1985	466 (24.60)	193 (10.19)	659 (34.79)	1894
1986	406 (20.38)	186 (9.34)	592 (29.72)	1992
1987	380 (21.75)	196 (11.22)	576 (32.97)	1747
1988	402 (21.28)	174 (9.21)	576 (30.49)	1889
1989	364 (19.69)	226 (12.22)	590 (31.91)	1849
1990	391 (19.54)	193 (9.65)	584 (29.19)	2001
1991	305 (17.99)	153 (9.03)	458 (27.02)	1695
1992	354 (17.49)	207 (10.23)	561 (27.72)	2024
1993	309 (13.89)	211 (9.48)	520 (23.37)	2225
1994	331 (14.45)	246 (10.74)	577 (25.19)	2291
1995	330 (13.49)	251 (10.26)	581(23.74)	2447
1996	255 (10.17)	278 (11.08)	533 (21.25)	2508
1997	288 (10.78)	278 (10.41)	566 (21.19)	2671
1998	259 (9.51)	254 (9.33)	504 (18.51)	2723
1999	236 (8.66)	289 (10.61)	525 (19.27)	2725
2000	239 (9.20)	224 (8.62)	463 (17.82)	2598
2001	226 (8.87)	225 (8.83)	451 (17.70)	2548
2002	220 (9.14)	220 (9.14)	440 (18.27)	2408
2003	225 (9.05)	212 (8.53)	437 (17.59)	2485
2004	160 (6.25)	212 (8.29)	372 (14.54)	2558
2005	193 (7.41)	250 (9.60)	443 (17.02)	2603
2006	191 (6.14)	263 (8.45)	454 (14.59)	3111
2007	165 (5.77)	231 (8.07)	396 (13.84)	2862
2008	121 (4.49)	223 (8.27)	344 (12.76)	2696
2009	123 (4.83)	203 (7.98)	326 (12.81)	2544
2010	106 (4.03)	234 (8.89)	340 (12.92)	2632
2011	77 (3.15)	178 (7.28)	256 (10.47)	2445
2012	97 (4.12)	201 (8.53)	298 (12.66)	2354
2013	79 (3.31)	216 (9.05)	295 (12.35)	2387
2014	80 (3.82)	182 (8.68)	262 (12.5)	2096

0.018 deaths/100,000 population before 2004 and by 0.046 deaths/100,000 population thereafter. After the introduction of treatment with inhaled corticosteroids (in 2004), there was an uptick in the observed downward trend for asthma mortality rates in the 0- to 4-year age group, the mean annual decline (β_1) being 0.092 deaths/100,000 population before 2004 and 0.074 deaths/100,000 population thereafter. It is of note that, when the post-2004 trends in all age groups were analyzed separately, age-adjusted and crude asthma mortality coefficients both showed un upward shift after 2012 or 2013 (Table 3).

DISCUSSION

This article demonstrates that, in Brazil, there was a linear decline in age-adjusted asthma mortality coefficients from 1980 to 2014 in the 0- to 4-year and 5- to 34-year age groups in Brazil, in contrast with the third-order polynomial fits (decreasing, increasing, and again decreasing) for the crude asthma mortality rates during the period studied. The reduction in asthma mortality coefficients was more prominent in the 0- to 4-year age group than in the 5- to 34-year age group, as was the decrease in the proportional representation in relation to the overall number of asthma-related deaths during the period analyzed. In the former group, we observed no significant change in mortality trends after 2004 (when treatment with inhaled corticosteroids became more widely available), whereas there was a marked decrease in asthma mortality rates after 2004 in the 5- to 34-year age group, as well as in older age groups.

Some potential limitations to the accuracy of population-based studies on asthma mortality should be considered. First of all, when the possibility that asthma

Table 2. Age-adjusted and crude asthma mortality rates, by age group, in Brazil—1980-2014.

Year	0 to 4 years (age-adjusted)	5 to 34 years (age-adjusted)	All age groups (crude)
1980	3.6279	0.9536	1.9207
1981	3.2371	0.9042	1.6895
1982	3.6125	0.9027	1.7224
1983	3.3948	0.8709	1.7349
1984	3.0616	0.915	1.5423
1985	2.8389	0.797	1.4387
1986	2.4708	0.7487	1.484
1987	2.3101	0.7826	1.2772
1988	2.4413	0.6684	1.3562
1989	2.2083	0.8629	1.3047
1990	2.3697	0.7231	1.3887
1991	1.8461	0.5544	1.1544
1992	2.1958	0.7387	1.3612
1993	1.8182	0.7576	1.468
1994	1.9196	0.8352	1.4903
1995	1.8876	0.873	1.5723
1996	1.6321	0.6402	1.5967
1997	1.8122	0.6101	1.6731
1998	1.6075	0.5256	1.683
1999	1.4441	0.6326	1.6621
2000	1.4594	0.4692	1.53
2001	1.3583	0.4736	1.478
2002	1.3044	0.4357	1.3788
2003	1.3164	0.4159	1.4049
2004	0.9238	0.4075	1.4281
2005	1.0823	0.4842	1.4132
2006	1.0556	0.4614	1.6656
2007	0.9974	0.4673	1.5116
2008	0.7542	0.4661	1.4218
2009	0.784	0.4149	1.3285
2010	0.7683	0.2358	1.3797
2011	0.4939	0.1736	1.2709
2012	0.6313	0.1961	1.2135
2013	0.5216	0.2110	1.1852
2014	0.5355	0.1783	1.0335
Delta (1980 vs. 2014)	−85.2%	−81.3%	−46.2%

was a secondary diagnosis has been excluded, especially in cases in which nonspecific respiratory failure was listed as the underlying cause of death, cases in which death could have been attributed to asthma exacerbation can be lost. Goldacre et al.[14] suggested that, in population-based studies, half of all asthma-related deaths are missed when only the underlying cause of death is considered. Underreporting constitutes another possible information bias, especially if mortality statistics depend on a deficient hospital-based health care system. In addition, there are possible diagnostic limitations and imprecise data employed when the death certificate is filled out. Furthermore, the change from ICD-9 codes to ICD-10 codes (in 1996) could have resulted in misinterpretations.

In the 0- to 4-year and 5- to 34-year age groups, there was a constant decline in asthma mortality rates over the 30-year period analyzed, whereas the crude asthma mortality rates showed a nonlinear trend. The younger group showed an 85.2% decrease in the age-adjusted asthma mortality rate, with a steady drop in its representativeness—from 26.07% to 3.82% of the overall absolute number of asthma-related deaths—during the period studied. The annual decrease of 0.0917 deaths/100,000 population in that age group (comprising 11.2 million individuals in Brazil) resulted in a significant decrease of more than 12 asthma-related deaths per year.

Despite the importance of the 0- to 4-year age group, there are certain challenges intrinsic to the diagnosis of asthma in very young children. Those challenges include making the differential diagnosis with diseases that have a similar clinical presentation (breathlessness and wheezing), such as bronchiolitis obliterans, foreign body aspiration, chest tumors, and malformations, as well as the difficulties in performing diagnostic procedures, such as spirometry tests with bronchodilators, in very young children.[15]

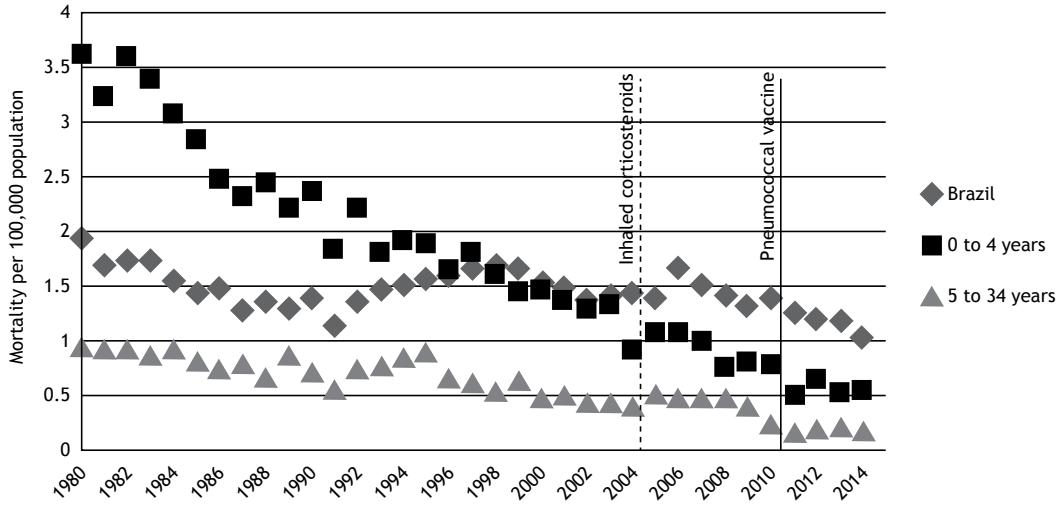

Figure 1. Crude and age-adjusted asthma mortality rates and trends in individuals in the 0- to 4-year and 5- to 34-year age groups in Brazil, from 1980 to 2014.

Although there was an 81.3% decrease in asthma mortality rates in the 5- to 34-year age group, there were no significant differences concerning the proportional contribution of that age group to the total number of asthma-related deaths in Brazil, which ranged from 9.06% to 8.68% of the absolute number of asthma-related deaths from 1980 to 2014. The annual decrease of 0.026 deaths/100,000 population in that age group (comprising 100.1 million individuals in Brazil) resulted in a mean decrease of 26 asthma-related deaths per year. It is noteworthy that, in the 5- to 34-year age group, the annual asthma mortality rate decreased by 0.018 deaths/100,000 population in 1980 and by 0.046 deaths/100,000 population in 2004. That was a linear decline that more than doubled the number of lives spared. Although that decline was less pronounced than the decline observed in the 0- to 4-year age group, it was equally significant in terms of the absolute numbers. Data obtained for the 5- to 34-year age group are of particular interest because of the better chances of obtaining a correct asthma diagnosis and preventing triggering events in individuals within that population, as well as because that age group accounted for most of the increase in asthma mortality rates seen during the 1980s.[16]

Recent studies have demonstrated stable or decreasing asthma mortality rates in most developed countries.[17] Prietsch et al.[18] recently reported a decrease in asthma mortality among pediatric patients (≤ 19 years of age) in Brazil as a whole, as was subsequently reported for the city of Rio de Janeiro.[19] Another recent study reported that asthma mortality rates have decreased in Brazil since the 1990s.[20]

We find it interesting that the linear downward trend observed in the present study did not apply to the crude asthma mortality rates. Rather, the crude asthma mortality rates showed a trend with three distinct phases: an initial downward trend from 1980 to 1989; an upward trend from 1990 to 2000; and another downward trend from 2001 to 2014. This behavior contrasts with the findings of a meta-analysis of asthma mortality trends in 20 countries, which, despite some variability across studies, showed a mean increase of 38% in asthma mortality rates from the mid-1970s to the mid-1980s, followed by a mean decrease of 63% from the end of the 1980s to the year 2005.[11] Although more data are needed, the crude asthma mortality rates apparently showed a major shift in trend in those countries, from an annual increase of 0.022 deaths/100,000 population from 1980 to 2004 to an annual decrease of 0.05 deaths/100,000 population thereafter. More recent asthma mortality studies have shown a decrease in mortality rates in various countries, including Serbia, Puerto Rico, Scotland, and the United States.[21-24] Therefore, we could expect a similar reduction in crude asthma mortality rates to occur in Brazil after 2004, the year that inhaled corticosteroids became available in public health care systems.

Although a correlation between the reduction in asthma mortality and the widespread use of inhaled corticosteroids to control airway inflammation has been proposed by some authors,[25-27] no specific studies have been conducted in order to investigate that correlation. In Brazil, the Unified Health Care System has been providing inhaled corticosteroids for patients with persistent asthma since 2004, when the Primary Health Care Guidelines for Asthma and Rhinitis were published, with the objective of broadening the scope of the health care provided to such patients.[28] That promoted the new downward trend in asthma mortality among individuals over 5 years of age. In addition to asthma control drugs, the inclusion of the pneumococcal vaccine in the Brazilian Immunization Program might also have played an important role in inducing the downward trend in asthma mortality, although it only recently came to be recommended for use in children under 2 years of age and there are therefore as yet no consistent data to be analyzed.

Table 3. Trend analysis of crude and age-adjusted asthma mortality rates, by age group, in Brazil—1980-2014.

Asthma mortality[a]	Mean beta coefficient (β_0)	Mean annual increase (β_1)	Speed (β_2)	Acceleration (β_3)	p-value (F)	Adjusted R^2	Trend
All age groups	1.483	0.018028	−0.000262	−0.000151	< 0.001	0.639	Third-order polynomial fit Decreasing from 1980 to 1989; increasing from 1990 to 2001; and decreasing from 2002 to 2014
0- to 4-year	1.717034	−0.091762			< 0.001	0.953	Linear decline
5- to 34-year	0.593431	−0.021520			< 0.001	0.866	Linear decline
All age groups before 2004[b]	1.497	0.022395	−0.001001	0.000228	< 0.001	0.624	Third-order polynomial fit Decreasing from 1980 to 1987; increasing from 1988 to 1998; and decreasing from 1999 to 2004
0- to 4-year before 2004	1.935	−0.092283			< 0.001	0.951	Linear decline
5- to 34-year before 2004	0.654108	−0.018479			< 0.001	0.728	Linear decline
All age groups after 2004	1.328294	−0.050429	0.005388		0.021	0.526	Second-order polynomial fit Decreasing from 2005 to 2013 and increasing thereafter
0- to 4-year after 2004	0.724580	−0.074360	0.009151		< 0.001	0.850	Second-order polynomial fit Decreasing from 2005 to 2012 and increasing thereafter
5- to 34-year after 2004	0.310778	−0.043610	0.005037		0.003	0.711	Second-order polynomial fit Decreasing from 2005 to 2012 and increasing thereafter

[a]Values expressed as deaths/100,000 population. [b]When treatment with inhaled corticosteroids became widely available.

Other factors might contribute to the decrease in asthma mortality, such factors including health and well-being improvements achieved through policies of inclusion in public health programs, such as the Family Health Program, resulting in a successful reduction in the number of ambulatory care-sensitive hospitalizations for a group of diseases, including asthma, for which access to effective primary care can reduce the likelihood of hospitalization,[29] as well as asthma-specific programs, which promote the identification of patients with severe asthma and efficient asthma control, with the expected reduction in the rates of mortality either directly or indirectly associated with asthma.[30] Recent studies have demonstrated that, in regions of Brazil where there is considerable social inequality, asthma mortality is correlated with poor access to health systems and asthma programs.[31] Unfortunately, data on reliable social indicators, which could further understanding of the effects that such indicators have on asthma in Brazil, are scarce and conflicting.

Within the population studied here, asthma mortality trends should follow the prevalence of severe asthma. In a study comparing phases one and three of the International Study of Asthma and Allergies in Childhood,[32] the prevalence of severe asthma symptoms in the pediatric population was found to be stable after a 7-year follow-up period. Given that the prevalence of severe asthma remained unchanged, that finding

suggests that other factors are involved. In addition to the incorporation of inhaled corticosteroids into public policies to control asthma in Brazil, factors that might play roles include increased diagnostic accuracy, expanded vaccination programs, and improvements in the reporting of deaths. The contribution of each of those factors is difficult to assess and, despite obvious advances, asthma control in Brazil continues to be insufficient.

Further studies, evaluating the correlation between asthma mortality and health inclusion programs, as well as between asthma mortality and specific socioeconomic indicators, could help explain the causes of the differences observed in the trends. Case-control studies of asthma deaths and near-deaths can provide additional insights into the risk factors associated with severe asthma attacks. In conclusion, we have shown that there has been a consistent decrease in asthma mortality among individuals 0-34 years of age in Brazil, and that that decrease has been more pronounced in the subset of individuals 5-34 years of age since the introduction of public policies that made treatment with inhaled corticosteroids more widely available. However, further studies are needed in order to identify the causes of this decrease, within this age group, as well as within age groups in which asthma mortality rates are higher, given that the crude asthma mortality rates continue to oscillate.

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Diaphragmatic mobility: relationship with lung function, respiratory muscle strength, dyspnea, and physical activity in daily life in patients with COPD

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ABSTRACT

Objective: To evaluate diaphragmatic mobility in relation to lung function, respiratory muscle strength, dyspnea, and physical activity in daily life (PADL) in patients with COPD. **Methods:** We included 25 patients with COPD, classified according to the Global Initiative for Chronic Obstructive Lung Disease criteria, and 25 healthy individuals. For all of the participants, the following were **evaluated:** anthropometric variables, spirometric parameters, respiratory muscle strength, diaphragmatic mobility (by X-ray), PADL, and the perception of dyspnea. **Results:** In the COPD group, diaphragmatic mobility was found to correlate with lung function variables, inspiratory muscle strength, and the perception of dyspnea, whereas it did not correlate with expiratory muscle strength or PADL. **Conclusions:** In patients with COPD, diaphragmatic mobility seems to be associated with airway obstruction and lung hyperinflation, as well as with ventilatory capacity and the perception of dyspnea, although not with PADL.

Keywords: Pulmonary disease, chronic obstructive; Diaphragm; Spirometry; Dyspnea; Maximal respiratory pressures.

INTRODUCTION

Several studies have shown a decrease in diaphragmatic mobility (DM) in patients with COPD.[1-4] However, COPD also has significant extrapulmonary effects,[5] which result in systemic inflammation, loss of muscle mass,[6,7] malnutrition, depression,[8] physical deconditioning,[9] and, consequently, reduced health status.[10]

Despite significant systemic involvement in patients with COPD, few studies have investigated the relationship between DM and the systemic changes caused by COPD. However, the relationship of DM with the six-minute walk distance,[2,11] dyspnea,[2] and mortality[12] has previously been described.

Several studies have shown a relationship between DM and lung function changes.[3,11,13] Recently, Davachi et al.[11] found that DM was greater in patients classified as having mild COPD than in those classified as having very severe COPD. They also found that DM was related to FVC and slow VC (SVC). It has previously been shown that DM is associated with air trapping,[3,14,15] maximal voluntary ventilation (MVV),[3] and lung hyperinflation.[1] These results support the hypothesis that decreased DM is related to lung disease severity.

To date, no studies have investigated the relationship between DM and physical activity in daily life (PADL), and few have related DM to dyspnea and lung function.[2,3] Therefore, the primary objective of the present study was to evaluate DM in relation to lung function, dyspnea, and PADL in patients with COPD. A secondary objective was to compare COPD patients and healthy individuals in terms of lung function, respiratory muscle strength, and DM.

METHODS

This was a quantitative descriptive cross-sectional study. It was approved by the local human research ethics committee (Protocol no. CAEE 08871312.7.0000.0118). All participants gave written informed consent. The study sample consisted of 25 patients with COPD (14 males and 11 females) and 25 healthy individuals (5 males and 20 females). We included patients diagnosed with COPD in accordance with the 2015 Global Initiative for Chronic Obstructive Lung Disease criteria[9] and meeting the following criteria: 1) having no associated pulmonary, cardiovascular, or musculoskeletal diseases; 2) having participated in no training programs in the 6 months prior to the study; 3) requiring no oxygen therapy supplementation; and 4) being a nonsmoker. The criteria for inclusion of healthy individuals in the present study were as follows: 1) having normal pulmonary function test results (FEV_1/FVC ≥ 0.7; FEV_1 ≥ 80% of predicted; and FVC ≥ 80% of predicted); 2) being a nonsmoker; and 3) having no cardiorespiratory, hepatic, neurological, or oncologic diseases. The exclusion criteria were as follows: 1) being unable to perform any of the required tests (being unable to understand the instructions or being uncooperative);

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2) experiencing COPD exacerbation during the study period; 3) having cardiorespiratory or musculoskeletal complications during the tests; and 4) having a body mass index (BMI) > 30 kg/m^2 (i.e., being obese).

Spirometry and respiratory muscle strength

Spirometry was performed with a previously calibrated portable digital spirometer (EasyOne®; ndd Medical Technologies, Andover, MA, USA), in accordance with the methods and criteria recommended by the American Thoracic Society and the European Respiratory Society.[16] The following parameters were measured: FVC; FEV_1; FEV_1/FVC before and 15 min after inhalation of a bronchodilator (albuterol, 400 µg); and inspiratory capacity (IC). A minimum of three acceptable maneuvers and two reproducible maneuvers were performed; for IC, however, the average of three maneuvers was used, as reported by Miller et al.[16] All spirometric variables are expressed as absolute values and as a percentage of reference values, in accordance with Pereira et al.[17]

A digital manometer (MVD500®; Globalmed, Porto Alegre, Brazil) attached to a mouthpiece with an air outlet of 1 mm in diameter was used in order to measure inspiratory and expiratory muscle strength. MIP and MEP were measured as indicators of inspiratory and expiratory muscle strength, respectively, in accordance with the Brazilian Thoracic Association guidelines.[18] MIP was measured after a maximal expiratory maneuver (near RV), whereas MEP was measured after a maximal inspiratory maneuver (near TLC). A minimum of three acceptable maneuvers and two reproducible maneuvers were performed. The values of MIP and MEP are expressed as absolute values and as a percentage of reference values, in accordance with Neder et al.[19] The average of the reproducible maneuvers was used in the present study.

DM

Patients initially underwent familiarization with diaphragmatic breathing for diaphragmatic proprioception and maximal evaluation of diaphragm amplitude during radiographic examination. Patients were asked to perform two series of ten repetitions of diaphragmatic breathing, proprioceptive stimulation being provided by placing their hands on their chest and abdomen and verbal encouragement being provided in order to enable patients to direct the air toward the lung bases, in accordance with Leal.[20]

After having become familiar with diaphragmatic breathing, patients performed three SVC maneuvers using a Wright spirometer (Ferraris Medical Ltd., Hertford, England). SVC maneuvers were performed from TLC to RV and from RV to TLC. The highest value was recorded for comparison with the value obtained during the evaluation of DM, in order to determine whether patient respiratory effort was the same before and during DM evaluation.

After having become familiar with the diaphragm and having performed all SVC maneuvers, patients underwent DM evaluation by anteroposterior chest X-rays, which were taken with patients lying supine on a fluoroscopy table. A radiopaque ruler was placed longitudinally under the trunk in the craniocaudal direction, near the thoracoabdominal junction, for subsequent correction of the magnification caused by the divergence of the X-rays. The same film was used for all examinations, which were performed during a maximal inspiratory maneuver and a maximal expiratory maneuver.

DM was measured by the method of Saltiel et al.[21]: a straight line was drawn from the highest point of the hemidiaphragm during exhalation to the hemidiaphragm during inhalation with the use of a 150-mm digital caliper (Messen; Sensor Technology Co., Guangdong, China; Figure 1).

Dyspnea

Dyspnea was measured with the modified Medical Research Council dyspnea scale,[22] the degree of dyspnea ranging from 0 (no dyspnea) to 4 (very severe dyspnea). Patients were instructed to select the number that best represented their perception of dyspnea.

PADL

PADL was evaluated with a triaxial accelerometer (DynaPort activity monitor; McRoberts, The Hague, the Netherlands), which is a small, lightweight device worn on a belt around the waist. It can distinguish among activities such as sitting, reclining, and walking, and it measures the time spent in each activity.[23] Patients were monitored 12 h per day for two consecutive days, patient monitoring beginning immediately after waking. Patients were subsequently classified as active (on the basis of the time spent walking) or sedentary (on the basis of the time spent sitting or lying down), the average of the two days being used for analysis. Patients were instructed on how to position the device and received a manual with clear instructions and explanatory illustrations. In addition, they were asked not to change their daily activities while wearing the device.

Sample size calculation

The power of the sample, which consisted of 25 patients, was calculated post hoc with the free statistical software program G*Power, version 3.1.9.2.

Statistics

All statistical analyses were performed with the IBM SPSS Statistics software package, version 20.0 (IBM Corporation, Armonk, NY, USA), descriptive (mean and standard deviation) and inferential statistics being used. Data normality was verified with the Shapiro-Wilk test. Either a parametric test or a nonparametric test was used depending on the data distribution. The independent sample t-test and the Mann-Whitney U test were used in order to determine the difference between the two groups. In order to evaluate the correlation of DM with BMI, FEV_1/FVC, FEV_1, FVC, IC, MVV, MIP, MEP, perception

of dyspnea, and PADL, Pearson's and Spearman's correlation coefficients were used for parametric and nonparametric variables, respectively. The magnitude of the correlations was described in accordance with Dancey and Reidy,[24] values of r = 0.10-0.39 indicating a weak correlation, value of r = 0.40-0.69 indicating a moderate correlation, and values of r = 0.70-1.00 indicating a strong correlation. The level of significance was set at 5% ($p < 0.05$) for all tests.

RESULTS

A total of 25 COPD patients and 25 healthy individuals who did not differ in terms of age, weight, or respiratory muscle strength participated in the present study. Although the individuals in the control group were classified as being overweight and those in the COPD group were classified as being normal weight,[25] there was no statistically significant difference between the two groups regarding the BMI. There were differences between the two groups regarding height, FEV_1/FVC, FEV_1, FVC, and DM. The results for the two groups are presented in Table 1.

The coefficients of determination for DM and the study variables in the COPD group are presented in Table 2. For a significance level of 5%, the following powers were found: 0.96 for FEV_1/FVC; 0.95 for FEV_1; 0.84 for FVC; 0.99 for IC; 0.99 for MVV; 0.95 for MIP; and 0.73 for the perception of dyspnea. Given that neither MEP nor PADL correlated with DM, neither variable was used.

In the COPD group, DM correlated moderately with lung function, inspiratory muscle strength, and the perception of dyspnea. In addition, it correlated strongly with MVV and IC. In the control group, DM did not correlate with any of the lung function or respiratory muscle strength variables (Table 2).

DISCUSSION

In the present study, DM was found to correlate moderately with FEV_1 and strongly with IC in COPD

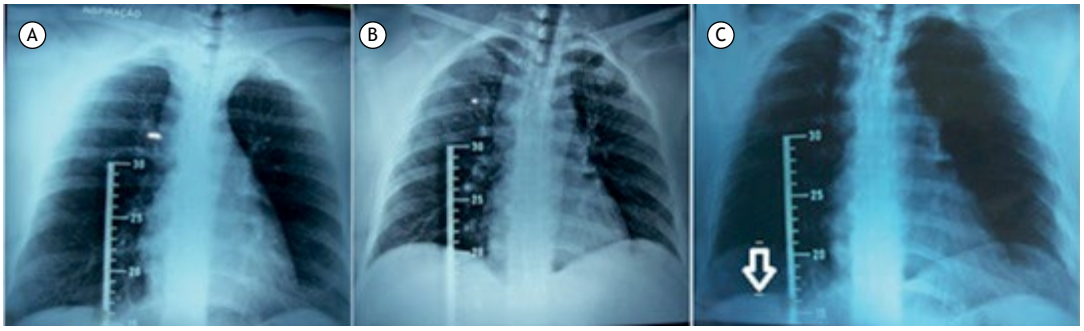

Figure 1. Anteroposterior chest X-rays. In A, chest X-ray taken during a maximal expiratory maneuver; in B, chest X-ray taken during a maximal inspiratory maneuver; and in C, superimposition of the two aforementioned images, the image of the radiographic ruler being used as reference to assess diaphragmatic mobility.

Table 1. Anthropometric, spirometric, and functional characteristics of the groups studied.

Variable	Control	COPD	p
Age, years	64.68 ± 6.63	67.56 ± 9.21	0.21
Height, m	1.59 ± 0.11	1.66 ± 0.08	0.01
Weight, kg	64.86 ± 9.85	68.38 ± 11.58	0.25
BMI, kg/m^2	25.13 ± 2.81	24.64 ± 3.08	0.52
FEV_1/FVC	0.79 ± 0.06	0.54 ± 0.12	0.001
FVC, % predicted	99.96 ± 13.95	71.84 ± 17.08	0.001
FEV_1, % predicted	98.20 ± 12.39	53.88 ± 21.62	0.001
IC, L	-	2.16 ± 0.76	-
IC, % predicted	-	91.32 ± 64.15	-
MVV, L/min	-	52.84 ± 26.40	-
MIP, cmH_2O	73.25 ± 18.66	62.88 ± 19.05	0.058
MEP, cmH_2O	96.48 ± 37.55	99.40 ± 24.60	0.74
mMRC scale score		1.24 ± 0.77	-
DM, mm	62.82 ± 14.86	41.73 ± 19.39	0.001
Active time, min	-	228.12 ± 105.80	-
Number of steps	-	6388.12 ± 3671.66	-
Movement intensity, m/s^2	-	0.18 ± 0.03	-
Sedentary time, min	-	500.12 ± 128.76	-

BMI: body mass index; IC: inspiratory capacity; MVV: maximal voluntary ventilation; mMRC: modified Medical Research Council; and DM: diaphragmatic mobility.

patients, which is possibly due to the fact that increased airflow obstruction, as assessed by FEV_1, and static lung hyperinflation, as assessed by IC, increase the workloads that affect the chest wall, placing the diaphragm at a geometric and mechanical disadvantage.[26,27] In addition, lung hyperinflation reduces the ability of the diaphragm to generate flow and pressure,[28] resulting in decreased diaphragmatic excursion.[29]

Lung hyperinflation is one of the primary changes in patients with COPD; however, air trapping is the principal factor limiting DM in such patients.[3] Structural changes result in diaphragm remodeling, which results in flattening of the diaphragm and, consequently, decreased diaphragmatic excursion.[30] The aforementioned changes explain the differences in DM and lung function between COPD patients and healthy individuals; they were expected and have previously been reported.[1-3,29]

In the present study, a strong correlation was found between DM and MVV in patients with COPD, showing that a greater DM translates to a better ventilatory capacity. This finding is in agreement with those of Kang et al.,[31] who found a significant correlation between DM and MVV and posited that there might be a relationship between decreased DM and hypercapnia in patients with COPD.

In patients with COPD, airflow limitation during exercise is due to reduced ventilatory capacity associated with increased pulmonary obstruction and, consequently, lung hyperinflation, as evidenced by reduced IC and ventilatory reserve.[32] In the present study, in which patients with moderate to severe obstruction participated, DM correlated moderately with IC, which also accounted for 65% of the variation in DM, reinforcing the influence of lung hyperinflation on diaphragmatic mechanics. However, it is known that the influence of air trapping on DM can be greater than that of lung hyperinflation itself.[3]

Although DM has been shown to correlate with parameters such as pulmonary obstruction, lung hyperinflation,[33] and air trapping,[3] Davachi et al.[11] found no relationship between DM and lung hyperinflation, which is possibly due to the fact that they selected patients with less severe COPD and, consequently, reduced airflow obstruction, resulting in less damage to the diaphragm.

In the present study, a moderate negative correlation was found between DM and the perception of dyspnea in patients with COPD, indicating that changes in the position of the diaphragm make ventilation difficult, reducing respiratory capacity and increasing the sensation of dyspnea.[34] These findings corroborate those of Paulin et al.,[2] who found that patients with decreased DM had a greater sensation of dyspnea after submaximal exercise.

Although no correlation was found between PADL and DM in the COPD patients in the present study, it is known that exercise capacity decreases with the progression of the disease.[35] This creates a vicious cycle of increasing dyspnea during physical activity, leading to physical inactivity, decreased physical conditioning, and an increased number of comorbidities and hospitalizations.[36] It has been shown that, in comparison with healthy, sedentary elderly individuals, most COPD patients spend more time sitting or lying down than walking or standing[23,37]; however, to date, no studies have established a relationship between DM and PADL in COPD patients.

It is of note that assessment of PADL by means of a triaxial accelerometer reveals how much individuals are physically active or inactive in their daily life.[38] However, assessment of PADL with a triaxial accelerometer probably depends on several factors other than DM evaluation, and this might explain the lack of correlation between these variables. In addition, it is possible that the number of patients in the study sample and the evaluation period were insufficient to observe this relationship.

In the present study, no relationship was found between DM and the BMI. Kantarci et al.[39] performed a multiple regression analysis and found that waist circumference apparently plays a more significant role

Table 2. Relationship between diaphragmatic mobility and the study variables in the COPD group.

Variable	p	r	r^2, %
BMI, kg/m^2	0.20	0.58	20
FVC, % predicted	0.01	0.48	23
FEV_1, % predicted	0.003	0.56	32
FEV_1/FVC	0.002	0.58	34
IC, L	0.001	0.80	65
MVV, L/min	0.001	0.73	54
MIP, cmH_2O	0.003	0.56	32
MEP, cmH_2O	0.10	0.33	11
mMRC scale score	0.01	−0.48	18
Active time, min	0.82	−0.04	0.2
Number of steps	0.85	−0.04	0.2
Movement intensity, m/s^2	0.26	0.23	5
Sedentary time, min	0.62	0.10	1

BMI: body mass index; IC: inspiratory capacity; MVV: maximal voluntary ventilation; and mMRC: modified Medical Research Council.

in the evaluation of DM than does the BMI, a finding that suggests that, although the BMI is a good indicator of nutritional status, it does not reflect individual differences in body composition, such as abdominal fat distribution.

We found a relationship between MIP and DM that can be explained by the mechanical disadvantage in which the diaphragm is as a result of air trapping, which leads the inspiratory muscles to work in a shortened position, thus affecting their potential for contraction.[30] Kodric et al.[40] showed that inspiratory muscle training improved DM in patients with diaphragmatic dysfunction following cardiac surgery, a finding that suggests a relationship between improved MIP and DM.

Our results suggest that DM is a parameter that can provide information on respiratory mechanics in patients with COPD and that is related to certain pulmonary parameters (FEV_1, FEV_1/FVC, FVC, IC, and MVV) and functional parameters. However, studies involving a higher number of patients are needed in order to examine the relationship between DM and PADL.

One potential limitation of the present study is that no stage I COPD patients were evaluated. However, this is a common problem in the literature, given that stage I COPD patients are usually asymptomatic and, consequently, do not seek medical attention. Nevertheless, the results obtained in the present study cannot be extrapolated to all stages of COPD severity. In addition, the posture adopted during DM evaluation might influence the result obtained; therefore, we suggest that DM be evaluated in the orthostatic and supine positions in future studies.

In summary, in patients with COPD, DM is related to airway obstruction, lung hyperinflation, ventilatory capacity, and the perception of dyspnea. However, it appears to have no relationship with PADL.

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ORIGINAL ARTICLE

Impaired pulmonary function after treatment for tuberculosis: the end of the disease?

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ABSTRACT

Objective: To evaluate the prevalence of pulmonary function abnormalities and to investigate the factors affecting lung function in patients treated for pulmonary tuberculosis. **Methods:** A total of 214 consecutive patients (132 men and 82 women; 20-82 years of age), treated for pulmonary tuberculosis and followed at a local dispensary, underwent spirometry and plethysmography at least one year after treatment. **Results:** Pulmonary impairment was present in 102 (47.7%) of the 214 patients evaluated. The most common functional alteration was obstructive lung disease (seen in 34.6%). Of the 214 patients, 60 (28.0%) showed reduced pulmonary function (FEV_1 below the lower limit of normal). Risk factors for reduced pulmonary function were having had culture-positive pulmonary tuberculosis in the past, being over 50 years of age, having recurrent tuberculosis, and having a lower level of education. **Conclusions:** Nearly half of all tuberculosis patients evolve to impaired pulmonary function. That underscores the need for pulmonary function testing after the end of treatment.

Keywords: Respiratory function tests; Tuberculosis, pulmonary; Spirometry; Lung diseases, obstructive.

INTRODUCTION

It has been estimated that approximately one third of the world's population is latently infected with *Mycobacterium tuberculosis*.[1] In 2011, there were an estimated 8.7 million new cases of tuberculosis worldwide, equivalent to 125 cases per 100,000 population.[1]

In patients infected with *M. tuberculosis*, whether treated or untreated, a variety of pulmonary and extrapulmonary sequelae and complications can occur, categorized as follows: parenchymal lesions, which include tuberculoma, thin-walled cavities, scarring, and end-stage lung destruction; or airway lesions, which include bronchiectasis, tracheobronchial stenosis, and broncholithiasis.[2] Structural changes lead to obstructive, restrictive, or mixed patterns of impaired pulmonary function. Studies in patients with pulmonary tuberculosis (PTB) have demonstrated that 33.3-94.0% of such patients develop impaired pulmonary function.[3] Although it is unknown how many PTB survivors are living today, when the incidence of tuberculosis and the success of therapy are considered, the number of PTB survivors appears to be substantial and increasing.[4] There have been few studies on the topic of impaired pulmonary function in PTB survivors, and most such studies have involved highly selected populations. The patients in those populations do not fully represent the populations affected by tuberculosis.[4-8] Little is known about the prevalence of a restrictive pattern after PTB. Although the evaluation of true restriction requires the measurement of TLC, the studies cited above used only spirometry. Most of those studies were conducted in countries where the incidence of tuberculosis is low; the prevalence and type of pulmonary impairment might differ in countries where that incidence is high.

The objectives of this study were to evaluate the incidence and extent of pulmonary function abnormalities in patients previously treated for PTB. We also studied the factors affecting pulmonary function in such patients.

METHODS

This study was carried out in the Department of Pulmonary Physiology, Research Institute of Phthisiopulmonology, I.M. Sechenov First Moscow State Medical University, in Moscow, Russia. The study was approved by the Ethical Review Board of the Association of Medical and Pharmaceutical Universities. All participants gave written informed consent, and confidentiality was ensured.

In Russia, the primary component of the tuberculosis control system is the regional dispensary, which provides services to patients with active disease and to those considered at risk of contracting or developing the disease. The patients are followed for some time after treatment.[9]

In the 2003-2007 period, a total of 757 PTB patients (between 20 and 90 years of age) were treated and followed at the local tuberculosis dispensary. All 757 patients were subsequently recruited by telephone. Letters were sent if no telephone contact was made. Of the 757 eligible patients, 214 agreed to take part in the study.

From April 2005 to December 2013, patients previously treated for PTB underwent pulmonary function tests

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(PFTs) in the Department of Pulmonary Physiology. All 214 of the patients had been treated successfully, and the PFTs were performed at least one year after the end of treatment. At the time of the PFTs, none of the patients showed any signs of active PTB.

All of the participating patients underwent spirometry and plethysmography, as well as completing a questionnaire designed to collect data related to demographic characteristics, smoking, medical history, and other aspects. The PFTs were performed by experienced technicians, in accordance with the recommendations of the American Thoracic Society/European Respiratory Society,[10,11] with a combination spirometer/plethysmograph (MasterScreen Body; Jaeger, Würzburg, Germany). Of the 214 patients, 69 had physician-diagnosed chronic lung disease. All 214 patients were urban dwellers without a personal history of exposure to biomass smoke. Those with a history of intermittent bronchodilator use received their usual treatment 30 min prior to testing. European Community for Coal and Steel equations for spirometry and lung volumes were applied.[12] Airway obstruction was defined as an FEV_1/VC ratio below the lower limit of normal (LLN) and a TLC above or equal to the LLN; a restrictive pattern was defined as a TLC below the LLN and an FEV_1/VC ratio above or equal to the LLN; a mixed pattern was defined as an FEV_1/VC ratio and TLC both below the LLN[13]; and a nonspecific pattern was defined as a TLC above or equal to the LLN, an FEV_1/VC ratio above or equal to the LLN, and an FEV_1 or FVC below the LLN.[14] We defined reduced pulmonary function as an FEV_1 below the LLN.

For quantitative variables, the differences between groups were assessed by the Mann-Whitney test or the Kruskal-Wallis test. For categorical variables, the groups were compared by the chi-square test. The predictive value of age for the presence of pulmonary impairment was evaluated by determining the area under the ROC curve. Accuracy was calculated for the best cut-off value, defined as that with the highest sum of sensitivity and specificity. Logistic regression was used in order to identify factors associated with impaired pulmonary function. Values of $p < 0.05$ were considered statistically significant.

RESULTS

Table 1 summarizes the main characteristics of the 214 subjects included in the analysis. There were 132 men and 82 women, with a mean age of 51.1 years (range, 20-82 years). Of the 214 subjects, 105 had previously been culture-positive and 90 had previously been culture-negative. For the remaining 19 subjects, the culture results were unknown.

The PFT results were normal in 112 (52.4%) of the 214 patients (Table 2). Pulmonary impairment was identified in 102 (47.7%) of the patients, the pattern being obstructive in 74 (34.6%), restrictive in 18 (8.4%), mixed in 8 (3.7%), and nonspecific in 2 (0.9%).

Of the 214 patients, 60 (28.0%) had an FEV_1 below the LLN. Using the American Thoracic Society/European Respiratory Society criteria,[13] we classified the degree of abnormality as mild in 6 (2.8%), moderate in 34 (15.9%), and severe in 20 (9.3%), as detailed in Table 2. Clinically significant pulmonary impairment, defined as an FEV_1 < 60% of the predicted value,[15] was identified in 35 (14.5%) of the subjects, being attributed to an obstructive pattern in 22 (10.3%), a restrictive pattern in 5 (2.3%), and a mixed pattern in 8 (3.7%). Of those 35 patients, 13 had not been diagnosed with a chronic pulmonary disease.

According to the ROC curve analysis for reduced pulmonary function, when the age of 50 was chosen as the cut-off value, the sensitivity was 73.3% and the specificity was 59.1%. The area under the curve was 0.67 (95% CI: 0.59-0.76; p = 0.002).

As can be seen in Table 3, the prevalence of any pulmonary impairment in the patients ≥ 50 years of age was 60.6% (range, 56.3-63.3%, depending on the specific age bracket), compared with 34.3% (range, 7.1-42.4%, depending on the specific age bracket) in

Table 1. Characteristics of the patients in the study sample (n = 214).

Characteristic	Value	Range
Gender[a]		
Male	132 (61.7)	
Female	82 (38.3)	
Age, years[b]	51.1 (14.2)	20-82
< 40[a]	46 (21.5)	
40-49	59 (27.6)	
50-59	49 (22.9)	
60-69	32 (15.0)	
≥ 70	28 (13.1)	
BMI, kg/m^2[b]	23.9 (4.4)	14.8-41.5
Education[a,c]		
College-educated	66 (31.4)	
High school only	144 (68.6)	
Smoking status[a]		
Current smoker	112 (52.3)	
Former smoker	26 (12.2)	
Never-smoker	76 (35.5)	
Pulmonary function[b]		
FVC, % of predicted	99.7 (21.4)	31-143
FEV_1, % of predicted	87.1 (25.0)	23-139
FEV_1/VC ratio	70.3 (13.5)	28.7-97
PEF, % of predicted	81.9 (28.7)	21-151
MMEF, % of predicted	61.9 (33.3)	5.4-161
TLC, % of predicted	99.9 (17.8)	38-136
FRC, % of predicted	111.4 (27.9)	45-191
RV, % of predicted	103.9 (30.2)	34-253
IC, % of predicted	91.2 (24.2)	27-165
RV/TLC ratio	34.7 (10.0)	16-74

BMI: body mass index; MMEF: maximal mid-expiratory flow; FRC: functional residual capacity; and IC: inspiratory capacity. [a]Values expressed as n (%).[b]Values expressed as mean (SD).[c]The level of education was unknown in 4 patients.

the patients < 50 years of age (p < 0.001; chi-square test). In the patients ≥ 50 of age, the prevalence of reduced pulmonary function was 40.4% (range, 37.5-42.9%, depending on the specific age bracket), whereas it was 15.2% (range, 0.0-20.3%, depending on the specific age bracket) in the patients < 50 years of age, and the difference between the two groups was statistically significant (p < 0.001; chi-square test).

Table 4 shows the pulmonary function parameters, stratified by culture results, number of episodes of PTB, and smoking history. The values for FVC, FEV_1, and the FEV_1/VC ratio were significantly lower in the patients who had previously had culture-positive PTB than in those who had previously had culture-negative PTB (p < 0.05 for all; Mann-Whitney test). There were 188 patients who had had only one episode of PTB and 26 who had had two or more episodes. Values for FEV_1 and the FEV_1/VC ratio were significantly lower in the patients who had had two or more episodes of PTB than in those who had had only one. More than 60% of the subjects evaluated in our study had a history of smoking. The prevalence of airway obstruction in ever-smokers (smokers and former smokers, collectively) and never-smokers was 47.1% and 22.4%, respectively (p < 0.001; chi-square test). The prevalence of reduced pulmonary function in ever-smokers and in never-smokers was 31.2% and

Table 2. Type and severity of pulmonary impairment in patients previously treated for pulmonary tuberculosis.[a]

Variable	(n = 214)
Type of impairment	
Normal	112 (52.4)
Obstructive pattern (FEV_1/VC ratio < LLN and TLC ≥ LLN)	74 (34.6)
Restrictive pattern (TLC < LLN and FEV_1/VC ratio ≥ LLN)	18 (8.4)
Mixed pattern (TLC and FEV_1/VC ratio < LLN)	8 (3.7)
Nonspecific pattern (TLC ≥ LLN, FEV_1/VC ratio ≥ LLN, and FEV_1 or FVC < LLN)	2 (0.9)
Reduced pulmonary function (FEV_1 < LLN)	60 (28)
FEV_1	
< 35% of predicted	9 (4.2)
35-49% of predicted	11 (5.1)
50-59% of predicted	15 (7.0)
60-69% of predicted	19 (8.9)
≥ 70% of predicted and < LLN	6 (2.8)
≥ LLN	154 (72)

LLN: lower limit of normal. [a]Values expressed as n (%).

Table 3. Relationship between age and pulmonary impairment in patients previously treated for pulmonary tuberculosis.[a]

Age, years	Gender	n	Any impairment	Pattern of impairment[b,c]			Reduced pulmonary function[d]
				Obstructive	Restrictive	Mixed	
	Male	7					
20-29	Female	7	1 (7.1)	1 (7.1)	0 (0)	0 (0)	0 (0)
	Total	14					
	Male	22					
30-39	Female	10	10 (31.3)	6 (18.8)	2 (6.3)	1 (3.1)	4 (12.5)
	Total	32					
	Male	39					
40-49	Female	20	25 (42.4)	24 (40.7)	1 (1.7)	0 (0)	12 (20.3)
	Total	59					
	Male	36					
50-59	Female	13	31 (63.3)	21 (42.9)	7 (14.3)	3 (6.1)	21 (42.9)
	Total	49					
	Male	18					
60-69	Female	14	18 (56.3)	13 (40.6)	2 (6.25)	2 (6.3)	12 (37.5)
	Total	32					
	Male	10					
≥ 70	Female	18	17 (60.7)	9 (32.1)	6 (21.43)	2 (7.1)	11 (39.3)
	Total	28					

LLN = lower limit of normal. [a]Values are given as n(%). [b]An obstructive pattern was defined as an FEV_1/VC ratio < the lower limit of normal (LLN) and a TLC ≥ LLN; a restrictive pattern was defined as a TLC < LLN and an FEV_1/VC ratio ≥ LLN; a mixed pattern was defined as an FEV_1/VC ratio < LLN and a TLC < LLN; and a nonspecific pattern was defined as a TLC ≥ LLN, an FEV_1/VC ratio ≥ LLN, and an FEV_1 or FVC < LLN. [c]Two patients presented with a nonspecific pattern (data not shown). [d]Defined as an FEV_1 < LLN.

22.4%, respectively (p = 0.226; chi-square test). In the smokers, former smokers, and never-smokers, the mean FEV_1 (as a percentage of the predicted value) was 87.0 ± 22.7%, 80.0 ± 27.5%, and 89.7 ± 27.1%, respectively (p = 0.201; Kruskal-Wallis test). We found that smoking had no influence on the prevalence of reduced pulmonary function. Only the FEV_1/VC ratio was lower in ever-smokers than in never-smokers (Table 4).

The risk factors for reduced pulmonary function were having previously had culture-positive PTB, being over 50 years of age, having a low level of education, and having experienced recurrence of tuberculosis. The prevalence of reduced pulmonary function was lower in college-educated patients than in those who had only a high school education (18.2% vs. 31.9%), and the difference was statistically significant (p < 0.05; chi-square test). We found that neither gender nor smoking status had any influence on the prevalence of reduced pulmonary function (Table 5).

DISCUSSION

A study conducted in the United States showed that 59% of patients treated for tuberculosis subsequently had abnormal pulmonary function.[4] In that study, more than half of the patients treated for PTB evolved to significantly impaired pulmonary function. These data suggest that impaired pulmonary function after PTB is a major cause of chronic lung disease.[4] The authors of that study found that 44% of the patients developed restrictive impairment,[4] compared with the 6.6% reported for the general population.[16] We also found that the prevalence of restrictive impairment was higher among the patients evaluated in our study than in the general population.

In the present study, approximately half of all PTB patients treated at the local tuberculosis dispensary suffered from impaired pulmonary function, a prevalence much higher than that observed in the general population. In addition to the risk factors for reduced pulmonary function identified in the present study—having previously had culture-positive PTB, being over 50 years of age, having a low level of education, and having experienced recurrence of tuberculosis—potential risk factors for impaired pulmonary function in patients previously treated for PTB include extensive disease before treatment, prolonged treatment duration, and poor radiographic improvement after treatment.[17]

We can presume that recurrent PTB is an important risk factor for pulmonary impairment and that patients with risk factors for recurrence require close monitoring and appropriate treatment in order to prevent future

Table 4. Conditional analysis of pulmonary impairment after treatment for pulmonary tuberculosis.

Variable	Condition		p
	Previous culture result[a]		
	Positive (n = 105)	Negative (n = 90)	
FVC, % of predicted[b]	96.7 (22.9)	106.0 (16.8)	0.006
FEV_1, % of predicted[b]	81.8 (24.9)	96.6 (22.0)	< 0.001
FEV_1/VC ratio[b]	67.9 (13.8)	73.6 (12.5)	0.002
TLC, % of predicted[b]	98.4 (19.4)	103.8 (12.7)	0.106
Any impairment[c]	58 (55.2)	30 (33.3)	0.002
Reduced pulmonary function[c]	39 (37.1)	13 (14.4)	0.004
	Number of episodes of pulmonary tuberculosis		
	Two or more (n = 26)	One (n = 188)	
FVC, % of predicted[b]	90.6 ± 28.9	100.9 ± 20.0	0.140
FEV_1, % of predicted[b]	71.7 ± 27.9	89.2 ± 23.9	0.002
FEV_1/VC ratio[b]	63.3 ± 12.8	71.2 ± 13.4	0.003
TLC, % of predicted[b]	92.3 ± 25.6	100.9 ± 16.2	0.12
Any impairment[c]	20 (76.9)	82 (43.6)	0.001
Reduced pulmonary function[c]	15 (57.7)	45 (23.9)	< 0.001
	Smoking		
	Ever (n = 138)	Never (n = 76)	
FVC, % of predicted[b]	100.2 ± 20.6	98.7 ± 23.0	0.979
FEV_1, % of predicted[b]	85.6 ± 23.7	89.7 ± 27.1	0.151
FEV_1/VC ratio[b]	67.9 ± 13.3	74.6 ± 12.9	< 0.001
TLC, % of predicted[b]	102.0 ± 16.0	96.0 ± 20.2	0.072
Any impairment[c]	74 (53.6)	28 (36.8)	0.019
Reduced pulmonary function[c]	43 (31.2)	17 (22.4)	0.171

[a]Determined for only 195 of the 214 patients in the sample. [b]Values expressed as mean (SD). [c]Values expressed as n (%). [d]Defined as an FEV_1 < LLN.

Table 5. Risk factors for reduced pulmonary function in patients previously treated for pulmonary tuberculosis.[a]

Risk factor	OR	95% CI	p
Recurrence of tuberculosis: yes vs. no.	4.33	1.86-10.11	< 0.001
Age: < 50 years vs. ≥ 50 years	3.77	1.95-7.25	< 0.001
Positive culture in the past[b]: yes vs. no	3.5	1.72-7.11	< 0.001
Education: high school only vs. college education	2.11	1.03-4.33	0.04
Smoking: ever vs. never	1.57	0.82-3.0	0.17
Gender: male vs. female	1.49	0.79-2.81	0.21

[a]Defined as an FEV_1 below the lower limit of normal. [b]Determined for only 195 of the 214 patients in the sample.

episodes of PTB. Hnizdo et al.[5] showed that the mean decrease in FEV_1 was 180 mL in patients who had experienced only one episode of PTB, 362 mL in those who had experienced two episodes, and 462 mL in those who had experienced three episodes.

The prevalence of reduced pulmonary function was significantly lower in college-educated patients than in those who had only a high school education; 18.2% and 31.9%, respectively ($p < 0.05$; chi-square test). As a rule, college-educated patients have a better socioeconomic status, better nutrition, less occupational risk and a more conscientious attitude toward treatment than do those without a college education.[18] The magnitude of the effect of socioeconomic status has been reported to be 200-300 mL of FEV_1.[18]

Although smoking has been established as a major risk factor for COPD, an estimated 25-45% of COPD patients are never-smokers and emerging evidence suggests that other risk factors are important.[18] A recent meta-analysis showed that smoking is a risk factor for tuberculosis. However, it is not clear whether smoking can increase the mortality risk in individuals who already have active tuberculosis.[19] The impact of smoking on pulmonary impairment in patients who have been treated for PTB is also unknown. Previous studies have produced inconsistent results.[4,6,8,17] In our study, despite the fact that the prevalence of obstruction was significantly higher in ever-smokers than in never-smokers, we found that smoking had no influence on the prevalence of reduced pulmonary function. The explanation for that finding remains uncertain. Chung et al.[17] found that a history of PTB was a stronger determinant of impaired pulmonary function than was smoking. Those authors also suggested that post-tuberculosis pulmonary inflammation can mask a smoking-related decline in pulmonary function.[17]

The overall prevalence of pulmonary impairment is much higher in patients treated for PTB than in the general population. In our patient sample, obstructive impairment was the most common pattern, followed by restrictive, mixed, and nonspecific impairment. These results are in accordance with those of other studies in the literature,[4] suggesting that pulmonary impairment after tuberculosis could be an underestimated cause of chronic lung disease, especially in countries where the tuberculosis burden is high. Reduced FEV_1 has been shown to be an independent predictor of all-cause and respiratory disease-related mortality.[20]

Inghammar et al.[21] showed that impaired pulmonary function was associated with an increased risk of active tuberculosis. However, if decreased lung function is a risk factor for the development of tuberculosis, it is also possible that pulmonary impairment is a risk factor for its recurrence. Further studies are needed in order to determine whether impaired pulmonary function can be viewed as a risk factor and to devise targeted measures to prevent the recurrence of tuberculosis.

The presence of symptoms is not a sensitive and specific indicator of airway limitation, and the use of a symptom questionnaire appears to be an ineffective means of identifying pulmonary impairment.[22] However, evidence suggests that pulmonary function testing is not used consistently. Even in developed countries, less than half of all patients newly diagnosed with chronic pulmonary diseases receive pulmonary function testing near the time of diagnosis.[23] Using a mechanical peak expiratory flow meter or a pocket spirometer as a screening tool can reduce the number of diagnostic PFTs required.[24] Although it has not been established that PFTs can predict recurrence, their use can probably help select a group of patients at higher risk of recurrence who require longer follow-up and prevention measures. This supports the idea that patients previously treated for PTB should undergo pulmonary function testing. However, pulmonary function testing has yet to be included in the guidelines for the treatment of tuberculosis.[25] We suppose that using $FEV_1 < 80\%$ of the predicted value (rather than FEV_1 below the LLN) as a cut-off value would serve as a reasonable strategy for patients under follow-up treatment, because of its simplicity and ease of use.

This study has some limitations. Very few of the patients received bronchodilators, and it is possible that bronchospasm is conducive to pulmonary impairment. In addition, the study was conducted at a single center, whereas a multicenter study could have produced results that would have been more robust. Furthermore, because of a lack of the pertinent data, we did not examine the influence that a history of cavitation had on pulmonary impairment. Tuberculosis treatment is much less effective in patients with cavitary disease than in those with noncavitary disease or culture-positive PTB, and the negative influence of cavitary disease on lung function could therefore be quite significant.[26]

In conclusion, we found that a history of PTB was a risk factor for pulmonary impairment. The eradication of the bacteria does not necessarily translate to the end

of the illness. After tuberculosis treatment, more than 40% of patients can evolve to pulmonary impairment, mainly obstructive disorders. This underscores the need for pulmonary function testing in patients who have been treated for PTB.

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ORIGINAL ARTICLE

Phenotypes of asthma in low-income children and adolescents: cluster analysis

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ABSTRACT

Objective: Studies characterizing asthma phenotypes have predominantly included adults or have involved children and adolescents in developed countries. Therefore, their applicability in other populations, such as those of developing countries, remains indeterminate. Our objective was to determine how low-income children and adolescents with asthma in Brazil are distributed across a cluster analysis. **Methods:** We included 306 children and adolescents (6-18 years of age) with a clinical diagnosis of asthma and under medical treatment for at least one year of follow-up. At enrollment, all the patients were clinically stable. For the cluster analysis, we selected 20 variables commonly measured in clinical practice and considered important in defining asthma phenotypes. Variables with high multicollinearity were excluded. A cluster analysis was applied using a two-step agglomerative test and log-likelihood distance measure. **Results:** Three clusters were defined for our population. Cluster 1 (n = 94) included subjects with normal pulmonary function, mild eosinophil inflammation, few exacerbations, later age at asthma onset, and mild atopy. Cluster 2 (n = 87) included those with normal pulmonary function, a moderate number of exacerbations, early age at asthma onset, more severe eosinophil inflammation, and moderate atopy. Cluster 3 (n = 108) included those with poor pulmonary function, frequent exacerbations, severe eosinophil inflammation, and severe atopy. **Conclusions:** Asthma was characterized by the presence of atopy, number of exacerbations, and lung function in low-income children and adolescents in Brazil. The many similarities with previous cluster analyses of phenotypes indicate that this approach shows good generalizability.

Keywords: Asthma/classification; Asthma/etiology; Child; Adolescent.

INTRODUCTION

Asthma is a syndrome of recurrent respiratory symptoms triggered by various factors, such as viral respiratory infections, environmental allergens, pollution, and climate changes. It is characterized by chronic airway inflammation and variable expiratory airflow limitation.[1] Asthma is not a single disease; rather, it comprises a syndrome with complex phenotypes. Various previous studies have attempted to subclassify asthma according to the symptoms, airway function, presence of atopy, and type of airway inflammation. Numerous asthma phenotypes have been described by using computational techniques, such as clustering; however, those studies predominately included adults,[2-4] and the results suggested a weak correlation between pathological processes and treatment response.[1]

Limited studies have focused on childhood asthma.[5-8] Fitzpatrick et al.[6] described four clusters in a group of 161 children and adolescents who primarily exhibited severe asthma; the obtained clusters were distinct from the clusters identified in adults because they were differentiated by the age at asthma onset, pulmonary function, presence of atopy, airflow limitation, and comorbidity. Howrylak et al.[7] described five clusters in a group of 1,041 children with mild-to-moderate asthma, which were differentiated by atopic burden, lung function, and history of exacerbation. Just et al.[8] only investigated children with allergic asthma and described three clusters according to sensitization and presence of severe exacerbation.

According to the 2014 Global Initiative for Asthma (GINA) strategy report,[9] the severity of asthma may be classified into five levels, and the key factors to determine asthma severity include symptom magnitude, pulmonary function, and dose of inhaled corticosteroid (ICS) to maintain asthma control. However, this classification does not reflect the heterogeneous characteristics of childhood asthma, which may lead to suboptimal treatments and increased risks of hospitalization, as well as loss of pulmonary function. For example, a great number of children and adolescents with severe asthma have normal lung function during symptom-free days, because FEV_1 does not correlate well with the symptoms; in addition, FEV_1 values lower than 80% are predicted

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to have a low sensitivity to distinguish among the levels of asthma severity in children.[10-12] Moreover, asthma symptoms vary in frequency and intensity through time and are triggered by various stimuli, such as viral infections and allergens. The reasons why some children exhibit only sporadic symptoms that are improved by short-acting bronchodilators and other children exhibit daily symptoms that require high doses of ICS and ongoing airway inflammation remain poorly understood.

Accurate asthma assessment is essential to avoid impairment and future risks of exacerbations, as well as to guide proper disease management.[1] Moreover, the identification of asthma phenotypes does not provide a better approach to asthma treatment, improve control, avoid adverse effects, or decrease the risk of serious asthma outcomes, such as exacerbations and loss of pulmonary function.[13] This suggests the importance of additional studies in order to establish the actual clinical utility of phenotype classification. In addition, the previously described asthma phenotypes[6-8] have been investigated in developed countries, and their applicability to other populations of children and adolescents with asthma remains to be established.

The purpose of the present study was to determine how low-income children with asthma in Brazil are distributed across a cluster analysis.

METHODS

This was a retrospective study involving 306 children and adolescents (6-18 years of age) with a clinical diagnosis of asthma who were outpatients at *Pinheiros* Primary Care Unit or at *Hospital Infantil Darcy Vargas*—both of which take part in the public health care system and are located in the city of São Paulo, Brazil—for at least one year of follow-up, between September of 2010 and December of 2014. Eligibility criteria were being between 6 and 18 years of age, a nonsmoker, and a representative of the community health care center. At enrollment, the participants were clinically stable with no signs of asthma exacerbation (30 days with no changes regarding symptoms or medication use). The severity of asthma was classified according to the revised 2014 GINA report,[9] whereas asthma phenotypes were based on clinical data obtained from the medical records of the patients. The study was approved by the Research Ethics Committee of *Hospital Infantil Darcy Vargas* (Protocol no. 1.540.338). Since the present study was retrospective, the authors signed a confidentiality agreement which precluded the need to obtain written informed consent from the patients.

Selection of variables for analysis

The variables selected for the cluster analysis were considered important to define the disease phenotype and are commonly measured in clinical practice.[3-5] Variables with high multicollinearity or that were similar for more than 95% of the patients were not included in the cluster analysis. Twenty variables were included in the cluster analysis: gender (male or female); obesity (body mass index [BMI] ≥ 30 kg/m^2); race (white, brown, or black); asthma severity based on prescribed treatment step (from 1 to 5)[9]; age at the onset of asthma (≤ 2 years, 3-6 years, or ≥ 7 years); asthma triggers (upper respiratory tract infection, exercise, or multiple triggers); blood eosinophils (absolute values and blood eosinophil levels > 5%); number of previous asthma hospitalizations (none, 1-3, or ≥ 4); tendency toward exacerbation—more than 3 exacerbations in the previous year—(yes or no); history of ICU admission (yes or no); specific serum IgE levels (via ImmunoCAP Specific IgE; Phadia, Uppsala, Sweden)—atopy identified to most common allergens—(none, dust mite allergens, or multiple allergens); gastroesophageal reflux (yes or no); sinus infection (yes or no); baseline FEV_1 (% predicted); FEV_1/FVC ratio; labile FEV_1—defined as a variation in pre-bronchodilator FEV_1 > 20% between visits in the previous year—(yes or no); presence of fixed airway obstruction—persistence of post-bronchodilator airway obstruction or FEV_1/FVC ratio lower than the lower limit of normality[14] despite the use of high doses of ICS and a 7-day course of prednisone—(yes or no); and best response to bronchodilator in the previous year.

Spirometric criteria were in accordance with Pellegrino et al.,[15] and the tests were performed with a Koko® spirometer (PDS Instrumentation Inc., Louisville, CO, USA). Bronchodilator reversibility tests were performed using 400 μg of albuterol. Predictive values were in accordance with those proposed by Quanjer et al.[14] Fixed airway obstruction was defined by lower limit of normal, which was based on the proportion of subjects in the groups whose test results fell below the fifth percentile, in accordance with the multiethnic reference values proposed by Quanjer et al.[14]

Statistical analysis

A uniform cluster analysis methodology was applied using an agglomerative two-step test and log-likelihood distance measure. The lowest Schwarz Bayesian information criterion was used to determine the number of clusters. This analytical technique identifies subgroups of a sample according to their similarities, which subsequently enables the determination of the variables that best discriminate such subgroups of the group a priori.[3] To compare differences between the clusters, one-way ANOVA and chi-square tests were used for parametric continuous and categorical variables, respectively. A forward stepwise discriminant analysis using Wilks' lambda and Fisher's linear discriminant function was performed. A discriminant analysis was applied to identify factors that independently discriminate pre-specified groups and determined whether the subjects assigned to one group were different from the subjects assigned to another group. The dependent variable included cluster classification; the independent variables included the same 20 variables used in the cluster

analysis. A second discriminant analysis was conducted for asthma severity based on prescribed treatment step (from 1 to 5) as the dependent variable and the 20 variables included in the initial analysis as the independent variables. The present study included 15 subjects per variable, which is three times higher than the minimum recommendation for discriminant analysis (five subjects per variable).[16] The statistical significance level was set at 5% for all tests. The IBM SPSS Statistics software package, version 19.0 (IBM Corporation, Armonk, NY, USA), was used for statistical analyses.

RESULTS

The clinical data regarding the 306 children and adolescents with asthma included in the study were available for the cluster analysis. Seventeen subjects were excluded due to incomplete data. The baseline characteristics of the remaining 289 subjects are presented in Table 1. In the sample studied, 177 subjects (61%) were male, the mean age was 12 years, and the vast majority exhibited atopic asthma (92%). The age at the onset of asthma in most subjects was < 2 years (68%); in addition, most were White (66%). Rhinitis and topic eczema were detected in 281 (97%) and in 13 (5%) of the patients, respectively. The sample was representative of the children and adolescents in the community who attended the public health care facilities. As for the severity of asthma, 107 subjects (35%) were classified as having mild asthma (steps 1 and 2), whereas 88 (29%) and 110 (36%) as having moderate asthma (step 3) and severe asthma (steps 4 and 5), respectively. Mean pulmonary function test results showed normal values; FEV_1 in % of predicted was 97.2% ± 12.3%, and FEV_1/FVC ratio was 0.86 ± 0.08.

Phenotypic characterization of asthma clusters

Table 2 shows the distribution of patients and the variables studied among the clusters. Cluster 1 (normal pulmonary function test results, mild eosinophilic inflammation, low tendency toward exacerbation, asthma onset at a later age, and mild atopy) included 94 (33%) of the subjects; they were equally distributed by gender (53%), and most were identified as having mild asthma (64% in steps 1 or 2) and mild eosinophilic inflammation (blood eosinophil levels > 5% in 37% of the subjects). Cluster 1 exhibited the lowest tendency toward exacerbation—66% had had no hospitalizations due to asthma in the previous year,

Table 1. Baseline characteristics of the children and adolescents with asthma stratified by asthma severity.[a]

Characteristic	Asthma severity			Total	p
	Mild (steps 1-2)	Moderate (step 3)	Severe (steps 4-5)		
Number of subjects	100	84	105	289	
Anthropometric data					
Male	60 (60)	44 (52)	73 (70)	177 (61)	0.05
Age, years	12 ± 3	13 ± 4	12 ± 3	12 ± 3	0.44
BMI, kg/m^2	19.9 ± 4.1	20.2 ± 4.2	19.8 ± 4.2	19.9 ± 4.2	0.81
Obesity	13 (13)	10 (12)	9 (9)	32 (11)	0.57
Race					
White	66 (66)	57 (68)	66 (63)	190 (66)	
Brown	30 (30)	25 (30)	35 (33)	90 (31)	0.93
Black	4 (4)	2 (2)	4 (4)	10 (3)	
Age at asthma onset, years					
≤ 2	67 (67)	59 (70)	72 (69)	199 (69)	
3-6	21 (21)	17 (20)	21 (20)	59 (20)	0.18
≥ 7	12 (12)	8 (9)	12 (11)	32 (11)	
Atopy	89 (89)	76 (89)	100 (95)	265 (92)	0.41
Pulmonary function					
FEV_1, % predicted	100.2 ± 12.0	97.5 ± 11.6	94.5 ± 13.1	97.2 ± 12.3	0.32
FEV_1/FVC	0.88 ± 0.06	0.85 ± 0.08	0.85 ± 0.09	0.86 ± 0.08	0.03
Fixed airway obstruction	8 (8)	12 (14)	18 (17)	38 (13)	0.14
Bronchodilator response	17.5 ± 9.3	20.1 ± 11.4	22.9 ± 16.6	20.2 ± 13.1	0.01
Hospitalization due to asthma in the previous year					
None	56 (56)	48 (57)	57 (45)	151 (52)	
1-3	24 (24)	21 (25)	28 (27)	73 (25)	0.31
≥ 4	20 (20)	15 (18)	30 (27)	66 (23)	
Exacerbation tendency	36 (36)	40 (48)	43 (41)	119 (41)	0.28
Hospitalization in an ICU	7 (7)	6 (7)	13 (12)	26 (9)	0.31

BMI: body mass index. [a]Values expressed as n (%) or mean ± SD.

30% showed a tendency toward exacerbation, and 5% had a history of ICU admission. Atopy was less common in cluster 1 subjects than in those in the other clusters (negative tests for specific serum IgE in 16% and mean total IgE = 721.1 ± 682.3 IU/mL). The pulmonary function was characterized by showing the highest values for pre- and post-bronchodilator FEV_1 (% of predicted) and for the FEV_1/FVC ratio. Labile bronchodilator response (mean FEV_1 = 16.5% ± 9.5% of predicted) and fixed airway obstruction were the lowest among the clusters, whereas the age at asthma onset was the highest (≥ 7 years of age in 19%).

Cluster 2 (normal pulmonary function test results, severe eosinophilic inflammation, severe atopy, high tendency for exacerbation, and early age at asthma onset) comprised the smallest number of subjects (n = 87; 30%). It primarily comprised male subjects (56%) with moderate asthma (step 3; 47%), increased blood eosinophilic inflammation (blood eosinophil levels > 5% in 98%), and increased IgE (mean = 1,361.6 ± 1,137.8 IU/mL). The specific serum IgE test was primarily positive for mites (37%), and upper respiratory tract infection was the most relevant asthma trigger (70%). Health care utilization in the previous year ranged between that in clusters 1 and 3; however, the tendency toward exacerbation was the highest (58%). Pulmonary function was predominantly normal; only 4 (5%) of the patients were diagnosed with fixed airway obstruction. Moreover, most of the subjects in cluster 2 had an early age at asthma onset (< 2 years in 77%).

Cluster 3 (poor pulmonary function test results, severe eosinophilic inflammation, severe atopy, and high tendency for exacerbation) comprised the largest group (n = 108; 37%). This cluster exhibited the highest proportion of male subjects (72%), with predominately severe asthma (step 4 or 5 in 54%), increased eosinophilic inflammation (eosinophil levels > 5% in 86%), and high IgE levels (mean = 1,222.6 ± 973.0 IU/mL). The specific serum IgE test was predominantly positive for multiple factors (90%), and the majority presented multiple asthma triggers (74%). The subjects in cluster 3 exhibited a greater number of exacerbations than did those in the other clusters (hospitalizations due to asthma in the previous year in 64% and history of ICU admission in 16%). The subjects in cluster 3 had the worst pulmonary function test results (the lowest pre- and post-bronchodilator FEV_1 in % of predicted and FEV_1/FVC ratio). Moreover, those subjects most often showed fixed airway obstruction, labile VEF_1, and poor bronchodilator responses than did those in the other clusters.

Discriminant analysis

The multiple discriminant analysis using the same 20 variables included in the cluster analysis indicated that 10 variables strongly discriminated the cluster: atopic burden (blood eosinophil levels and specific serum IgE test), pulmonary function (fixed airway obstruction, labile FEV_1, and poor bronchodilator response), health care utilization (tendency toward exacerbation and hospitalization in the previous year), asthma triggers, asthma severity, and age at onset of asthma. The discriminant function model exhibited good accuracy and predicted 90% of the case allocations correctly. The second discriminant analysis, in which asthma severity (prescribed treatment step 1, 2, 3, 4, or 5) was used as a dependent variable exhibited poor accuracy and predicted only 31% of the case allocations correctly.

DISCUSSION

Asthma in children and adolescents is a complicated and heterogeneous disorder with distinct phenotypes. We identified three clusters by using an unsupervised cluster analysis in low-income children and adolescents with a wide range of levels of asthma severity. In cluster 1, there were less frequent health care utilization, milder atopy, older age at asthma onset, milder asthma, and normal lung function. The patients in cluster 2 showed normal pulmonary function test results, more severe eosinophilic inflammation, more severe atopy status, a moderate number of exacerbations, and asthma onset at an earlier age. Finally, the patients in cluster 3 presented with poor pulmonary function, severe eosinophilic inflammation, severe atopy status, and high number of exacerbations.

The demographic characteristics of our patients are consistent with childhood asthma, the characteristics of which include a higher proportion of boys, early age at asthma onset, and there are presence of atopy and a high prevalence of rhinitis. The coexistence of atopy, rhinitis, and asthma has also been previously observed in a cross-sectional study including children with asthma.[17] The authors suggested that asthma, rhinitis, and eczema can be classified altogether as an allergic comorbidity.

The cluster analysis indicated only three clusters of children and adolescents with shared phenotypic characteristics, whereas Fitzpatrick et al.[6] described four clusters, and Howrylak et al.[7] described five clusters. The characteristics that differentiated each cluster were similar to the characteristics reported in previous studies[6,7,18]; the common characteristics among the current and the previous studies included atopic burden, lung function, and health care utilization. However, the age at the onset of asthma in our study was a distinguishing feature when we compare it with the study by Fitzpatrick et al.[6] The clusters previously reported exhibited more heterogeneous clinical features when compared with those in the present study, which was grouped into only three clusters. We also observed that there was an association of a high proportion of patients with allergy due to multiple factors with poorer pulmonary function, severe asthma, more severe eosinophilic

Table 2. Characteristics of the children and adolescents with asthma stratified by cluster analysis.[a]

Characteristic	All	Cluster 1	Cluster 2	Cluster 3	p
Number of subjects	289	94	87	108	
Anthropometric data					
Male	177 (61)	50 (53)	49 (56)	78 (72)	0.01
Age, years	12 (3)	11 (4)	12 (3)	13 (3)	0.04
BMI, kg/m^2	19.9 ± 4.2	19.4 ± 3.5	19.6 ± 4.0	20.6 ± 4.0	0.10
Obesity	32 (11)	11 (12)	8 (9)	13 (12)	0.79
Race					0.06
White	190 (66)	59 (63)	54 (62)	76 (70)	
Brown	90 (31)	35 (37)	27 (31)	28 (25)	
Black	10 (3)	0 (0)	6 (7)	4 (4)	
Asthma severity, step					< 0.001
1	74 (25)	47 (50)	2 (2)	25 (23)	
2	26 (9)	13 (14)	12 (14)	1 (1)	
3	84 (29)	19 (20)	41 (47)	24 (22)	
4	98 (34)	13 (14)	31 (36)	53 (49)	
5	8 (3)	2 (2)	1 (1)	5 (5)	
Age at asthma onset, years					< 0.001
≤ 2	199 (69)	52 (55)	67 (77)	79 (73)	
3-6	59 (20)	24 (25)	20 (23)	15 (14)	
≥ 7	32 (11)	18 (19)	0 (0)	14 (13)	
Asthma triggers					< 0.001
URTI	138 (48)	53 (56)	61 (70)	24 (22)	
Exercise	23 (8)	8 (8)	11 (12)	4 (4)	
Multiple	129 (44)	33 (35)	15 (17)	80 (74)	
Hospitalization due to asthma in the previous year					< 0.001
None	151 (52)	62 (66)	50 (57)	39 (36)	
1-3	73 (25)	19 (20)	22 (25)	32 (30)	
≥ 4	66 (23)	13 (14)	15 (17)	37 (34)	
Exacerbation tendency	119 (41)	28 (30)	51 (58)	40 (37)	< 0.001
Hospitalization in an ICU	26 (9)	5 (5)	4 (5)	17 (16)	< 0.01
Atopic status					
IgE, IU/mL	1101.3 ± 980.7	721.1 ± 682.3	1361.6 ± 1137.8	1222.6 ± 973.0	< 0.001
Specific serum IgE test results					< 0.001
Negative	25 (9)	15 (16)	9 (10)	1 (1)	
Mites	61 (21)	18 (19)	32 (37)	11 (10)	
Multiple	204 (70)	61 (65)	46 (53)	96 (89)	
Blood eosinophils	8.1 ± 5.0	4.3 ± 3.1	10.6 ± 4.7	9.4 ± 4.8	< 0.001
Blood eosinophils > 5%	214 (74)	35 (37)	85 (98)	93 (86)	< 0.001
Reported comorbidities					
Allergic rhinitis	281 (97)	91 (97)	86 (99)	103 (95)	0.38
Topic eczema	13 (5)	4 (4)	3 (3)	6 (6)	0.77
Reflux	18 (6)	5 (5)	3 (3)	10 (9)	0.22
Bronchiectasis	6 (2)	2 (2)	2 (2)	2 (2)	0.97
Sinus infection	19 (7)	7 (7)	4 (5)	8 (7)	0.67
Pulmonary function					
Pre-BD FEV_1, % predicted	97.2 ± 12.3	102.1 ± 9.7	97.7 ± 13.9	92.9 ± 12.3	< 0.05
Post-BD FEV_1, % predicted	104.3 ± 13.3	108.8 ± 10.5	106.1 ± 15.4	98.5 ± 10.2	< 0.05
FEV_1/FVC	0.86 ± 0.08	0.90 ± 0.05	0.86 ± 0.06	0.82 ± 0.09	< 0.001
FEV_1 lability[b]	160 (55)	31 (33)	40 (46)	89 (82)	< 0.001
Fixed airway obstruction	38 (13)	1 (1)	4 (5)	33 (31)	< 0.001
Bronchodilator response	20.2 ± 13.1	14.3 ± 8.2	18.0 ± 9.7	27.2 ± 15.6	< 0.001

BMI: body mass index; URTI: upper respiratory tract infection; and BD: bronchodilator. [a]Values expressed as n (%) or mean ± SD. [b]Variation > 20% in pre-BD FEV_1 in one year.

inflammation, and a higher number of exacerbations. These findings are supported by a previous study demonstrating that patients presenting multiple allergy sensitizations also had a higher level of severity (moderate to severe asthma), a greater proportion of asthma exacerbations, and a significantly greater proportion of inflammatory markers.[8]

In our study, the discriminant analysis that used asthma severity as the dependent variable exhibited poor accuracy and predicted only 31% of the case allocations correctly. Moreover, only the FEV_1/FVC ratio and the response to bronchodilators were significantly different among the groups. Health care utilization and fixed airway obstruction were not distinguishing features of asthma severity. Similarly to other studies involving children[6-8] or adults,[2-4] the asthma phenotypes did not correspond to the levels of asthma severity proposed by the GINA guidelines.[9] Moreover, asthma exacerbations and different levels of asthma severity were identified in all of the clusters, a finding that corroborates the study by Fitzpatrick et al.[6] Despite few asthma symptoms and normal lung function, children with asthma also had severe exacerbations. For example, even children and adolescents with mild asthma reported ICU admissions. These findings might have occurred because of the poor socioeconomic conditions in our population; sometimes it is difficult for them to receive proper medical treatment during their infrequent asthma exacerbations, which might worsen their respiratory status and lead them to an ICU.

The degree of pulmonary function impairment in children and adolescents is significantly lower than that previously observed in adults. Although fixed airway obstruction was more frequently found in the patients in cluster 3, it was also identified in those in the other two clusters (13% of the subjects). Therefore, spirometry alone is not a good parameter to determine asthma severity, and the use of spirometry for the management of childhood asthma seems not to improve, by itself, the quality of life of the patients.[19] Most patients (87%) had no fixed airway obstruction, and this fact may present a window of opportunity for proper treatment.

In our population, we did not identify an association between obesity and asthma severity, as previously reported in adults.[20]

In summary, childhood asthma is characterized by the presence of atopy, a high rate of exacerbations, and fairly preserved lung function. We identified various similarities with the previous clusters that had been described in children and adolescents, and this indicates that this approach has good generalizability. Our study might contribute to a better understanding of asthma phenotypes due to the lack of studies investigating asthma phenotypes in low-income children and adolescents.

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Association of tuberculosis with multimorbidity and social networks

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Study carried out in the Departamento de Epidemiología, Servicios de Salud de Sonora, Hermosillo, México, and in the Departamento de Salud Pública, Escuela de Medicina, Facultad de Salud, Universidad Industrial de Santander, Bucaramanga, Colombia.

ABSTRACT

The combination of tuberculosis with other diseases can affect tuberculosis treatment within populations. In the present study, social network analysis of data retrieved from the Mexican National Epidemiological Surveillance System was used in order to explore associations between the number of contacts and multimorbidity. The node degree was calculated for each individual with tuberculosis and included information from 242 contacts without tuberculosis. Multimorbidity was identified in 49.89% of individuals. The node degrees were highest for individuals with tuberculosis + HIV infection ($p < 0.04$) and lowest for those with tuberculosis + pulmonary edema ($p < 0.07$). Social network analysis should be used as a standard method for monitoring tuberculosis and tuberculosis-related syndemics.

Keywords: Tuberculosis/epidemiology; HIV; Nutrition, public health.

Tuberculosis is the second leading cause of death from an infectious disease worldwide, occurring primarily in developing countries.[1] In Mexico, the highest rates of morbidity and mortality from tuberculosis occur in only 0.95% of all municipalities, one of which is Hermosillo, the capital of the state of Sonora, in northwestern Mexico, near the United States-Mexico border. Spatial analysis has revealed clusters of tuberculosis cases there, in areas of high social deprivation.[2] Other risk factors for tuberculosis include belonging to an ethnic minority, consuming drugs or alcohol, having been in prison, being a panhandler, being HIV-positive, being male, and being young.[3] Transnational migration and the complex population dynamics of border areas such as the city of Hermosillo have also been considered particularly important, given that they can contribute to drug resistance.[4]

Although the associations between certain social determinants and the occurrence of tuberculosis have been explored,[5] the relationships among individuals have been less studied. Although one recent study explored social groups (social networks) among individuals with tuberculosis,[6] no social network analysis (SNA) methods were used. This type of analysis is important because it explores a new dimension of variables that goes beyond the traditional epidemiological approach based on the study of differences among persons, times, and places. SNA is the standard quantitative approach to the study of relationships among nodes, as in the case of individuals with tuberculosis. For instance, this methodology has been used in order to study how tuberculosis is transmitted during endemic and epidemic periods,[7-12] making it possible to identify the individuals and characteristics that facilitate transmission.

Tuberculosis has been reported in association with malnutrition, diabetes, smoking, alcoholism, chronic pulmonary disease, and HIV infection.[13,14] The combination of tuberculosis with other diseases, which is now known as "multimorbidity,"[15] is important because it can complicate clinical treatment and increase costs, among other reasons.[14] Given that previous social network analyses of individuals with tuberculosis have not addressed the topic of multimorbidity, the objective of the present study was to explore possible associations between the number of contacts and multimorbidity.

Epidemiological surveillance data for the city of Hermosillo were analyzed with the use of the Mexican National Epidemiological Surveillance System Integrated Information Platform (tuberculosis module). General data on patients registered with the Sonora State Medical Department were retrieved from the aforementioned system over a period of five months. In addition, reported data on contacts and comorbidities were collected for all patients admitted for medical examinations.

Some of the characteristics of the study participants were described by measures of central tendency and dispersion. A truth table was then constructed to describe the different presentations of multimorbidity in the individuals with tuberculosis. With those data, first-order egocentric social networks of individuals with tuberculosis were constructed; for those networks, a symmetric matrix was generated and subsequently converted into graphs with the program NetDraw, version 2.111.[16] The degree of each node in the network was then calculated with the program UCINET, version 6.232.[17] The degree of a node is a measure of centrality corresponding to the number of edges connected to a given node (i.e., its number of

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direct contacts).[18] Finally, the Mann-Whitney U test was used in order to compare the groups of individuals with and without each of the secondary diagnoses, the program Stata, version 13 (StataCorp LP, College Station, TX, USA), being used to that end.

Of the individuals with tuberculosis (n = 90), most (76.67%) were male, whereas, of those without tuberculosis (n = 242), approximately half (50.40%) were female ($p < 0.001$). The individuals with tuberculosis varied widely in age (from 3 to 79 years), the median age being 30.5 years. Table 1 shows the distribution of multimorbidity among the individuals with tuberculosis, 49.89% of whom had tuberculosis and another disease. The most common comorbidities (and combinations of comorbidities) were diabetes, malnutrition, HIV infection, malnutrition + alcoholism, and heart failure + pulmonary edema, which together accounted for approximately three fifths of all comorbidities.

Figure 1 shows all first-order egocentric social networks of individuals with tuberculosis in the city of Hermosillo. The low density of the network is notable, as is the range of node degrees (from 0 to 9). A comparison of the node degrees for all types of multimorbidity (or lack thereof) revealed significant differences only between the node degree for tuberculosis + HIV infection and that for tuberculosis + pulmonary edema. The node degree for tuberculosis + HIV infection was higher than were those for tuberculosis + any other disease, whereas the node degree for tuberculosis + pulmonary edema was lower than was that for tuberculosis without pulmonary edema.

To the best of our knowledge, this study presents the first results of SNA of individuals with tuberculosis alone or in combination with other diseases in Mexico. Comorbidity was found to be common, and the most common comorbidities were malnutrition, alcoholism,

Table 1. Multimorbidity among individuals with a recent diagnosis of tuberculosis in the city of Hermosillo, Mexico (n = 90).

Secondary diagnosis	Tuberculosis (primary diagnosis)																n	p
HIV infection	☑	☑	☑														7	0.0420
Alcoholism				☑	☑	☑	☑	☑	☑								12	0.1788
Diabetes										☑							7	0.1875
Malnutrition	☑	☑		☑	☑	☑	☑				☑						17	0.5950
Cancer				☑	☑							☑					3	0.1249
Heart failure													☑				3	0.1168
Pulmonary edema				☑									☑	☑			5	0.0763
Other diseases					☑	☑		☑				☑			☑		13	0.0226
Cases (n)	1	1	5	1	1	2	5	1	1	7	6	1	3	1	8	47		
(%)	1.11	1.11	5.56	1.11	1.11	2.22	5.56	1.11	1.11	7.78	6.67	1.11	3.33	1.11	8.89	51.11		
Comorbidity (%)	2.27	2.27	11.36	2.27	2.27	4.55	11.36	2.27	2.27	15.92	13.64	2.27	6.82	2.27	18.19			

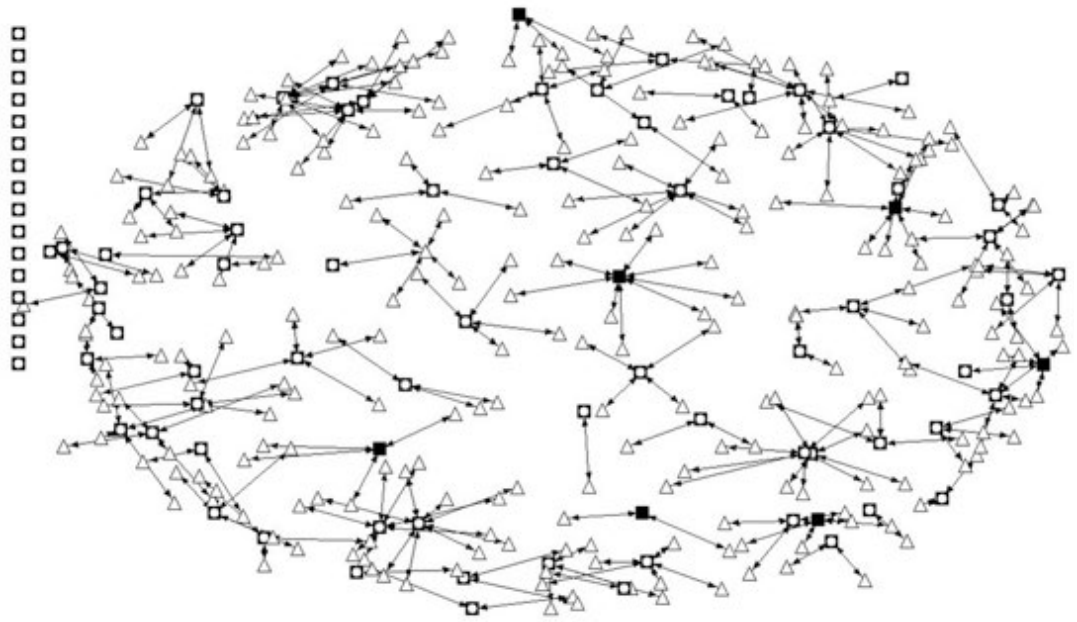

Figure 1. Social networks of individuals with tuberculosis in the city of Hermosillo, Mexico (n = 342). Squares represent individuals with tuberculosis, whereas triangles represent individuals without tuberculosis; black nodes represent individuals with HIV infection.

HIV infection, and diabetes, findings that are consistent with the literature.[14] In addition, individuals with tuberculosis + HIV infection tended to have more contacts than did those with tuberculosis + any other disease, whereas the opposite was true for those with tuberculosis + pulmonary edema. On the basis of our data, this might be related to the age of the individuals with tuberculosis; those with tuberculosis + HIV infection tended to be younger, whereas those with tuberculosis + pulmonary edema tended to be older. Another possible explanation is that those with tuberculosis + HIV infection can easily live in the community while receiving treatment, whereas those with tuberculosis + pulmonary edema typically require hospital treatment and therefore become isolated from their social networks.

Some of the most important limitations of the present study are related to problems inherent to how data are collected in the Mexican National Epidemiological Surveillance System and the system protocols. The system is based on Official Mexican Standard NOM-017-SSA2-1994 and includes relatively few variables. In addition, the complete network was unavailable; only immediate (i.e., degree 1) networks were available. Given the cross-sectional design of the study, it was impossible to establish the temporality between the network of contacts and infection. This is important because differences in the number of contacts can reflect events that occurred before or after the diagnosis of tuberculosis or some of the concomitant diseases.

This is a pioneering study of multimorbidity and the social networks of individuals with tuberculosis. By incorporating the importance of the different positions and roles of individuals in their social relationships, it is possible to begin to go beyond the view of person-time-place variables as predictors of disease. This means that the analysis begins to change from one of comorbidity to one of syndemics. This term, coined by Merill Singer and Scott Clair,[19] makes it possible to describe the co-occurrence of diseases and their mutual reinforcement in epidemics or clusters. It also contributes to understanding their presence in terms of the consequences of social inequities and injustice.[20] This type of approach has been recommended to complement the conventional methods used for contact investigations,[11] and surveillance systems should therefore incorporate social network tools as a first step toward exploring nonbiological determinants.

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Respiratory manifestations in late-onset Pompe disease: a case series conducted in Brazil

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ABSTRACT

Objective: To describe respiratory function in a series of patients with late-onset Pompe disease after the definitive diagnosis and before enzyme replacement therapy. **Methods:** This was a cross-sectional study involving patients with a definitive molecular diagnosis of late-onset Pompe disease. The data analyzed included age at symptom onset; age at definitive diagnosis; type of initial symptoms; time from symptom onset to diagnosis; FVC in the sitting and supine positions; six-minute walk distance; and locomotor ability. Analyses were carried out using frequencies, medians, minimum values, and maximum values. **Results:** Six patients were included in the study. The median age at symptom onset was 15 years (range, 13-50 years), and the median age at diagnosis was 39.5 years (range, 10-64 years). The median time from symptom onset to diagnosis was 8 years (range, 0-45 years). In all cases, the initial manifestation of the disease had been motor weakness. The median FVC in percentage of the predicted value (FVC%) in the sitting and supine positions was 71.0% (range, 22.9-104.6%) and 58.0% (range, 10.9-106.9%), respectively. The median ΔFVC% was 24.5% (range, −4.59 to 52.40%).The median six-minute walk distance was 391.7 m (range, 97-702 m). **Conclusions:** In this case series, the time from symptom onset to diagnosis was long. Although respiratory signs or symptoms were not the initial manifestations of the disease, 66.7% of the patients showed reduced FVC% in the sitting and supine positions at diagnosis.

Keywords: Glycogen storage disease type II; Respiratory function tests; Respiratory muscles/pathology.

INTRODUCTION

Pompe disease (PD), also known as glycogen storage disease type II, is an autosomal recessive hereditary disease caused by mutations in the gene encoding acid alpha-glucosidase, an enzyme that is responsible for the degradation of glycogen, especially at the muscle level.

Data on the incidence of PD are inaccurate, because of the rarity, underdiagnosis, and ethnic distribution of the disease. Data from the United States estimate that its overall incidence is approximately 1:40,000.[1] More recent studies that have been conducted in Taiwan and Austria and are based on neonatal screening programs have found higher incidences of approximately 1:28,000.[2,3] In Latin America, only 88 patients had been reported to have the disease by 2012.[4] Data from Brazil are unavailable.

PD is characterized by lysosomal accumulation of glycogen, especially in skeletal and cardiac striated muscles, beginning when acid alpha-glucosidase activity falls below the critical level of 30%. It is classified as classic infantile PD, with symptom onset occurring before the first year of life, accounting for approximately 28% of all cases; and as late-onset PD, when symptoms appear after that period, including children, youths, and adults. Disease progression in late-onset PD is slower than that in infantile PD, but it is quite variable. Clinical manifestations and disease severity vary according to age at symptom onset, rate of progression, and extent of organ involvement.[5-7]

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Until recently, treatment of PD was considered to be only palliative. In 2006, the commercial use of enzyme replacement therapy (ERT) with recombinant human alpha-glucosidase (alglucosidase alpha; Myozyme®, Genzyme, Cambridge, MA, USA) was approved in the USA and Europe, and, in 2007, it was also approved in Brazil. The treatment seems to improve respiratory and locomotor functions, as well as survival, in both forms of the disease.[8-10]

Muscle weakness is the major symptom in late-onset PD. The paravertebral and proximal lower limb muscles are usually the first to be affected, making it difficult to perform activities of daily living and favoring postural changes.[5] The respiratory consequences of muscle weakness result in restrictive lung disease, with a reduction in vital capacity accompanied by a reduction in FEV_1. Initially, breathing is compromised only during sleep, but later on, hypoventilation will occur during the day as well. There is impairment in the cough mechanism and airway clearance, leading to recurrent respiratory infections. Respiratory dysfunction will occur in approximately 75% of patients.[11] Without treatment, FVC is expected to decrease by 1.0% to 4.6% annually.[5,12,13] Respiratory failure is the major cause of death.[14-16]

The predominance of diaphragmatic weakness over weakness of other respiratory muscles seems to be a characteristic of PD.[17,18] Therefore, the use of methods capable of assessing the activity of the diaphragm alone can be useful in describing and monitoring the disease. Measurement of transdiaphragmatic pressure is the gold standard for the diagnosis of diaphragmatic dysfunction; however, other simpler methods, such as measurement of FVC in the supine position and difference between sitting and supine FVC have been described and recommended for the clinical follow-up of PD.[16,19-21]

At present, little is known about pulmonary manifestations in patients with PD in Brazil, which contributes to the management difficulty in this population. The objective of the present study was to characterize the profile of patients with PD and to describe respiratory function in a series of such patients followed at a referral center for rare diseases in Brazil, after the definitive diagnosis and before ERT.

METHODS

This was a cross-sectional study involving data obtained from the medical records of patients with a definitive diagnosis of late-onset PD and followed at the Center for Medical Genetics of the Fernandes Figueira National Institute for Women's, Children's, and Adolescents' Health, *Fundação Oswaldo Cruz* (Fiocruz, Oswaldo Cruz Foundation), located in the city of Rio de Janeiro, Brazil, between 2010 and 2015. Data on clinical history and respiratory function for the period after the diagnosis and prior to the initiation of ERT were analyzed. The exclusion criterion was a lack of data on respiratory function at diagnosis. The study was approved by the local research ethics committee, as part of the International Pompe Disease Registry.

Patient's characteristics and clinical history included data on gender, type of pathogenic mutation, age at symptom onset, type of initial symptoms (motor or respiratory), age at definitive diagnosis, and time from symptom onset to definitive molecular diagnosis. The major initial motor symptoms that are commonly reported and described for PD and that were sought from the medical records included lower limb proximal muscle weakness and/or upper limb proximal muscle weakness; difficulty running, climbing stairs, or walking; frequent falls; trunk muscle weakness; and scoliosis. Respiratory symptoms included orthopnea, dyspnea after exercise, dyspnea at rest, and sleep-disordered breathing.[22] The sample was further characterized on the basis of locomotor function as assessed by the Walton and Gardner-Medwin (WGM) scale[23] and the six-minute walk distance (6MWD). The WGM scale characterizes locomotor ability and has a score ranging from 0 to 10, with 0 indicating that the patient performs all activities normally and 10 indicating that the patient is completely bedridden. The 6MWD was recorded in meters and as a percentage of the predicted value, using equations from Iwama et al.[24] and Priesnitz et al.,[25] for each age group.

The respiratory function variables of interest included FVC, as measured in the sitting and supine positions, and FEV_1, both of which are expressed as a percentage of the predicted value (FVC% and FEV_1%); as well as FEV_1/FVC ratio (in %)[26]; difference between sitting and supine FVC (ΔFVC%), as calculated using the equation [(sitting FVC − supine FVC)/sitting FVC] × 100; use of (invasive or noninvasive) mechanical ventilatory support; and presence of an artificial airway. Volumes were measured with a MasterScope® spirometer (Jaeger, Hoenberg, Germany), in accordance with the criteria established by the American Thoracic Society,[27] and FVC values ≥ 80% of predicted were considered normal for the sitting position.

Data were analyzed using descriptive statistics via IBM SPSS Statistics for Windows, version 20.0 (IBM Corp., Armonk, NY, USA). Nominal variables are presented as frequency, and numerical variables are presented as median and range (minimum to maximum).

RESULTS

During the study period, we identified seven patients with late-onset PD, all of whom were followed at the institution. Only one patient was excluded because he had no spirometry results for the period in question. The individual results are described in Tables 1 and 2. Of the included patients, four (66.7%) were male. All patients were compound heterozygous for the mutation found. The intronic mutation c-32-13T>G, which is known as potentially mild, was present in 100% of the cases, and the nonsense mutation c.2560C>T, which is known as very severe,[28] was present in three (50%) of the cases.

The median age at symptom onset was 15 years (range, 13-50 years), and muscle weakness was found as the initial symptom in all patients, except in patient 2, who was asymptomatic at diagnosis. Frequent falls and difficulty climbing stairs, running, or performing vigorous exercise were reported. The median age at diagnosis was 39.5 years (range, 10-63 years), and diagnosis was made in two adolescents and four adults in accordance with the criteria established by the World Health Organization. The median time from first symptoms to confirmation of the diagnosis of PD was 8 years (range, 0-45 years), ranging from 0 to 2 years for the adolescents and from 4 to 45 years for the adults. All patients were able to walk. The minimum WGM scale score achieved was zero and the maximum WGM scale score achieved was 6, which indicates walking only with assistance. The median 6MWD was 391.7 m (range, 97-702 m and 19-110% of the predicted value for age).

Taking into account FVC in the sitting position, four patients (66.7%) showed respiratory system impairment at diagnosis, with FVC% < 80% of predicted and normal FEV_1/FVC ratio, characterizing restrictive lung disease, as is expected for neuromuscular diseases. Only one patient already used noninvasive mechanical ventilatory support intermittently, being the one who showed the lowest FVC% in the sitting and supine positions (22.9% and 10.9%, respectively) and the highest ΔFVC% (52.38%). None of the patients used invasive ventilatory support or had been tracheostomized. The median FVC% in the sitting position was 71% (range, 22.9-104.6%), the median FVC% in the supine position was 58% (range, 10.9-106.9%), the median ΔFVC% was 24.5% (range, −4.59% to 52.4%), the median FEV_1% was 70.35% (range, 27.0-106.8%), and the median FEV_1/FVC ratio (in %) was 102.4% (range, 96.3-118.0%). Stratification by age group showed that only two adolescents had spirometry results within the normal range.

DISCUSSION

The clinical history characteristics of our patients with PD were similar to those found in the literature. The type of initial symptoms was predominantly motor, the median age at diagnosis was 39.5 years, and the delay between symptom onset and diagnosis was 8 years. Data from Byrne et al.,[16] obtained through analysis of the PD patient registry administered by the Genzyme Corporation, revealed a predominance of motor symptoms, a median age at diagnosis of 37.1 years, and a delay in diagnosis of 4 years. The delay in diagnosis was slightly greater in the analysis carried out by Kishnani et al.[22] The median age at symptom onset was lower in our group of patients (15.0 years vs. 28.8 years).

The rarity of PD, the variability of its clinical presentation, its overlap of signs and symptoms with other neuromuscular diseases, and limited access to the health care system often result in a very long time to diagnosis. The delay in diagnosis seems to be greater in older subjects, which indicates improved knowledge of the disease today.[16,22] Taking into account that patients who are younger and less severely affected respond more favorably to administration of ERT,[13] the importance of early diagnosis and early treatment initiation is evident.

Table 1. General description of the patients in the present case series.[a]

ID	Gender	Birth, year	AGA mutation		Age at symptom onset, years	Type of initial symptoms	Age at molecular diagnosis, years	Delay in diagnosis, years
			Allele 1	Allele 2				
1	M	1992	c.-32-13T>G	c.2560C>T	15	Motor	17	2
2	F	2000	c.-32-13T>G	c.2560C>T	-	Asymptomatic	10	-
3	M	1988	c.-32-13T>G	c.2646+2T>A	13	Motor	25	10
4*	M	1958	c.-32-13T>G	c.1912G>T	50	Motor	54	4
5**	M	1954	c.-32-13T>G	c.1912G>T	13	Motor	58	45
6	F	1951	c.2560C>T,	c.-32-13T>G	40	Motor	63	23

ID: identification; F: female; and M: male. *Patients 1 and 2 and patients 4 and 5 were siblings.

Table 2. Functional description of the patients in the present case series.

ID	Sitting FVC, % of predicted	Supine FVC, % of predicted	ΔFVC, %	FEV_1, % of predicted	FEV_1/ FVC, % of predicted	Ventilatory support	WGM scale score	6MWD	
								m	% of predicted
1	104.6	94.4	9.72	106.8	100.7	No	0	500	77
2	102.2	106.9	-4.59	105.7	104	No	0	495	79
3	58.5	48.4	17.31	65.7	111.6	No	1	702	110
4	60.7	42.2	30.45	58.7	96.3	No	3	376	64
5	22.9	10.9	52.38	27	118	Yes	6	180	39
6	77	45	41.63	75	100	No	6	97	19

ID: identification; ΔFVC: difference between sitting and supine FVC; WGM: Walton and Gardner-Medwin; and 6MWD: six-minute walk distance.

More than 500 mutations have currently been identified, and the expected effects range from very severe to non-pathogenic.[28] The mutation most commonly observed in our group of patients is also the one most commonly reported by other authors.[16,29] However, the phenotypic behavior is not explained exclusively by the genotype found, especially in late-onset disease. Phenotypic differences are present even in members of the same family, including siblings.[29] Patients 1 and 2 and patients 4 and 5, respectively, were siblings with the disease. In both cases, differences were observed in presentation and severity. However, the diagnosis of the younger siblings was facilitated by their family history, enabling a better functional condition at diagnosis. Records show that 32% of patients with late-onset PD had a sibling with a diagnosis of PD[16]; therefore, we believe that family screening may be useful in identifying asymptomatic patients and may contribute to a better prognosis.

Monitoring of respiratory function in patients with PD is imperative.[6,7,20] In 2013, Ambrosino et al.[21] described basic management of respiratory dysfunction in PD, including periodic evaluations every 3-12 months, depending on the rate of disease progression; monitoring of respiratory signs and symptoms; spirometry in the sitting and supine positions; measurement of MIP; measurement of peak cough flow; blood gas analysis; and, in some cases, polysomnography and swallowing studies. Consensus statements and guidelines for the management of PD also have similar recommendations.[6,7,20,30]

The pathophysiology of chronic respiratory failure in neuromuscular diseases includes not only respiratory muscle weakness but also changes in chest wall compliance, central respiratory control, and swallowing, which, in turn, are responsible for Ineffective cough, alveolar hypoventilation, chest deformities, sleep apnea, atelectasis, airway hyperreactivity, and recurrent pneumonia.[31] Unlike other neuromuscular diseases, in which loss of walking ability precedes ventilatory failure,[5,17] in PD, respiratory symptoms may manifest early, being the initial symptom in 8.5% of cases.[4] Despite our small sample size, the results for locomotor ability and the 6MWD results, when compared against the spirometry results, seem to corroborate the hypothesis that impairment of the respiratory and locomotor systems is heterogeneous.[32] The patient with the greatest 6MWD already showed reduced FVC% in the sitting and supine positions and reduced ΔFVC%, whereas the patient with the shortest 6MWD did not have the most severe lung disease.

In our study, none of the patients followed had respiratory symptoms as the first manifestation. However, at diagnosis, we observed signs of respiratory system impairment, as identified by reduced FVC% in the sitting position (FVC < 80% of predicted), in 66.7% of them. Despite the absence of respiratory symptoms as the initial manifestation of the disease and the delay between symptom onset and the first spirometry, we cannot rule out the existence of some degree of respiratory impairment in the very early stages of PD, but without ignoring that age and duration of symptomatic disease also seem to contribute to a worsening of functional findings. It is possible that mild respiratory symptoms were present but went unnoticed because they overlapped with motor symptoms that were more prominent. Questioning and standardized description of the signs and symptoms found, especially at the onset of the disease, may facilitate knowledge and follow-up of patients.

Measures of respiratory muscle strength such as MIP and MEP may be highly relevant to identifying the onset of respiratory muscle impairment, given that changes in them may precede volume reduction as identified by vital capacity. Unfortunately, in our group of patients, we found no such data in the medical records of one of the patients, and two were unable to perform acceptable and reproducible maneuvers. Therefore, MIP and MEP measures could not be included in the analysis, and this represents a limitation of the study.

Diaphragmatic weakness is a dysfunction that is characteristic of PD,[17,18] being considered the major cause of disordered breathing during sleep and respiratory failure.[33] Prigent et al.,[34] using magnetic stimulation of the phrenic nerve, and Wens et al.,[18] using magnetic resonance imaging, confirmed the predominance of diaphragmatic weakness over weakness of thoracic respiratory muscles in PD. The most accurate method for assessing diaphragmatic function is to measure transdiaphragmatic pressure during maximal respiratory effort or during spontaneous breathing or use bilateral magnetic stimulation of the phrenic nerves. These methods have the disadvantage of being invasive and not being well accepted by patients, especially when they need to be repeated several times, resulting in them rarely being indicated in clinical practice.[35] A simpler way to assess diaphragmatic weakness is to measure sitting and supine FVC% and calculate their difference, which correlates strongly with variation in cranio-caudal diameter as observed by magnetic resonance imaging.[18,36] Normal subjects may show a reduction from sitting to supine FVC% as high as 10%.[37] Reductions > 25% characterize diaphragmatic weakness, with a sensitivity of 79% and a specificity of 90%.[19] In our sample, 66.7% of the patients showed ΔFVC% > 10%, and 50% showed ΔFVC% > 25%. This assessment is recommended for the diagnosis and follow-up of patients with PD because it is a potential marker of the severity of the respiratory dysfunction. A > 10% reduction strengthens the diagnosis of PD.[30] Other methods have also been described for diaphragmatic assessment, including fluoroscopy, ultrasonography, electromyography, and optoelectronic plethysmography[38]; however, they are still infrequently used in clinical practice in PD.

The explanation for the predominance of diaphragmatic involvement in respiratory dysfunction remains unclear. Animal model studies suggest that muscle damage is associated with spinal motoneuron pathology, especially phrenic motoneuron pathology,

and this contributes to a more pronounced deficit in the motor function of the diaphragm.[17,39,40]

As respiratory muscle weakness progresses, the use of noninvasive ventilatory support is indicated, helping to control nocturnal hypoventilation and sleep apnea syndrome, as well as acute and chronic respiratory failure.[14,21] Only one patient in our case series used this resource. Specific indications regarding when to start using ventilatory support in PD have not been described. The use of recommendations for neuromuscular diseases in general contributes to this process.

Respiratory system involvement was present in 66.7% of our patient sample, and diaphragmatic dysfunction as characterized by ΔFVC% > 25% was present in 50% of our series at diagnosis, suggesting that even if it is not the initial manifestation, respiratory system involvement may occur early in a significant number of cases. Further studies are needed for a better understanding of this involvement, especially of diaphragmatic dysfunction. The sign and symptom profile used by Llerena et al.[7] and Kishnani et al.,[22] the recommendations included in the International Pompe Disease Registry, and the respiratory management proposed by Ambrosino et al.[21] may be of great importance in the approach to patients with suspected PD or already diagnosed with PD.

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Extracorporeal respiratory support in adult patients

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ABSTRACT

In patients with severe respiratory failure, either hypoxemic or hypercapnic, life support with mechanical ventilation alone can be insufficient to meet their needs, especially if one tries to avoid ventilator settings that can cause injury to the lungs. In those patients, extracorporeal membrane oxygenation (ECMO), which is also very effective in removing carbon dioxide from the blood, can provide life support, allowing the application of protective lung ventilation. In this review article, we aim to explore some of the most relevant aspects of using ECMO for respiratory support. We discuss the history of respiratory support using ECMO in adults, as well as the clinical evidence; costs; indications; installation of the equipment; ventilator settings; daily care of the patient and the system; common troubleshooting; weaning; and discontinuation.

Keywords: Extracorporeal membrane oxygenation; Respiratory distress syndrome, adult; Hypoxia; Hypercapnia.

INTRODUCTION

Patients with severe ARDS presenting with refractory hypoxemia or hypercapnia have mortality rates that vary from 45% to 90% depending on the definition of refractoriness.[1,2] Extracorporeal membrane oxygenation (ECMO) has been used worldwide with encouraging results as rescue therapy for severe ARDS in adult patients.[3-6] ECMO is able to provide blood oxygenation, carbon dioxide removal, and circulatory support when suitable, allowing protective/ultraprotective mechanical ventilation.[7] In the present review, we aimed to explore some of the most relevant aspects involved in respiratory support using ECMO.

ECMO FOR RESPIRATORY SUPPORT IN ADULTS: HISTORY AND CLINICAL EVIDENCE

After an initial sequence of positive results with the use of ECMO in severely hypoxemic patients with ARDS,[8,9] the growing interest in ECMO support led to the first randomized clinical trial funded by the National Institutes of Health.[10] That trial was based on the rationale that hypoxemia and hypercapnia are the determinants of death in ARDS patients. Therefore, patients in the intervention group were supported with ECMO in order to improve their blood gases, and the ventilator settings were kept similar to those in the control group. The trial was interrupted early due to the equally high mortality rates in both groups.

After that trial, a group in Italy[11] published their experience using ECMO support in 43 patients, in whom high positive end-expiratory pressure (PEEP) values (15-25 cmH_2O), together with what they considered low peak pressures (35-45 cmH_2O) and low RR (3-5 breaths/min), were applied with the rationale of reducing the lung injury caused by the ventilator. In that case series, with an expected mortality rate of over 90%, survival was considered good in the 21 patients (49%) who had been discharged home. The hypothesis that the quasi-apneic ventilation (made possible because of ECMO) promoted lung protection generated enthusiasm again, leading to the second trial of ECMO for respiratory support in patients with severe ARDS in the United States, also funded by the National Institutes of Health.[12] Again, the trial results were disappointing, showing similar rates of survival in both groups (38%).

Despite that second setback, respiratory ECMO remained in use as a rescue therapy for severe hypoxemia or hypercapnia. With the growing knowledge of the substantial contribution of ventilator-induced lung injury as a cause of death in ARDS patients,[13] various groups published their experiences with the novel rationale of using respiratory ECMO to promote protective or ultraprotective ventilation, using peak airway pressures < 20-25 cmH_2O and very low tidal volumes (0.5-1.0 mL/kg). Some authors also showed that it was possible to use less sedation in order to allow more efficient interaction with the patient.[3,7] In

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those studies, survival rates among those severely ill patients with ARDS were as high as 88%.

Based on those favorable experiences, a multicenter randomized controlled trial was performed in the United Kingdom (UK) by the National Health System.[4] A total of 180 patients with severe ARDS were randomized to undergo conventional low airway pressure ventilation (in a local hospital) or ultraprotective ventilation using ECMO for respiratory support. Patients randomized to the ECMO group were transferred by the British Royal Air Force to Glenfield Hospital in Leicester, UK, without ECMO support. At that hospital, after approximately 12 h of protective ventilation, ECMO support was started if severe respiratory failure persisted. In that trial, ECMO was considered a cost-effective strategy for the UK. However, only 68 of the 90 patients randomized to the ECMO group actually received ECMO. The remaining 22 patients (24%) improved during the 12-h period of observation on protective mechanical ventilation. In a sense, the real hypothesis tested was whether the referral strategy, rather than the ECMO support, was effective.

The big ECMO boom occurred in 2009 with the publication of the abovementioned trial,[4] as well as with the outbreak of pandemic influenza A (H1N1). A great number of patients developed severe hypoxemic respiratory failure and received ECMO support. Survival rates in those patients were surprisingly high (above 70%)[5,6,14,15] despite the severity of their respiratory failure.

In conclusion, the current evidence favors the use of ECMO for respiratory support in adult patients with severe ARDS. However, the evidence is still scant and weak while we await the results of the ongoing Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome (EOLIA) trial, which is estimated to be completed in February of 2018.[16]

ECMO CONFIGURATION

The venovenous (vv) and venoarterial (va) ECMO configurations are shown in Figure 1. For respiratory purposes, we favor the use of the vv-ECMO configuration, which can adequately oxygenate blood and remove CO_2, allowing the use of gentle, protective mechanical ventilation. In the vv configuration, the oxygenator is in series with the native lungs; therefore, the residual function of the lungs remains important for systemic oxygenation.

The vv configuration does not provide circulatory support. For patients with respiratory failure but without severe circulatory dysfunction, vv-ECMO is associated with outcomes similar to those of va-ECMO, but with fewer complications.[17,18] In patients with severe ARDS and shock, hemodynamic instability can be due to an associated medical condition (e.g., sepsis and severe left ventricular dysfunction). In that scenario, va-ECMO is indicated in order to provide respiratory and circulatory support. Alternatively, shock can be secondary to acute *cor pulmonale,* a condition found in more than 22% of the patients on protective ventilation, with severe hypoxemia, or with acidemia.[19] Such conditions justify an attempt to use vv-ECMO even in patients with shock. Restoration of blood gases towards normal obtained with vv-ECMO can reduce pulmonary artery pressure and improve right ventricular function.[20] If that attempt with vv-ECMO fails, the patient can be switched to a hybrid configuration or to a va configuration.

Depending on the clinical indication, different hybrid cannulations can be used.[21] The two classical reasons to use a hybrid configuration are to improve blood drainage (to provide circulatory support) and to avoid the Harlequin syndrome (hypoxemia restricted to the upper part of the body). Sometimes the blood flow through the vein does not meet the demand generated by the pump. As a result, the negative pressure can suck

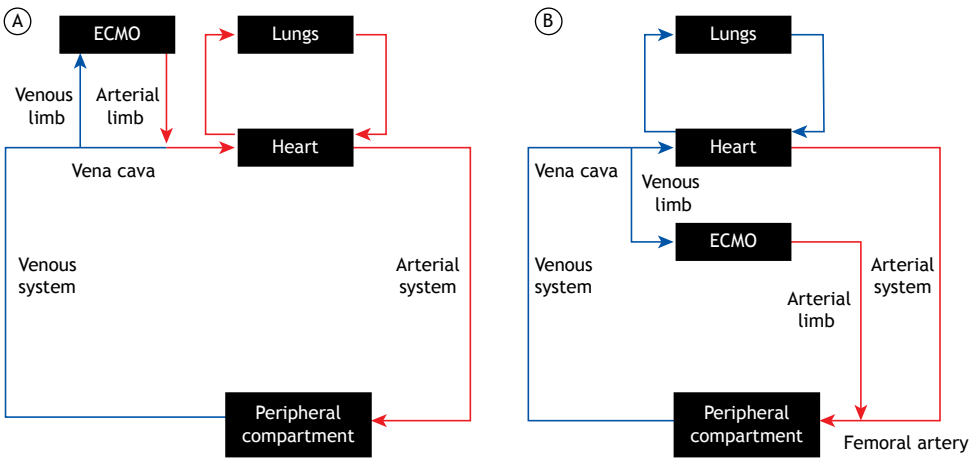

Figure 1. Basic extracorporeal membrane oxygenation (ECMO) configurations. Panel A shows the venovenous ECMO configuration, in which the extracorporeal system is in series with the lungs, providing only respiratory support. Panel B shows the venoarterial ECMO configuration, in which the extracorporeal system is in parallel with the heart and lungs, providing respiratory and cardiovascular support.

the venous wall into the access ports of the cannula, a situation referred to as the "sucking-up" phenomenon, leading to transient obstruction of the inlets and to a decrease in ECMO blood flow. The obstruction is usually brief (sometimes fractions of a second) until the vein is again filled with blood originating from the venous return. The process repeats itself indefinitely and usually leads to the chattering of the ECMO circuit. Prompt corrections involve either reducing ECMO blood flow (which might worsen hypoxemia) or administering fluid challenges (which can worsen lung function). An alternative solution is the insertion of an additional venous cannula using a "Y" piece in order to improve venous drainage. This hybrid configuration is known as venoarterial-venous (vav)-ECMO.

To avoid the Harlequin syndrome, a single-lumen (venous) cannula can be inserted, and blood return can occur through arterial and venous cannulas connected to a "Y" piece (vav-ECMO configuration). This configuration can be derived from an ongoing va- or vv-ECMO support session.

ECMO PHYSIOLOGY AND CIRCUIT

To reach adequate arterial oxygenation, extracorporeal blood flows higher than 60% of the cardiac output (> 3 L/min) are frequently necessary. Such flows are obtained by using peristaltic or centrifugal pumps, large-bore cannulas, and a circuit. The large diameter of the cannulas is important to avoid significant hemolysis. Although peristaltic and centrifugal pumps induce comparable amounts of hemolysis, we favor the use of the latter in the ICU, because they are able to avoid circuit rupture in the rare instance that blood flow obstruction occurs. Blood drains through a venous circuit, in which negative pressures as low as between −30 and −104 mmHg can be reached, passes through the pump, is propelled to the oxygenator with pressures up to the 350-400 mmHg range, and is then returned to the patient (Figure 2). In modern oxygenators, resistance to the passage of blood is low, although it still increases at higher blood flows and at higher temperatures.[22]

The oxygenator promotes gas exchange based on the diffusion principle. Fresh gas (or sweep gas), rich in oxygen and devoid of CO_2, crosses a respiratory membrane (polymethylpentene hollow fibers) in countercurrent flow with venous blood. The CO_2 removal from the blood is highly effective, depending on the blood flow, sweep gas flow, and venous CO_2 concentration.[23] Oxygen transfer can be more complicated, because it depends on blood flow, total oxygen-carrying capacity of the blood (which is mainly determined by hemoglobin concentration), and the effectiveness of oxygen diffusion through the respiratory membrane, which is 16-20 times lower than that of CO_2 diffusion. At low blood flows, the partial pressure of oxygen in the return circuit is very high, and oxygen transfer is mainly perfusion-limited. At higher blood flows, the partial oxygen pressure in the return circuit decreases, even though hemoglobin saturation remains high and oxygen transfer is both diffusion- and perfusion-limited. As a result, arterial blood oxygenation improves with increases in blood flow through the ECMO system

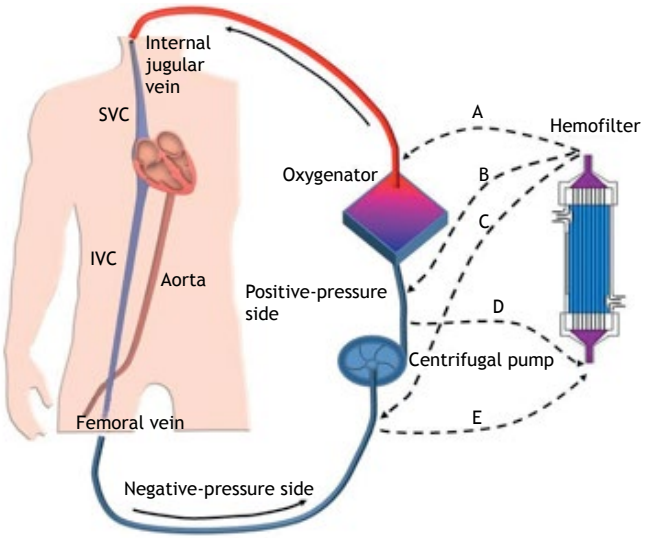

Figure 2. Venovenous extracorporeal membrane oxygenation (ECMO) configuration and possible connections with a hemofilter, with or without a dialysis machine. The drainage cannula is inserted into the femoral vein and advanced up to the inferior vena cava (IVC), whereas the return cannula is inserted into the internal jugular vein and advanced up to the superior vena cava (SVC). In this example, blood is drained by the suctioning action of a centrifugal pump into the negative-pressure side of the extracorporeal circuit. Downstream of the pump, blood is propelled into the positive-pressure side of the circuit, crosses the oxygenator, and is returned to the SVC. The dashed lines indicate different possibilities of connection to a hemofilter—downstream of the oxygenator (path A); downstream of the pump and upstream of the oxygenator (path B); upstream of the ECMO pump (path C); downstream of the ECMO pump (positive-pressure side, path D); and upstream of the ECMO pump (negative-pressure side, path E)—in patients requiring simultaneous renal replacement therapy.

despite the diffusion-determined loss of efficiency.[24] The sweep gas flow has little impact on oxygen transfer.[25]

In the vv-ECMO support configuration, systemic oxygenation depends on cardiac output, residual function of the native lungs, and vv-ECMO blood flow, whereas arterial CO_2 elimination mainly depends on the ECMO sweep gas flow, cardiac output, CO_2 production, and residual function of the native lungs. In the peripheral va-ECMO configuration (the most common venoarterial insertion used in the ICU at the bedside), blood is returned to the aorta against the flow of blood ejected by the left ventricle during systole. At low cardiac outputs, the coronary arteries, brachiocephalic trunk, left carotid artery, and left subclavian artery receive oxygenated blood returning from the ECMO system. If cardiac output improves and the lungs continue to show poor residual function, the upper half of the body can receive deoxygenated blood coming from the pulmonary veins, whereas the lower half of the body receives oxygenated blood coming from the ECMO circuit, a situation known as the Harlequin syndrome.

ECMO COSTS AND COST-EFFECTIVENESS

The cost of ECMO support is high. At current prices in Brazil, the equipment costs from US$ 8,000 to US$ 36,000 per patient. The gain in cost-effectiveness per quality-adjusted life year is reasonable in developed countries,[4] and it is possibly acceptable in Brazil.[26]

SUITABLE CANDIDATES FOR ECMO FOR RESPIRATORY SUPPORT

ECMO for respiratory support is potentially useful in patients with severe hypoxemia or severe hypercapnia, resulting in low pH (usually < 7.20) despite lung-protective mechanical ventilation. ECMO support is often tried after failed attempts at multiple rescue therapies, such as prone positioning, alveolar recruitment maneuvers, and use of nitric oxide, alone or in combination.

Our group uses the following inclusion criteria[27]:

Major criteria (both required)

- Acute pulmonary disease
- Possibility of recovery from disease

Complementary criteria (at least one required)

- PaO_2/FiO_2 ratio < 50 mmHg with an FiO_2 = 1 for at least 1 h, with or without rescue maneuvers
- PaO_2/FiO_2 ratio < 50 mmHg with an FiO_2 > 0.8 for at least 3 h, despite rescue maneuvers
- Hypercapnia with a pH < 7.2 despite an RR > 35 breaths/min, requiring tidal volumes ≥ 6 mL/kg of ideal body weight and plateau pressures > 30 cmH_2O
- Murray's score (lung injury score) > 3.0 in the presence of clinical deterioration

ECMO support is contraindicated in patients with chronic illnesses that impair their quality of life and in those with severe acute multiorgan dysfunction. Some scores can be used in order to predict mortality in patients on ECMO for respiratory support.[28,29] One of those (Respiratory Extracorporeal Membrane Oxygenation Survival Prediction)[29] is easily accessible from the Internet (www.respscore.com) and provides prognostic information that can be used in order to help select the patients. Being > 75 years of age is considered by some a relative contraindication. Long duration of mechanical ventilation prior to ECMO support initiation (generally > 7 days) is strongly associated with a poor prognosis and is also a relative contraindication to ECMO support.[28,29]

VASCULAR CANNULATION

Only peripheral venous cannulations, which are usually done at the bedside using the Seldinger technique, will be discussed here. An ultrasound vascular examination helps to select the cannulas, generally with a gauge 2 mm smaller than the vessel diameter.[27] The ultrasound also allows safe vascular punctures and the correct positioning of the cannulas.[30]

Using the vv-ECMO configuration, the drainage cannula (19-25 Fr/55-70 cm of length) is usually inserted into the femoral vein. The oxygenated venous blood returns to the patient using the reinfusion cannula, also known as arterial cannula (17-19 Fr/30-40 cm in length). The femoral-jugular configuration (with venous and arterial cannulas, respectively) is the most widely studied configuration and can provide blood flows within the 6-7 L/min range with little recirculation.[31] To optimize drainage, we favor placing the venous cannula at the junction of the inferior vena cava with the right atrium. The jugular-femoral configuration (with venous and arterial cannulas, respectively)[3] and the femoral-femoral configurations have also been used by experienced ECMO groups,[6] although higher recirculation has been reported when those configurations are compared with the femoral-jugular configuration.[31,32] The double-lumen (bicaval) cannula is another option to provide vv-ECMO support. The cannula is inserted through the jugular vein and must be positioned using transesophageal echocardiography or fluoroscopy. These double-lumen cannulas, which are still unavailable for clinical use in Brazil, have been associated with lower blood flows, high recirculation rate,[33] hemolysis,[34] and venous thrombosis.[35] Conversely, in patients requiring long-term ECMO support, such as those awaiting lung transplantation, the double-lumen cannula facilitates mobilization and can be a good choice.

ECMO SUPPORT SETTINGS

After the circuit has been primed (typically with crystalloid solutions warmed to 36°C), the ECMO blood flow is initiated at 500 mL/min, and the sweep gas flow is maintained at 1-2 L/min (FiO_2 = 1) until the extracorporeal system is filled with blood. Blood flow and the sweep gas flow are subsequently increased to 2,000 mL/min when using the vv-ECMO configuration. Blood flow and the sweep gas flow are then elevated

to a 1:1 ratio, with a target SpO_2 of at least 85%. In extracorporeal support due to hypercapnic respiratory failure, it is important to avoid overly rapid corrections of hypercapnia when initiating ECMO support. Failing to do so might promote alkalemia and a right shift of the oxygen-hemoglobin dissociation curve, as well as cerebral vasoconstriction. In those patients, we usually start the sweep gas flow at half of blood flow. For all patients, subsequent fine tuning of ECMO settings should be based on arterial blood gases: ECMO blood flow should be adjusted based on oxygen levels, and the sweep gas flow should be managed for adequate CO_2 and pH. The interval between blood sample collections varies according to ECMO blood flow; using low blood flows (~2,000 mL/min), intervals as long as 1.5 h are usually necessary to reach $PaCO_2$ equilibrium. With high blood flows (~3,500 mL/min), a shorter time (30 min) is usually sufficient.[36]

The oxygenation target varies among ECMO centers. Our group sought to reach a PaO_2 within the 55-60 mmHg range[37] with a normal pH (7.35-7.40).[27] In patients with high cardiac outputs and very low residual lung function, such targets can be impossible to reach, despite the use of ECMO. In such patients, instead of further damaging the lungs with injurious ventilator settings, it might be preferable to tolerate lower levels of oxygenation (permissive hypoxemia) in the absence of hypercapnic acidemia.[38] This strategy of permissive hypoxemia has also been proposed as a means of promoting ultraprotective or protective mechanical ventilation. An experienced ECMO group in Sweden, for example, allows systemic arterial saturation as low as 70% during the vv-ECMO initial run, when the residual function of the native lungs can be close to zero.[3] That group identified no significant neurocognitive or physical deficits in a cohort of patients with severe hypoxemia supported with vv-ECMO.[39] It is important to note, however, that other authors found an association between severe hypoxemia and long-term neurocognitive dysfunction in ARDS patients not supported by ECMO.[40]

The protective or ultraprotective mechanical ventilation during ECMO support is commonly achieved by using a PEEP of 10-15 cmH_2O, a plateau pressure of 20-25 cmH_2O, an RR of 10-15 breaths/min, an inspiratory time of 0.8-1.0 s, and an FiO_2 of 0.3 (or the minimum to achieve the desired PaO_2).[4,7,41] In patients with more severe lung injury, the use of higher PEEP values (13-15 cmH_2O) is associated with improved outcomes.[42,43] The approach of our group consists in first reducing the plateau pressure to < 25 cmH_2O after ECMO initiation, then setting the PEEP to 10-15 cmH_2O and the RR to 10 breaths/min, thereafter reducing the FiO_2.[27] Sometimes, at very low tidal volumes (e.g., < 0.5 mL/kg), chest expansion can be difficult to notice. That finding should not raise concern unless it is associated with an elevation of the HR, hypotension, or any other sign of worsening pulmonary hypertension.[4,27] When tidal volume is reduced to such extreme levels, the inhaled air should be warmed and humidified using an active (heated) humidifier.[44] A closed tracheal suctioning system can also be used in order to avoid depressurization during airway suctioning. Whenever possible, suctioning should be performed using assisted pressure-controlled mode or pressure-support mode, because the ventilator can compensate for the loss of flow to the suctioning system, thus minimizing alveolar derecruitment.[45]

After clinical stabilization, when the acute phase of lung inflammation subsides, spontaneous ventilation using pressure support can be allowed. The sweep gas flow can be adjusted aiming at optimal patient comfort. Higher sweep gas flows are associated with lower $PaCO_2$ levels and less respiratory effort.[46]

PATIENT MANAGEMENT

The ECMO-supported patient should be treated as a regular critically ill patient. Analgesia can be administered preemptively in all cannulated patients, at least until an objective evaluation of the pain is possible. Sedation should be titrated to promote or facilitate the protective or ultraprotective ventilation during the first hours of ECMO support, always avoiding life-threatening agitation. Some patients will require neuromuscular blocking agents to guarantee adequate mechanical ventilation in the first hours of ECMO support. Later in the course of the underlying disease, when the acute inflammatory phase has waned, titrating the sweep gas flow to a normal or slightly high pH can allow protective mechanical ventilation even in patients who are awake and interacting with family members and health care providers.[3] Although feeding should be initiated as soon as possible, its impact on fluid balance during the first days of ECMO support should be taken into account.[47] Antimicrobials must not be used prophylactically. Infectious complications during ECMO support, especially ventilator-associated pneumonia, are common and should be treated as usual.[48]

The adequate level of hemoglobin is still a matter of debate. Oftentimes, patients remain hypoxemic despite the use of ECMO. To optimize systemic oxygen delivery, some centers use transfusion of blood components to maintain hemoglobin levels > 14 g/dL[4] or > 10 g/dL and platelet counts > 100,000/mm^3.[49] In the absence of hypoxemia, we adopt a more conservative approach: at an SaO_2 > 88%, our hemoglobin threshold for transfusion of red blood cells is 7.0 g/dL and our platelet count threshold for platelet transfusion is 50,000/mm^3.[50] We use those thresholds as general guidelines, and the decision is always individualized after thorough evaluation of each patient. Early mobilization and early ambulation of patients on ECMO support improve motor outcomes and rehabilitation.[51]

RENAL REPLACEMENT THERAPY

The renal replacement therapy (RRT) circuit can be connected to a separate vascular access or directly to the ECMO circuit (Figure 2). Keeping dialysis independent from ECMO makes all the procedures related to the RRT occur exactly as they would in patients without

ECMO support. However, that decision involves the risk of obtaining a new central venous access in patients who have often been fully anticoagulated.

Alternatively, the RRT circuit can be connected in series with the ECMO circuit (Figure 2). The best configuration of the inlet and outlet lines of the dialysis machine is a matter of controversy. We do not recommend connecting the dialysis system downstream of the oxygenator, because of the risk of air embolism. The choice between making the connection upstream of the ECMO pump (negative-pressure side) and making it downstream of the ECMO pump (positive-pressure side) will depend on the dialysis machine. In some RRT machines, negative pressure will trigger low-pressure alarms if the outlet lines are connected upstream of the ECMO pump. Connection on the positive-pressure side (i.e., downstream of the pump and upstream of the oxygenator), where pressures can reach up to 350 mmHg, is a safe and effective option.[52]

Finally, it is possible to take advantage of the pressure differences within the ECMO circuit to drive blood across the hemofilter without a dialysis machine. To that end, the inlet line of the hemofilter drains blood from the positive-pressure side and returns blood to the negative-pressure side. With that configuration, it is possible to deliver slow continuous ultrafiltration therapy, with an infusion pump controlling the amount of fluid removal or the amount of dialysate in counter-current with blood (which would require two pumps). This option can be hazardous, because the amount of flow through the hemofilter will vary depending on the ECMO-circuit pressures, as well as because infusion pumps can underestimate fluid loss.[52]

The risks and benefits of each of the options should be considered. We believe that, at centers where the staff have sufficient experience, connecting the dialysis machine directly to the ECMO circuit might be advantageous because it avoids the risk of central venous access and has been associated with a lower risk of infection.[52]

PHARMACOKINETICS

Modern ECMO circuits produce significant pharmacokinetic changes. First, hemodilution due to the priming volume of approximately 500-600 mL can dilute drugs soon after the initiation of ECMO support. Second and most importantly, the ECMO circuit is coated with biopassive and bioactive products to enhance biocompatibility and to reduce thrombogenesis, respectively.[53] The circuit coating is able to adsorb lipophilic[54] and protein-bound drugs. There is information on the pharmacokinetics of some drugs (Table 1).[55,56] Whenever possible (e.g., in the case of analgesics and vasopressors), close clinical surveillance of the pharmacokinetic effects of ECMO support is indicated.

Anticoagulation

The coating of the ECMO circuit contains heparin, which provides partial protection against clotting. Further anticoagulation is necessary to avoid clot formation in the ECMO system and to prevent vascular thrombosis in the insertion sites of the cannulas, thus avoiding dysfunction of the oxygenator, hemolysis, post-phlebitis syndrome, arterial ischemia, and pulmonary embolism. Between 10% and 33% of patients on ECMO support experience thrombotic or bleeding events.[57] Monitoring of anticoagulation varies according to the experience of each center.[57] Table 2 shows the anticoagulation techniques used at 187 ECMO centers worldwide.[57] Measuring the activity of anti-factor Xa is considered the gold standard, being the only monitoring tool that correlates well with serum levels of heparin. However, it is unavailable at many centers and is associated with high costs.[57]

Continuous infusions of unfractionated heparin with usual control of activated partial thromboplastin time (aPTT) are associated with a long system lifespan.[58] Our group uses unfractionated heparin and aPTT obtained at intervals from 6 h to 24 h, depending on the moment of ECMO support, always maintaining the aPTT ratio between 2.0 and 3.0. When the heparin infusion needs to be discontinued, high ECMO blood flows, usually above 3,500 mL/min, help avoid clot formation. During vv-ECMO support, some periods without anticoagulation can be allowed.

ECMO MONITORING

The ECMO system must be checked at least once a day. The presence of clots in the circuit, oxygenator, or pump head indicates insufficient anticoagulation. The auscultation of a friction noise in the pump head indicates fibrin deposition on the impeller blades. We daily perform brief (less than a second) elevations of the sweep gas flow to the maximum in order to remove water condensation from the oxygenator ("the oxygenator cough maneuver"), improving the exchange surface. In patients at risk of cerebral hypoperfusion, such as those with increased intracranial hypertension, we avoid the routine use of the cough maneuver, because it can lead to transient hypocapnia and consequent cerebral vasoconstriction. In those patients, we perform the maneuver in selected circumstances (when there is worsening of oxygenation due to ineffective gas exchange of the membrane). The battery can be checked by turning off the external power source. We then provide adequate gel lubrication of the ultrasonic blood flow meter. It is always important to have emergency equipment on the pump console cart: a hand crank, an empty pack to use in cases of massive air embolism, three clamps (at least), and gel for the flow meter. Avoid the use of alcohol on the polycarbonate material to prevent cracks.

Some ECMO groups routinely monitor blood gases and pressures upstream and downstream of the oxygenator. Increased transmembrane pressure is an early warning sign of oxygenator failure due to thrombus formation. Conversely, a concomitant increase in upstream and downstream oxygenator pressures

Table 1. Pharmacokinetics of some medications when using extracorporeal membrane oxygenation support.

Bioavailability	
Reduced	Maintained
Propofol	Morphine
Midazolam	Meropenem
Fentanyl	Fluconazole
Lorazepam	Micafungin
Vancomycin	
Ceftriaxone	
Imipenem	

Table 2. Anticoagulation techniques used in 187 extracorporeal membrane oxygenation centers worldwide.

Technique	Routine use	Occasionally	Never
aPTT	94%	-	6%
ACT	97%	-	3%
Anti-factor Xa	18%	25%	35%
Fibrinogen	97%	3%	-
Thromboelastography	18%	25%	57%
Non-heparin anticoagulants	-	8%	90%

aPTT: activated partial thromboplastin time; and ACT: activated coagulation time.

without a change in pump rotations may indicate kinking of the arterial cannula. Our group restricts that monitoring to situations in which hypoxemia or hypercapnia occurs. We also monitor the blood flow/pump rotation ratio, which depends on the preload and afterload of the pump, to identify circuit or oxygenator obstructions to blood flow.[59]

The fixation and insertion of the cannulas must also be checked daily. The determination of SpO_2 can be used in order to monitor arterial oxygenation. In patients on va-ECMO, it is important to determine the SpO_2 on the right arm, which more closely represents the oxygen availability to the brain and myocardium. Once-daily determination of arterial blood gases is usually enough for patients on vv-ECMO. In patients on va-ECMO, cardiac activity can occasionally be extremely depressed, and—in the absence of pulsatility—pulse oximetry will not work. In those patients, blood samples for arterial blood gas analysis should be obtained more frequently, preferably from the right arm.

Twice a week, we screen for hemolysis by measuring lactate dehydrogenase, bilirubins, haptoglobin, aspartate aminotransferase, alanine aminotransferase, and, if possible, free hemoglobin. Measuring D-dimer levels can be also useful for predicting the progression of clotting within the membrane.

Transesophageal echocardiography can be an important tool to monitor patients on vv- or va-ECMO. In vv-ECMO, transesophageal echocardiography can monitor for incident right heart failure, whereas in va-ECMO it can be used in order to diagnose thrombus formation in the aortic root and in the left ventricle, as well as to monitor the function of native cardiac output.

REFRACTORY HYPOXEMIA AND HYPERCAPNIA DURING ECMO SUPPORT

Hypercapnia during ECMO support is very rare, considering that relatively low ECMO blood flows are usually enough to wash out CO_2. Sometimes, at low ECMO blood flows, CO_2 removal has a "ceiling effect", and further increases in the sweep gas flow have little impact on $PaCO_2$. Under those circumstances, the ECMO blood flow and the sweep gas flow should both be increased in order to treat hypercapnia.

Conversely, hypoxemia during ECMO support is a more common and difficult-to-manage situation, and knowledge of the interaction between the patient and ECMO might help at the bedside. We favor a stepwise approach for such situations, as described below:

1. Check ECMO blood flow: initial settings include keeping ECMO blood flow at a minimum of 60% of the cardiac output in order to reduce the fraction of non-oxygenated venous blood flow that will mix with oxygenated blood.
2. Check for recirculation: the oxygenated blood from the arterial cannula might be once again drained by the ECMO system, causing recirculation, which can reduce ECMO efficiency. The relative position of the cannulas can be assessed with chest X-ray and ultrasound at the bedside. When the tips of arterial and venous cannulas are in close proximity (Figure 3), recirculation is likely to occur. It is recommended that the tip of the femoral venous cannula be placed at the level of the suprahepatic inferior vena cava. If oxygen saturation in the drainage cannula is > 70% or if its difference in relation to the SaO_2 is < 20%, recirculation can be a contributing factor to persistent hypoxemia. Consider repositioning the drainage cannula or changing to a hybrid configuration.
3. Check for excessive oxygen consumption: aggressively treat fever and agitation. Consider neuromuscular blockers if the patient exhibits increased respiratory effort.
4. Check for oxygenator failure: thrombus formation due to inappropriate anticoagulation or to prolonged ECMO support might impair gas exchange. Consider replacing the oxygenator if there are signs of hemolysis or inappropriate fibrinolysis.
5. Optimize ventilator settings if possible: increase the FiO_2 if it is < 60%, and increase the PEEP if appropriate. Also consider using alveolar recruitment maneuvers and the prone position, as well as neuromuscular blockers or inhaled nitric oxide.
6. Consider reducing the cardiac output of the patient, if appropriate, with beta-blockers. Although this option is associated with improvement in oxygenation, it has not been tested formally in a randomized clinical trial and therefore remains experimental.

The decision of whether and how far hypoxemia or hypercapnia can be tolerated should be individualized, considering the clinical condition of the patient.

TROUBLESHOOTING

Communication with the hospital blood bank is important to make sure there is enough blood in stock in case of emergency.

If for any reason the ECMO device stops, prompt restoration of mechanical ventilation is mandatory with predefined "emergency settings." Those settings must be written down, visible, and placed near the ventilator (for instance, FiO_2 = 1, PEEP = 10 cmH_2O, peak pressure = 30 cmH_2O, and RR = 35 breaths/min).

In cases of interruption of power supply or any other pump console failure, the hand crank must be used in order to pump the blood. The previously mentioned "sucking-up" phenomenon is common. It can cause sudden falls in the measured ECMO blood flow with preserved pump rotations, which is commonly associated with the chattering of the ECMO circuit. Additionally, the pump head, normally dark red because it is filled with venous blood, can become light red or even white (the color of the impeller blades) when the flow from the drainage cannula is insufficient (a phenomenon referred to as cavitation). Some maneuvers can be of help: 1) increasing the bed angle; 2) placing the patient in the lateral decubitus position; 3) decreasing the ECMO blood flow and then increasing it slowly; 4) increasing the PEEP; 5) transfusing packed red blood cells if appropriate; 6) attempting fluid challenges; and 7) starting or increasing epinephrine infusion when appropriate.[21]

Air embolism can occur when the venous pre-pump system, where the pressure is negative, is being handled. If air embolism occurs, immediately interrupt the ECMO blood flow (the outlet of the pump head must be turned down in order to avoid pushing the air forward) and change to emergency mechanical ventilation settings (see above). Then proceed to remove the air with syringes or emergency bags. If a circuit rupture is identified, the ECMO flow must be interrupted and the damaged segment of the circuit must be replaced. Hemolysis is relatively common and can be avoided by reducing the ECMO blood flow, correcting cannula malpositioning, and enhancing anticoagulation, especially if there are clots in the circuit. If the RRT circuit is connected to the ECMO circuit, the use of a separate dialysis catheter should be considered.[60] During vv-ECMO support, cardiac arrest should be treated as usual, except that ventilation is unnecessary.

ECMO DISCONTINUATION

Every day, we perform an autonomy test by reducing the sweep gas flow to zero. To guarantee the absence of sweep gas flow, we usually clamp the air line that is connected to the oxygenator. Immediately before the autonomy test, acceptable mechanical ventilation parameters must be set. In patients on controlled mechanical ventilation, we favor the use of a PEEP of 10-15 cmH_2O, a tidal volume of 6 mL/kg of ideal body weight, a RR of 35 breaths/min, and an FiO_2 of 0.6.[4] If the patient is on pressure support ventilation, the pressure support can be adjusted to between 6 cmH_2O and 20 cmH_2O depending on the clinical and

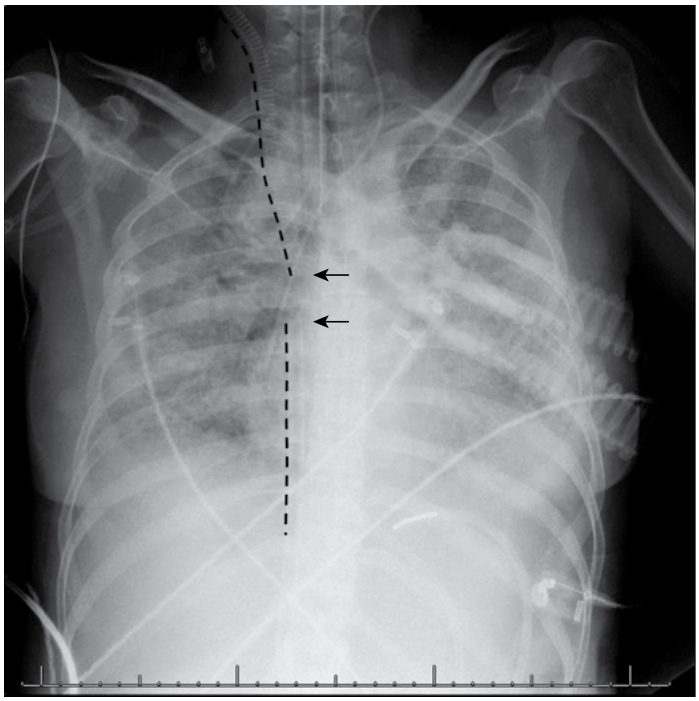

Figure 3. An X-ray of the chest (taken with a portable X-ray machine at the bedside) of a patient with hypoxemic respiratory failure submitted to extracorporeal membrane oxygenation support. Note the positioning of the cannulas (dashed lines) with their tips (arrows) in close proximity, which may favor the occurrence of recirculation.

physiological condition of the patient. When the sweep gas flow is turned off, patient comfort and SpO_2 must be observed closely. If the patient is stable for 1-6 h, arterial blood gas analysis is performed. If the PaO_2 is > 55 mmHg and the pH is within the normal range (7.35-7.45), we consider (depending on the clinical status) the withdrawal of ECMO support.[23] Patients with borderline oxygenation and right ventricular dysfunction might not tolerate sudden changes in oxygenation, because hypoxia can worsen or the patient can develop *cor pulmonale*. In those patients, we gradually change the FiO_2 of the sweep gas flow from 1.0 to 0.21, after which we slowly reduce it to zero.

We remove the venous cannulas at the bedside and apply pressure to the insertion sites for at least 30 min. We later place suture reinforcements around the orifices and leave the sutures in place for at least 24 h. Arterial cannulas are withdrawn in the operating room.

FINAL CONSIDERATIONS

ECMO for respiratory support is a suitable rescue therapy for patients with severe ARDS or other causes of respiratory failure, assuming that the patients are not beyond hope. Costs do not seem prohibitive. A trained multidisciplinary ICU team is fully capable of initiating and conducting ECMO support. Although emergencies are infrequent among patients on vv-ECMO support, a training program is necessary to keeping the team competent and confident.

Our group has created a YouTube channel, designated "*Grupo de ECMO HCFMUSP*", with the purpose of training our educational team. The channel is open access.

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Primary epithelioid angiosarcoma of the chest wall complicating calcified fibrothorax and mimicking empyema necessitatis

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We describe the case of a 72-year-old male patient with primary epithelioid angiosarcoma of the chest wall (PEACW). The patient complained of a painful lump in his chest. His medical history was consistent with calcified fibrothorax secondary to a tuberculous infection during childhood. Empyema necessitatis (EN) was initially suspected. An X-ray of the chest (Figure 1A) showed characteristics similar to those seen on previous X-rays. A CT scan demonstrated a heterogeneous mass that focally destroyed a rib and invaded chest wall muscles (Figure 1B). A CT-guided biopsy of the mass (Figure 1C) revealed a high-grade PEACW. Unfortunately, the patient died from brain and pulmonary metastases three weeks later.

The development of a chest wall lump in a patient with chronic calcified fibrothorax of tuberculous origin should prompt the possibility of EN. However, only a few cases of PEACW developing in patients with a chronic calcified fibrothorax have been published in the literature.[1-3] To our knowledge, there have been no reported cases in which PEACW complicating calcified fibrothorax was accurately diagnosed on the basis of percutaneous biopsy. Despite its rarity, PEACW should be suspected in patients with chronic calcified fibrothorax that develops as a chest wall mass.

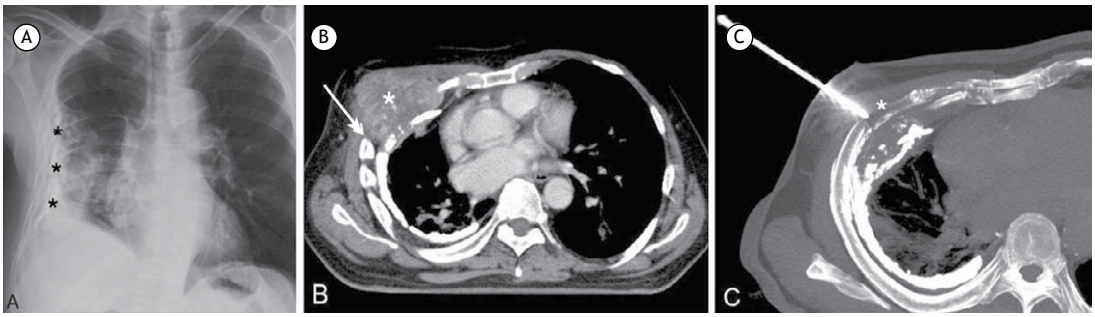

Figure 1. In A, a posteroanterior chest X-ray showing right calcified fibrothorax (asterisks). In B, axial contrast-enhanced CT of the chest scan showing a heterogeneous hypervascular mass (asterisk) infiltrating the right serratus anterior and pectoralis muscles, as well as the fourth rib (long arrow). Note the extensive calcified fibrothorax on the right. In C, axial CT of the chest, with maximum intensity projection, showing a large-core needle biopsy (14-gauge) traversing the chest wall for histological analysis of the mass (asterisk).

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CASE REPORT

Pleuroparenchymal fibroelastosis: report of two cases in Brazil

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ABSTRACT

Pleuroparenchymal fibroelastosis (PPFE) is a rare lung disease. It can be idiopathic or associated with any one of various conditions. To our knowledge, this is the first report of two cases of PPFE in Brazil. Our first patient presented with pleural and subpleural fibrosis in the upper lobes; a spiculated nodule in the left upper lobe; and a mild reticular pattern in the lower lobes. Surgical lung biopsy revealed PPFE in the upper lobes, including the nodule, and unclassified interstitial pneumonia in the left lower lobe. Our second patient had a history of exposure to domestic birds, indicating a risk of hypersensitivity pneumonitis, and presented with advanced lung disease, predominantly in the upper lobes, together with subpleural fibrosis.That patient underwent lung transplantation. In the explant specimen, PPFE and granulomas were identified, suggesting hypersensitivity pneumonitis as an associated cause.

Keywords: Lung diseases, interstitial/diagnosis; Lung diseases, interstitial/etiology; Alveolitis, extrinsic allergic.

INTRODUCTION

Fibroelastosis is a rare interstitial pneumonia.[1] In Brazil, there have been no published reports of diagnosed cases of fibroelastosis. In the present report, we describe two cases of pleuroparenchymal fibroelastosis (PPFE). We provide a brief review of the literature and point out the findings of interest in the cases described.

CASE 1

A 67-year-old male patient reported occasional cough and chest X-ray abnormalities detected many years ago. He was an 11-pack-year former smoker and had a history of exposure to mold. The initial tests showed an SpO_2 of 95% on room air, fine rales at the left lung base, and squawks on the anterior surface of the left hemithorax. No other changes were observed. Pulmonary function testing revealed an FVC of 4.28 L (87% of predicted); an FEV_1 of 3.42 L (92% of predicted); an FEV_1/FVC ratio of 0.80; a TLC of 6.34 L (84% of predicted), and a DLCO of 19.0 mL/min/mmHg (54% of predicted). Chest CT scans showed intense pleural and subpleural fibrosis, as well as septal thickening, predominantly located in the upper lobes (Figure 1). There was a spiculated nodule in the left upper lobe and a mild reticular pattern in the lower lobes.

A surgical lung biopsy was performed, with sampling of the left upper and lower lobes. Microscopic examination revealed compact fibrosis with elastosis, with no evidence of malignancy in the resected nodule, as well as clearly delineated areas of pleural/subpleural fibrosis in nonfibrotic parenchyma and little scarce mononuclear cell infiltrate (Figure 2). A biopsy of the lower lobe showed unclassified interstitial fibrosis (image not shown).

CASE 2

A 29-year-old male nonsmoker experiencing dyspnea presented with a one-year history of dyspnea on minimal exertion and dry cough. The patient had lost 12 kg in weight during that period. He had a 10-year history of exposure to parakeets and worked cutting plastic. Physical examination revealed emaciation; tachycardia (HR = 130 bpm); and an SpO_2 of 79% on room air. Auscultation revealed fine rales bilaterally. Arterial blood gas analysis showed a pH of 7.33; a $PaCO_2$ of 69 mmHg; a PaO_2 of 43 mmHg; a bicarbonate level of 36.1 mmol/L; a base excess of 7.7 mmol/L; and an SaO_2 of 74.9%. Spirometry showed an FVC of 0.76 L (15% of predicted); an FEV_1 of 0.74 L (17% of predicted); and an FEV_1/FVC of 0.97. Chest CT showed intense pleural and subpleural fibrosis, as well as septal thickening, predominantly located in the

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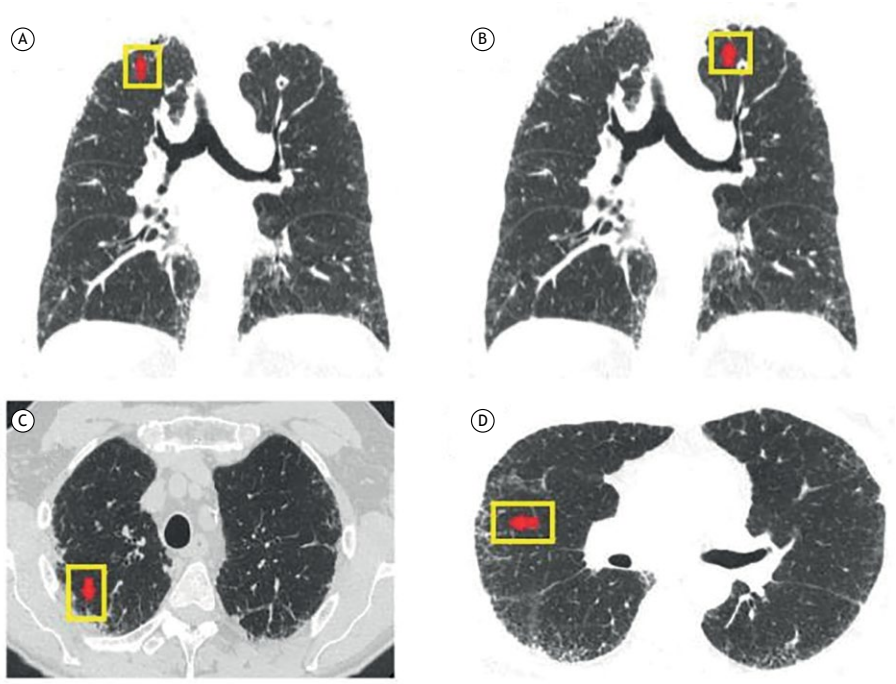

Figure 1. Coronal (A) and axial (B, C, and D) CT scans of the chest showing intense pleural and subpleural fibrosis, as well as septal thickening, predominantly located in the upper lobes and a spiculated nodule in the left upper lobe.

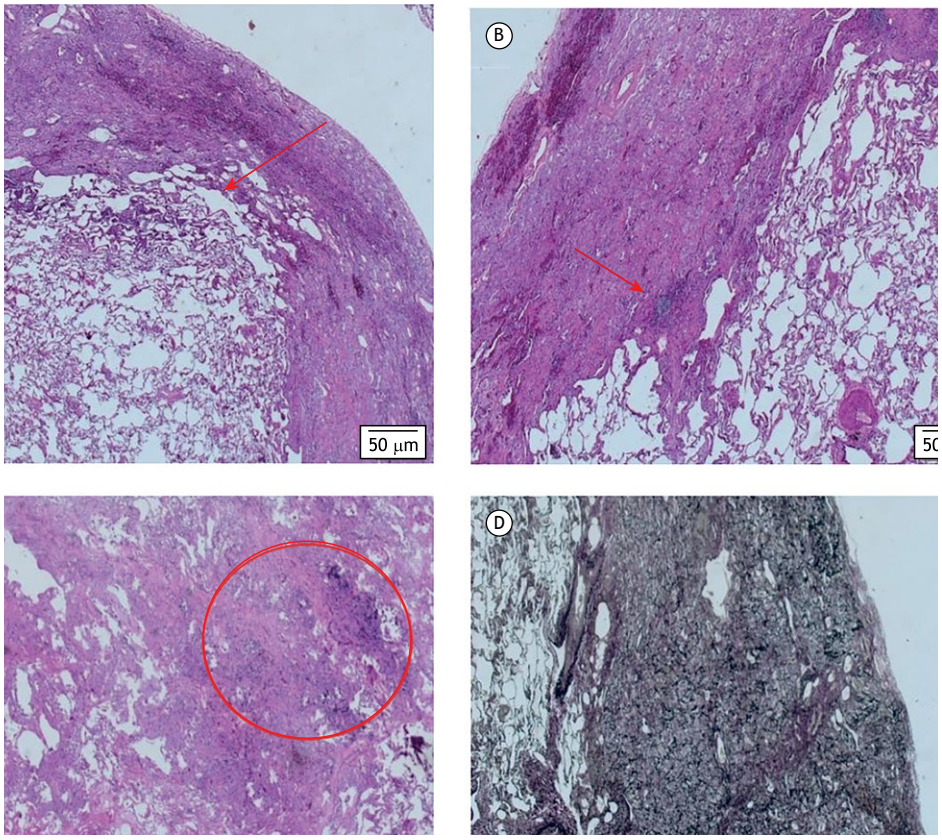

Figure 2. Photomicrographs of a surgical lung biopsy specimen from the left upper lobe. In A, clearly delineated areas of pleural/subpleural fibrosis in nonfibrotic parenchyma (arrow; H&E, magnification: ×28). In B, pleural/subpleural fibrosis and scarce mononuclear cell infiltrate (arrow; H&E, magnification: ×28). In C, compact fibrosis with elastosis, with no evidence of malignancy (arrow; H&E, magnification: ×40). In D, an increase in elastic fibers in the areas of pleural fibrosis (arrow; Verhoeff staining for elastic fibers, magnification: ×28).

upper lobes. The diagnosis was chronic hypersensitivity pneumonitis, and lung transplantation was indicated.

The lung explant histopathological findings are shown in Figure 3.

DISCUSSION

PPFE is classified as belonging to the group of rare idiopathic interstitial pneumonias.[1] Approximately 100 cases have been reported.[2]

In 1975, Davies et al. reported the cases of 5 patients with pulmonary fibrosis confined to the upper parts of the lungs, similar to the lesions observed in ankylosing spondylitis.[3] In 1992, Amitani et al. reported the cases of 13 patients with fibrosis of unknown etiology, located in the upper lobes.[4] Histopathological examination was performed in nine cases. Various cases were subsequently described in Japan, being reviewed by Kwabata et al. in 2003.[5] In 2004, Frankel et al. reported the cases of 5 patients with upper lobe-predominant fibrosis characterized by intense fibrosis of the visceral pleura and intense subpleural fibrosis, with a mixture of elastic fibers and dense collagen.[6] In that study, the disease was called pulmonary PPFE, a term that has persisted to the present day.[6]

Radiologically, PPFE is characterized by pleural and subpleural fibrotic thickening in the upper lobes, with consequent reduction in volume and retraction of the hilum toward the apices.[7] In Brazil, it is likely that many of such cases are diagnosed as tuberculosis cases. Although PPFE was originally considered to be restricted to the upper lobes, it was subsequently shown to be able to involve other lobes, in its initial stage or during its progression, often extending from the upper lobes toward the lower lobes. Reticular opacities in the lower lobes, similar to those seen in nonspecific interstitial pneumonia or with a usual interstitial pneumonia pattern, can be observed.[8]

Dyspnea on exertion and dry cough are the major symptoms. Recurrent lower respiratory tract infections and spontaneous pneumothorax can also occur.[8,9]

The age distribution is bimodal, with peaks between 21 and 30 years of age and between 51 and 60 years of age.[10] There is no gender predominance.[10]

Smoking does not appear to be a risk factor.[2] PPFE can progress slowly or rapidly. Its etiology can be unknown (idiopathic) or be associated with various causes, such as occupational exposures to asbestos and aluminum; bone marrow and/or lung transplantation (the most common cause); history of chemotherapy; history of radiotherapy; autoimmune diseases (such as ankylosing spondylitis and ulcerative colitis); hypersensitivity pneumonitis; and family history of PPFE.[2,9-13]

Physical examination can reveal anteroposterior flattening of the chest (platythorax).[13] Crackles are audible in half of the cases.[8] The usual functional pattern is a restrictive pattern, with decreased DLCO.[7]

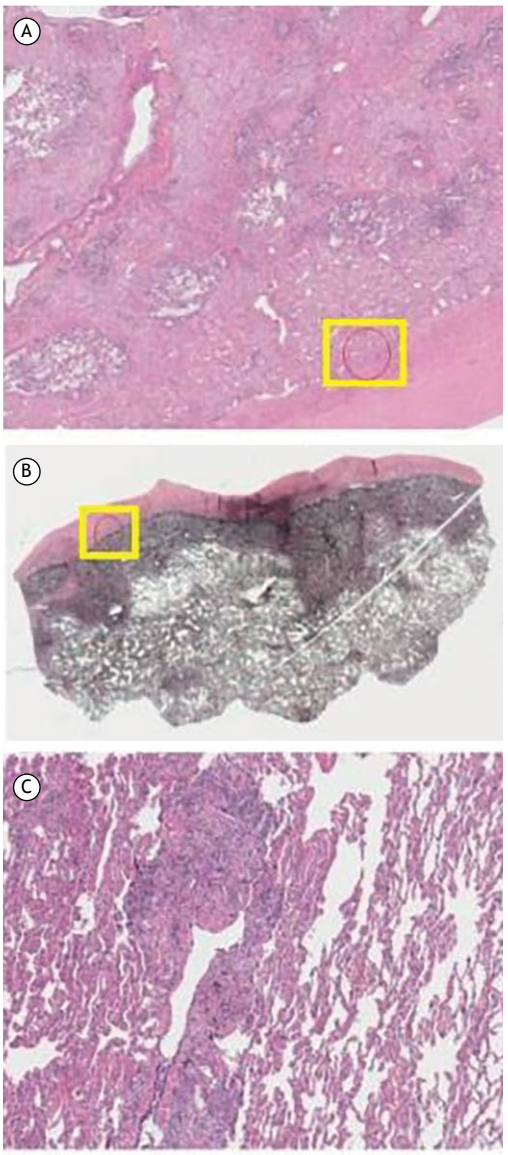

Figure 3. Upper lobe explant histological findings. In A and B, presence of fibrous thickening of the visceral pleura and subpleural lung parenchyma, with little dense collagen deposition and abundant elastic fibers that are evident on Verhoeff staining. In C, signs of small airways disease, either by obliteration or by distortion of the bronchial wall, accompanied by malformed granulomas and multinucleated giant cells containing cholesterol crystals, located interstitially or intra-alveolarly.

There is no specific treatment. Patients have been empirically treated with corticosteroids and other immunosuppressants, with no proven evidence of improvement.[2,12]

The cases reported here have some points of interest. In Case 1, the patient was a former smoker and, in addition to presenting with apical nodular thickening and interlobular septal thickening, he presented with a spiculated nodule in the left upper lobe. The nodule was hypermetabolic on positron emission tomography.

Histological analysis of the resected specimen revealed that the nodule represented a focus of fibroelastosis. A similar case was reported in 2011.[14] Recently, three cases of lung cancer (non-small cell carcinoma) superimposed on fibroelastosis have been described.[15] Fibrosis centered on small airways and bronchiolitis obliterans have been described,[16,17] and that explains the squawks heard on auscultation in Case 1.

Case 2 is an example of secondary fibroelastosis. In that case, fibroelastosis was secondary to hypersensitivity, which was confirmed by the finding of granulomas in the lung explant, in addition to the classic findings suggestive of fibroelastosis. Cases with concomitant findings of hypersensitivity pneumonitis have been described.[2,16] Lung transplantation in occasional cases of PPFE has been reported.[18]

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http://dx.doi.org/10.1590/S1806-37562016000000379

Radial-probe EBUS for the diagnosis of peripheral pulmonary lesions

Juliana Guarize[1], Stefano Donghi[1], Maurício Guidi Saueressig[1,2,3]

We would like to make some comments regarding the article by Jacomelli et al.,[1] which describes an initial experience using radial-probe endobronchial ultrasound (EBUS) for the investigation of 51 pulmonary lesions.

First, we have found data inconsistencies in Tables 1 and 2 in the aforementioned article. The authors reported, both in the body of the text and in Table 1, that the diagnostic sensitivity of radial-probe EBUS for radial-probe EBUS-visible nodules was 74.1%: 20 surgically confirmed diagnoses among 27 radial-probe EBUS-visible nodules. However, in the second column of Table 2, we found that 21 diagnosed cases of radial-probe EBUS-visible nodules (10 cases of malignant disease and 11 cases of nonmalignant disease) were listed, which differs from the sum of 20 cases recorded in the last row of the same column. Also in Table 2, one case of hamartoma was erroneously included among the malignant nodules.

The study reports, in its results, the value of 66.7% (34 diagnoses in 51 cases) as the overall sensitivity (diagnostic yield) of radial-probe EBUS for malignant and benign diseases. However, we do not understand why, for the calculation of this sensitivity, 3 radial-probe EBUS-invisible lesions were included with the 31 radial-probe EBUS-visible lesions that were diagnosed by this method.

In addition, the prevalence of neoplasia, a relevant factor for the analysis of the diagnostic yield,[2] was not informed; nor was the final diagnosis of the 12 radial-probe EBUS-invisible pulmonary lesions. Therefore, the presentation of results by Jacomelli et al.[1] differs in some aspects from that of important publications on the subject.[2,3]

In the Department of Interventional Pulmonology of the *Instituto Europeo di Oncologia* in Milan, Italy, we have used radial-probe EBUS to investigate pulmonary nodules and masses since 2012. We use a miniprobe within a guide sheath (K-203 Guide Sheath Kit; Olympus Medical Systems Corp., Tokyo, Japan) and fluoroscopy for localization and subsequent transbronchial biopsy of the lesions. In all procedures, a pathologist is present in the endoscopy room for rapid on-site cytological evaluation, as previously described.[4] We believe that this is essential for increasing the diagnostic yield of the procedure, as we will describe below.

In 2015, we investigated 161 pulmonary lesions (nodules and masses) using radial-probe EBUS. Three patients who were lost to follow-up were excluded from the statistical analysis. The examination was not diagnostic (its results were nonspecific and unrelated to the final diagnosis, or the bronchial epithelium or lesions were not visible by radial-probe EBUS) in 33 cases (23 cases of malignant disease and 10 cases of benign disease). Among those cases, there were 11 radial-probe EBUS-invisible lesions, which exclusively comprised opacities less than 40 mm. The overall sensitivity of the radial-probe EBUS-guided biopsies was 79% (108 malignant and 17 benign biopsies). The prevalence of malignant disease was 83%. The sensitivity, specificity, negative predictive value, and accuracy for malignancy among the lesions detected by radial-probe EBUS were, respectively, 88%, 100%, 57%, and 89.5%.

Finally, we must emphasize the importance of the article by Jacomelli et al.,[1] because, in addition to being the first one on radial-probe EBUS in Brazil, it is an example of use of the growing arsenal of endoscopic tools for the investigation and treatment of pulmonary lesions.

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AUTHORS' REPLY

Marcia Jacomelli[1], Sergio Eduardo Demarzo[1], Paulo Francisco Guerreiro Cardoso[2], Addy Lidvina Mejia Palomino[1], Viviane Rossi Figueiredo[1]

We are grateful for the criticisms of our study that was published in the JBP in 2016.[1] We have reviewed all cases and interpretations and requested the necessary corrections to improve the description of the results.

Of all 54 patients who underwent bronchoscopy with radial-probe endobronchial ultrasound (EBUS) for the diagnosis of pulmonary lesions, 3 were excluded because they were lost to follow-up and we could not perform comparisons with the final results obtained by other methods or by clinical follow-up. Therefore, there remained 51 patients who were included in the analysis (Table 1). Among those 51 cases, we made 34 diagnoses by the bronchoscopic procedure, all of which were confirmed by other methods or by clinical-radiological follow-up, amounting to an overall diagnostic yield of 66.7% (nodules and masses). We divided those 51 cases into radial-probe EBUS-visible lesions (n = 39) and radial-probe EBUS-invisible lesions (n = 12). Among the radial-probe EBUS-visible lesions, we made a total of 31 diagnoses (79.5%), including 20 nodules (74.1%) and 11 masses (91.7%). Among the 12 radial-probe EBUS-invisible lesions, we made only 3 diagnoses (25%). This shows that, if the lesion is visible by radial-probe EBUS, there is greater likelihood of making a final diagnosis by the bronchoscopic methods.[2,3] A correction must be made to the last row of Table 1, which should read: not identified by radial-probe EBUS.

In Table 2, hamartoma was erroneously placed among the cases of malignant disease, which were originally designated "tumors" and therefore included all benign and malignant cases. Also in Table 2, in the row that reads inflammatory disease, we made a total of 2 diagnoses by the bronchoscopic method that were confirmed (n = 2; 66.7%), meaning that the total number of diagnoses made in the pulmonary nodule group amounts to 20 diagnoses. These errors must be corrected in Table 2.

Regarding rapid on-site evaluation of the specimen by a pathologist and fluoroscopy, we know how important these techniques are to the procedure; however, they are not available in the majority of our procedures. In addition, guide sheaths are not yet available for use in Brazil, which largely precludes the collection of adequate material in some cases.

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2. Departamento de Cardiopneumologia, Disciplina de Cirurgia Torácica, Instituto do Coração, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.

Manuscript: Radial-probe EBUS for the diagnosis of peripheral pulmonary lesions.

Publication: J Bras Pneumol. 2016;42(4):248-53.

DOI: http://dx.doi.org/10.1590/S1806-37562015000000079

On page 251 of the original publication, left column, second paragraph, lines 14 to 18, where it is written

"Malignant nodules were found in 14 (51.8%) of the 27 cases, with a predominance of non-small cell lung cancer. The radial-probe EBUS results were positive in 10 (71.4%) of those 14 malignant nodules."

it should read

"Tumors were found in 14 (51.8%) of the 27 nodules, with a predominance of non-small cell lung cancer. The radial-probe EBUS results were positive in 10 (71.4%) of those 14 tumoral nodules (Table 2)."

On page 251 of the original publication, Table 1 should be disregarded. The correct table should read

Table 1. Characteristics of the lesions in the patients submitted to radial-probe EBUS (N = 51).

Characteristic	Case	Pulmonary lesion	
		Nodule	Mass
All lesions			
N (%)	51 (100.0)	37 (72.5)	14 (27.5)
Size (cm), mean ± SD	2.5 ± 1.3	1.9 ± 0.7	4.1 ± 0.9
Sensitivity, n (%)	34 (66.7)	23 (62.2)	11 (78.6)
Lesions visible by radial-probe EBUS			
N (%)	39 (76.5)	27 (69.2)	12 (30.8)
Size (cm), mean ± SD	2.6 ± 1.2	1.9 ± 0.7	3.9 ± 0.9
Sensitivity, n (%)	31 (79.5)	20 (74.1)	11 (91.7)
Lesions not visible by radial-probe EBUS			
N (%)	12 (23.5)	10 (83.3)	2 (16.7)
Size (cm), mean ± SD	1.6 ± 1.1	1.3 ± 0.6	3.7 ± 0.7
Sensitivity, n (%)	3 (25.0)	3 (30.0)	0 (0.0)

On page 252 of the original publication, Table 2 should be disregarded. The correct table should read

Table 2. Final diagnoses of the lesions that were visible by radial-probe EBUS and and diagnostic yield.[a]

Diagnosis	Pulmonary lesions			
	Nodules		Lung masses	
	Cases	Diagnostic yield	Cases	Diagnostic yield
Non-small cell lung cancer	10 (37.0)	7 (70.0)	8 (66.7)	7 (87.5)
Small cell lung cancer	2 (7.4)	2 (100.0)	1 (8.3)	1 (100.0)
Adenoid cystic carcinoma	1 (3.7)	1 (100.0)		
Hamartoma	1 (3.7)	0 (0.0)		
Metastatic breast cancer			1 (8.3)	1 (100.0)
Tuberculosis or fungal infection	4 (14.8)	2 (50.0)		
Inflammatory disease	3 (11.1)	2 (66.7)	2 (16.7)	2 (100.0)
Nonspecific benign disease	6 (22.2)	6 (100.0)		
Total	27 (100.0)	20 (74.1)	12 (100.0)	11 (91.7)
Tumors	14 (51.8)	10 (71.4)	10 (83.3)	9 (90,0)

[a]Values expressed in n (%).

On page 252 of the original publication, left column, second paragraph, lines 16 to 18, where it is written

"The sensitivity of the procedure tripled for lesions that were visible by radial-probe EBUS compared to those that were not visible (73% vs. 25%)."

it should read

"The sensitivity of the procedure tripled for lesions that were visible by radial-probe EBUS compared to those that were not visible (79.5% vs. 25.0%)."

On page 252 of the original publication, right column, third paragraph, lines 1 to 8, where it is written

"The differential diagnosis between malignancy and infectious disease is important in Brazil. In the present study, we identified non-neoplastic disease in

13 (48.1%) of the 27 pulmonary nodules that were visible by radial-probe EBUS and in 2 (16.7%) of the 12 pulmonary masses that were visible by radial-probe EBUS, the final diagnoses including fungal infections and tuberculosis."

it should read

"The differential diagnosis between malignancy and infectious disease is important in Brazil. In the present study, we identified inflammatory/infectious disease in 13 (48.1%) of the 27 pulmonary nodules that were visible by radial-probe EBUS and in 2 (16.7%) of the 12 pulmonary masses that were visible by radial-probe EBUS, the final diagnoses including fungal infections and tuberculosis."

Manuscript: Factors associated with quality of life in patients with severe asthma: the impact of pharmacotherapy.

Publication: J Bras Pneumol. 2015;41(6):496-501.

DOI: http://dx.doi.org/10.1590/S1806-37562015000004545

On page 496 of the original publication, abstract, Results, line 12, where it is written

"Better AQLQ scores were associated with asthma control—overall (OR = 0.38; 95% CI: 0.004-0.341; p < 0.001)"

it should read

"Better AQLQ scores were associated with asthma control—overall (OR = 0.038; 95% CI: 0.004-0.341; p < 0.001)"

On page 500 of the original publication, Table 4, second column, fifth row, where it is written

"0.380 (0.004-0.341)"

it should read

"0.038 (0.004-0.341)"

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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

Na Fronteira do Conhecimento – Formando pessoas e produzindo ciências
Data: 17 e 18 de fevereiro
Local: São Paulo – SP

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

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