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Respiratory muscles in COPD: be aware of the diaphragm

Pauliane Vieira Santana[1,a], Andre Luis Pereira de Albuquerque[1,b]

COPD is a limiting respiratory disease associated with high morbidity and mortality.[1] COPD is characterized by chronic airflow limitation due to small airway disease and parenchymal destruction.[1] Dyspnea and exercise intolerance (EI) are common in patients with COPD and are associated with reduced quality of life and increased mortality.[2,3] Dyspnea and EI might result from an imbalance in the load/capacity ratio of the respiratory muscles in COPD patients. Chronic airflow limitation imposes a load on respiratory muscles (as does lung hyperinflation), flattening the diaphragm and reducing its ability to generate tension. In patients with COPD, various other factors can impair respiratory muscle function, including activation of proteases, oxidative stress, malnutrition, ageing, and comorbidity-related systemic factors; however, changes in chest wall geometry and diaphragm position are the most commonly recognized and studied mechanisms contributing to respiratory muscle dysfunction.[4]

Diaphragm function has been largely evaluated in COPD patients. It has been demonstrated that inspiratory muscle weakness is related to dyspnea.[5-7] In addition to being related to EI and increased dyspnea, respiratory strength has been reported to be related to survival in COPD patients.[3] Therefore, it is relevant that respiratory muscles and diaphragm function in particular be assessed in COPD patients.

In an article published in the current issue of the JBP, Gonçalves et al.[8] showed that COPD patients with thoracic hyperkyphosis (TH) had lower diaphragmatic mobility when compared with a group of patients with COPD and no TH. Furthermore, the authors showed a negative correlation between diaphragmatic mobility and TH: a greater thoracic kyphosis translates to a lower diaphragmatic mobility. The authors hypothesized that a decrease in diaphragmatic mobility results in changes in the body posture in patients with COPD. However, TH might be a consequence of ageing alone and, in fact, impair diaphragmatic mobility.

Regardless of the real cause of TH (COPD or ageing), few studies have explored the impact of postural changes in patients with COPD, although thoracic alterations are commonly observed in clinical practice. Thus, elderly individuals, in whom COPD is more prevalent, can present with severe TH that can compromise diaphragmatic mobility and ventilatory function, of these patients, as well as contributing to further respiratory impairment in COPD patients.

Taking into account the clinical implications of diaphragmatic mobility, Dos Santos Yamaguti et al.[9] noted that diaphragmatic mobility was lower in COPD patients than in healthy elderly individuals, and that air trapping was related to reduced diaphragmatic mobility. By means of ultrasound study, Paulin et al.[10] showed that patients with COPD and low diaphragmatic mobility presented with increased limitation in exercise capacity and increased post-exertional dyspnea during the six-minute walk test. More recently, using chest X-rays, Rocha et al.[11] noted that, in patients with COPD, diaphragmatic mobility was related to airway obstruction, lung hyperinflation, ventilatory capacity, and perception of dyspnea, but not to physical activity in daily life.

As demonstrated by Gonçalves et al.,[8] diaphragmatic dysfunction might be present in COPD patients with TH; however, as demonstrated in the study by Gonçalves et al.,[8] this topic has yet to be fully elucidated. First, there is question of the clinical relevance of the findings, given that no association was found between reduced diaphragmatic mobility and reduced maximal inspiratory pressure. Perhaps there is a decrease in diaphragmatic strength (transdiaphragmatic pressure) rather than in total inspiratory strength (when accessory inspiratory muscles are acting). Second, the fact that lung volumes, symptoms, and exercise capacity were not evaluated limits the clinical implications of lower mobility. Third, diaphragmatic mobility was assessed by chest X-rays. Although this method is noninvasive and easily performed, it involves the use of ionizing radiation, the transportation of the patient to the radiology sector, and patient cooperation in order to perform diaphragmatic breathing measurements. Diaphragm ultrasound (DUS) has been widely used in order to evaluate diaphragm dysfunction because of its advantages (safety, feasibility, repeatability, and reproducibility).[12,13] In addition, DUS allows the measurement of thickness and thickening of the diaphragm, a surrogate for contractility.[14] Moreover, a recent study has demonstrated that diaphragmatic dysfunction defined by reduced thickening fraction on DUS (< 20%) is related to prognostic implications in acutely exacerbated COPD patients.[15] Lastly, the study by Gonçalves et al.[8] is a descriptive study, and, therefore, it is impossible to evaluate the cause-and-effect relationship between TH and reduction of diaphragmatic mobility. Table 1 shows the most common variables studied by means of imaging methods for evaluating the diaphragm, as well as their clinical implications in healthy individuals and in patients with respiratory disorders.

Considering the importance and clinical relevance of this topic, although symptoms were not measured in that study,[8] it is clear that TH resulted in lower diaphragmatic mobility in COPD patients and, therefore, has a potential to

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Table 1. The most common variables studied by means of imaging methods for evaluating the diaphragm and their clinical implications in healthy individuals and in patients with respiratory disorders.

Variable	Clinical implication	Method
Mobility	Lung function Inspiratory muscle strength Dyspnea Exercise capacity Prediction of weaning from MV Diagnosis of diaphragmatic dysfunction	Chest X-rays Diaphragm ultrasound
Thickness	Inspiratory muscle strength Diagnosis of diaphragmatic dysfunction Assessment of progression of atrophy during MV	Diaphragm ultrasound CT
Thickening fraction (%)	Lung function Inspiratory muscle strength Diagnosis of diaphragmatic dysfunction Assessment of progression of atrophy during MV Assessment of respiratory effort during MV Prediction of weaning from MV	Diaphragm ultrasound

MV: mechanical ventilation.

impair diaphragmatic strength. Future studies exploring the impact of chest wall alterations on diaphragm performance and their clinical implications in COPD patients are of high interest.

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Anterior mediastinal mass

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

A 61-year-old asymptomatic male patient sought medical attention. A chest X-ray revealed an opacity in the anterior mediastinum. A CT scan showed a round, anterior mediastinal mass with a heterogeneous content. The density of the most hypodense central area was −61 Hounsfield units (Figure 1).

Most mediastinal tumors are asymptomatic and are detected incidentally on a chest X-ray performed for another reason. Occasionally, mediastinal tumors cause nonspecific symptoms related to the compression/invasion of adjacent anatomical structures (chest pain, cough, dyspnea, dysphagia, superior vena cava syndrome, etc.). With regard to anterior mediastinal tumors, only a minority causes specific symptoms, such as myasthenia gravis, which is found in approximately 40% of patients with thymoma. The major etiologies of anterior mediastinal masses are thymomas, lymphomas, germ cell tumors (particularly teratomas), thyroid masses, and aortic aneurysms.

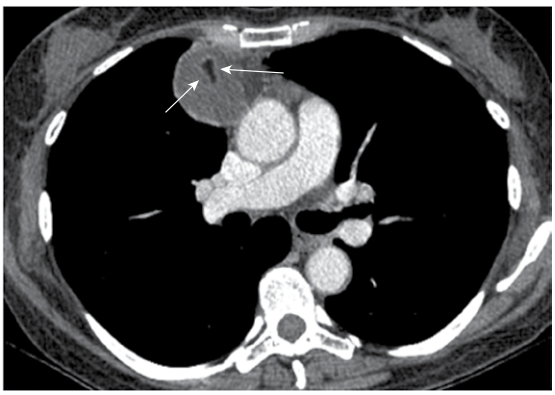

Figure 1. Axial contrast-enhanced CT image at the level of the pulmonary artery trunk shows a round, anterior mediastinal mass with a heterogeneous content and a focal hypodense area, with a density of −61 Hounsfield units, corresponding to fat (arrows).

A useful CT criterion for narrowing the differential diagnosis is tumor density. On CT, fat is characterized by negative densities, ranging from −30 to −150 Hounsfield units. The finding of fat narrows the diagnosis substantially. Major anterior mediastinal masses that can exhibit fat include lipomas, liposarcomas, mediastinal lipomatosis, and teratomas. In addition, fat can also be found in herniation of abdominal contents into the chest cavity, such as in Morgagni hernia.

Lipomas are benign encapsulated tumors that originate from adipose tissue and resemble normal fat. Liposarcomas are malignant tumors with fatty differentiation. They usually present as masses with heterogeneous density showing areas of fat and soft tissue. Mediastinal lipomatosis refers to excessive deposition of unencapsulated fat in the mediastinum, usually associated with corticosteroid therapy, obesity, or Cushing's disease. Thymolipomas are rare benign encapsulated tumors composed of adipose and thymic tissue in variable proportion. Morgagni hernias, despite not being mediastinal tumors, enter the differential diagnosis because they exert a mass effect and can contain omental fat. Teratomas are tumors containing tissues originating from one or more germ cell layers (ectoderm, mesoderm, or endoderm). They are almost always benign but have a potential for malignancy. Approximately 75% of teratomas contain fat, and 50% contain calcifications. Macroscopically, they can contain a large variety of materials, such as fat, hair, bones, and teeth. Expectoration of hair (trichoptysis) is a quite rare but pathognomonic sign of teratoma.

In our patient, the finding of focal fat within the mass was highly suggestive of teratoma. The diagnosis was confirmed by surgical resection of the mass.

RECOMMENDED READING

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Understanding diagnostic tests. Part 3.

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

In the previous articles from this series[1,2] we discussed important characteristics used in order to evaluate diagnostic tests: sensitivity, specificity, positive predictive value, and negative predictive value. In this final part, we discuss positive likelihood ratio (LR+), negative likelihood ratio (LR−), and ROC curves.

LIKELIHOOD RATIOS

LRs combine sensitivity and specificity to quantify how helpful a new diagnostic test is in changing (increasing or decreasing) the probability of having a disease compared with the prevalence of that disease (pretest probability) in the population studied. The LR+ of a test is the probability of a positive result in patients with the disease divided by the probability of a positive result in patients without the disease, whereas LR− is the probability of a negative result in patients with the disease divided by the probability of a negative result in patients without the disease. LR+ ranges from 1 to infinity, and an LR+ of 1 indicates that the probability of a positive test result is the same for patients with and without the disease; therefore, the test is useless. An LR+ greater than 1 supports the presence of the disease, and the greater LR+ is, the more a positive test result increases the probability of the disease when compared with the pretest probability. LR− ranges from 1 to 0, and the closer the LR is to 0, the lower the probability of the disease is if the test result is negative.

ROC CURVES

We use ROC curves to make a global assessment of the value of a diagnostic test by calculating the area under the curve (AUC). The values of the AUC can vary from 0 to 1.0, and values over 0.8 indicate that the diagnostic test has very good accuracy. The ROC curve plots sensitivity (true positives) against "1 – specificity" (false negatives) for all the possible cut-off values of the new test (Figure 1). As we have previously discussed, there is always a trade-off between sensitivity and specificity when we define a cut-off value for quantitative test results. If a new test were perfect, there would be a complete separation of values between patients with and without the disease, the cut-off value would be the lowest value among patients with disease, and the AUC would be 1. However, since there are no perfect tests, there will always be some false positive or some false negative results. The more accurate a test is, the greater the AUC is, which is the probability that a random person with the disease has a higher value of the measurement than a random person without the disease.[3]

MAKING SENSE OF DIAGNOSTIC TEST PERFORMANCE CHARACTERISTICS

If you are wondering which of the parameters described is more useful to evaluate a diagnostic test—sensitivity, specificity, LRs, or ROC curve—the answer is: it depends! Each parameter describes a specific characteristic of the test, and depending on how you will use the test, one or another may be more useful. Now that you understand these concepts, interpreting a test result will be much more than just looking at the result.

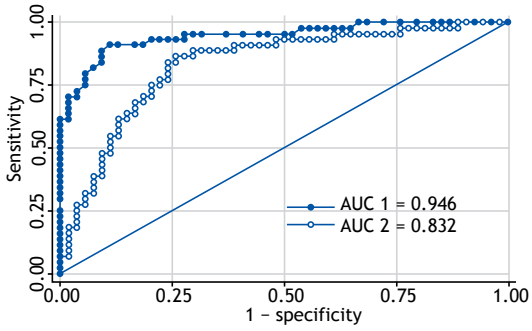

Figure 1. ROC curve plotting sensitivity vs. "1 – specificity" for two different tests. Both tests have good accuracy; however, test 1 (closed circles) has an area under the curve (AUC) of 0.946 and test 2 has an AUC of 0.832 (open circles), meaning that test 1 has overall better accuracy to discriminate between patients with and without the disease. This figure was created with fictitious data.

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ORIGINAL ARTICLE

Comparison of diaphragmatic mobility between COPD patients with and without thoracic hyperkyphosis: a cross-sectional study

Márcia Aparecida Gonçalves[1,a], Bruna Estima Leal[1,b], Liseane Gonçalves Lisboa[2,c], Michelle Gonçalves de Souza Tavares[3,d], Wellington Pereira Yamaguti[4,e], Elaine Paulin[1,f]

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ABSTRACT

Objective: To compare diaphragmatic mobility, lung function, and respiratory muscle strength between COPD patients with and without thoracic hyperkyphosis; to determine the relationship of thoracic kyphosis angle with diaphragmatic mobility, lung function, and respiratory muscle strength in COPD patients; and to compare diaphragmatic mobility and thoracic kyphosis between male and female patients with COPD. **Methods:** Participants underwent anthropometry, spirometry, thoracic kyphosis measurement, and evaluation of diaphragmatic mobility. **Results:** A total of 34 patients with COPD participated in the study. Diaphragmatic mobility was significantly lower in the group of COPD patients with thoracic hyperkyphosis than in that of those without it ($p = 0.002$). There were no statistically significant differences between the two groups of COPD patients regarding lung function or respiratory muscle strength variables. There was a significant negative correlation between thoracic kyphosis angle and diaphragmatic mobility ($r = -0.47$; $p = 0.005$). In the sample as a whole, there were statistically significant differences between males and females regarding body weight ($p = 0.011$), height ($p < 0.001$), and thoracic kyphosis angle ($p = 0.036$); however, there were no significant differences in diaphragmatic mobility between males and females ($p = 0.210$). **Conclusions:** Diaphragmatic mobility is lower in COPD patients with thoracic hyperkyphosis than in those without it. There is a negative correlation between thoracic kyphosis angle and diaphragmatic mobility. In comparison with male patients with COPD, female patients with COPD have a significantly increased thoracic kyphosis angle.

Keywords: Pulmonary disease, chronic obstructive; Kyphosis; Diaphragm.

INTRODUCTION

A respiratory disease that is characterized by chronic airflow obstruction, lung hyperinflation, and air trapping, COPD is preventable and treatable.[1] However, the aforementioned pathophysiological factors can lead to a decrease in diaphragmatic mobility among other problems.[2,3]

Diaphragmatic mobility has been found to be lower in patients with COPD than in healthy elderly individuals. In addition, air trapping has been shown to be the major factor limiting diaphragmatic mobility in COPD patients.[2] A decrease in diaphragmatic mobility has been found to result in reduced exercise capacity and increased sensation of dyspnea after submaximal exercise.[3]

In addition to impaired diaphragmatic function, patients with COPD can present with postural changes such as posterior pelvic tilt, anterior pelvic rotation, and increased thoracic kyphosis when compared with healthy individuals.[4] Other changes in rib cage configuration have been reported in COPD patients, including an increased anteroposterior chest diameter,[5] horizontally oriented ribs,[6] and an increased thoracic curvature,[4] all of which appear to be associated with changes in lung mechanics.

Despite the scarcity of quantitative studies of postural changes in patients with COPD, clinical practice shows that COPD patients have a forward head posture, a decreased cervical lordosis, rounded shoulders, and an increased thoracic kyphosis angle.[7]

Although a decrease in diaphragmatic mobility and an increase in thoracic kyphosis are common in patients with COPD, it has yet to be determined whether patients with an increased thoracic kyphosis angle (a determinant of thoracic hyperkyphosis) have decreased diaphragmatic mobility.

The objectives of the present study were as follows: 1) to compare diaphragmatic mobility between COPD patients with and without thoracic hyperkyphosis; 2) to determine the relationship of thoracic kyphosis angle with diaphragmatic mobility and lung function variables in COPD patients; and 3) to compare diaphragmatic

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mobility and thoracic kyphosis between male and female patients with COPD.

METHODS

Patients and procedures

This was a quantitative analytical cross-sectional study. A total of 58 patients were recruited from among those being followed at the Pulmonology Outpatient Clinic of the *Hospital Universitário Professor Polydoro Ernani de São Thiago*, located in the city of Florianópolis, Brazil. The study was approved by the Human Research Ethics Committee of the *Universidade do Estado de Santa Catarina*, located in the same city, Brazil (CAAE: 08857612.2.0000.0118). All participating patients gave written informed consent, in accordance with Brazilian National Health Council Resolution 466/12.

The study sample intentionally comprised patients who had been diagnosed with COPD in accordance with the Global Initiative for Chronic Obstructive Lung Disease criterion of $FEV_1/FVC < 0.70$ after bronchodilator use.[1] Other inclusion criteria included 1) being clinically stable, i.e., no hospitalizations or respiratory attacks in the last month or before testing, 2) requiring no oxygen supplementation, 3) having no associated respiratory, cardiovascular, or musculoskeletal diseases, 4) having participated in no respiratory therapy programs in the six months prior to the study, 5) having recently undergone no spinal or lower limb surgery, and 6) having had no fractures in the last six months.

The exclusion criteria were as follows: experiencing COPD exacerbation during the study period; 2) having cardiorespiratory or musculoskeletal complications during the tests; 3) being unable to perform any of the required tests (being unable to understand the instructions or being uncooperative); and 4) dropping out during testing.

Anthropometry

Body weight was measured with a previously calibrated scale (W200/5; Welmy S.A., Sao Paulo, Brazil). Participants stood erect, barefoot and wearing light clothing, with the head in the vertical position, looking straight ahead. Height was measured with a stadiometer, with participants standing barefoot and as erect as possible, with both ankles together. The body mass index (BMI) was calculated by the formula weight/height^2 (kg/m^2). On the basis of their BMI, participants were stratified into the following categories: underweight (≤ 18.5 kg/m^2); normal weight (18.5-24.9 kg/m^2); overweight (25-29.9 kg/m^2); and obese (≥ 30 kg/m^2).[8]

Lung function

A previously calibrated portable digital spirometer (EasyOne®; ndd Medical Technologies, Zurich, Switzerland) was used in order to assess lung function, in accordance with the methods and criteria recommended by the American Thoracic Society and the European Respiratory Society.[9] The following parameters were measured: FVC; FEV_1; and FEV_1/FVC. Participants performed respiratory maneuvers before and 15 min after inhalation of a bronchodilator (albuterol, 400 µg). A minimum of three acceptable maneuvers and two reproducible maneuvers were performed. All spirometric variables were expressed as absolute values and as a percentage of reference values, in accordance with Pereira et al.[10]

Respiratory muscle strength

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 respiratory muscle strength. MIP and MEP were measured as indicators of inspiratory and expiratory muscle strength, respectively, in accordance with the Brazilian Thoracic Association guidelines.[11] MIP was measured after a maximal expiratory maneuver (from RV to TLC), whereas MEP was measured after a maximal inspiratory maneuver (from TLC to RV). Participants performed three to five maneuvers in order to obtain three acceptable maneuvers (i.e., without leaks and lasting at least 2 s) and at least two reproducible maneuvers. The highest values of three correctly performed maneuvers (the difference among values being ≤ 10%) were recorded as MIP and MEP.[12]

Thoracic kyphosis angle

The thoracic kyphosis angle was measured with the flexicurve ruler, which is an 80-cm strip of flexible metal covered in durable plastic (TRIDENT® Indústria de Precisão, Itapuí, Brazil). During thoracic kyphosis angle measurements, participants wore a disposable gown with the opening to the back and were instructed to stand still with their elbows and shoulders extended along the body. Subsequently, the spinous processes of C7 and T12 were identified and marked with a grease pencil. One end of the flexicurve ruler was placed on the C7 spinous process and the ruler was molded to the thoracic kyphosis, the other end of the ruler being placed on the T12 spinous process. The ruler was then transferred to graph paper, onto which the shape was traced. Subsequently, a straight line was drawn connecting C7 to T12, being designated Xtotal (the length of the entire thoracic curve, in cm). Another straight line was drawn connecting the kyphosis apex to Xtotal, being designated H (the apex kyphosis height, in cm). Yet another straight line was drawn from T12 to H, being designated Xhalf (half the length of the thoracic curve, in cm; Figure 1). Finally, the flexicurve kyphosis angle was calculated with the use of a third-degree polynomial.[13]

In adult patients, thoracic kyphosis angles of 20-50° were considered normal, whereas, in elderly patients, thoracic kyphosis angles of up to 56° were considered normal.[14]

Diaphragmatic mobility (right hemidiaphragm)

Diaphragmatic mobility was evaluated by anteroposterior chest X-rays. Initially, a radiopaque ruler

was placed longitudinally under the right hemithorax in the craniocaudal direction, near the thoracoabdominal junction. Subsequently, anteroposterior chest X-rays were taken with patients lying supine on a fluoroscopy table. Prior to that, patients had been asked to perform two series of ten repetitions of diaphragmatic breathing, 1 min apart and supervised by a respiratory therapist, in order to become familiar with diaphragmatic breathing for maximal evaluation of diaphragm amplitude during radiographic examination.

After having become familiar with diaphragmatic breathing, patients performed two slow vital capacity maneuvers using a spirometer (Wright/Haloscale Respirometer®; Ferraris Medical Ltd., Hertford, England). Slow vital capacity maneuvers were performed from TLC to RV and from RV to TLC. The highest value was recorded for comparison with the value obtained during evaluation of diaphragmatic mobility, in order to determine whether patient respiratory (inspiratory and expiratory) efforts were the same before and during evaluation of diaphragmatic mobility.

The same film was used for all examinations, which were performed during a maximal inspiratory maneuver and a maximal expiratory maneuver. Diaphragmatic mobility was determined by measuring the distance between points at maximum inhalation and exhalation[15] (Figure 2).

For correction of the magnification caused by the divergence of the X-rays, the distance between two radiopaque ruler graduation marks corresponding to 10 mm was measured. The corrected diaphragmatic mobility (in mm) was obtained by the following formula:

$$\text{Corrected mobility} = \frac{\text{measured mobility} \times 10}{\text{measured distance between two ruler graduation marks}}$$

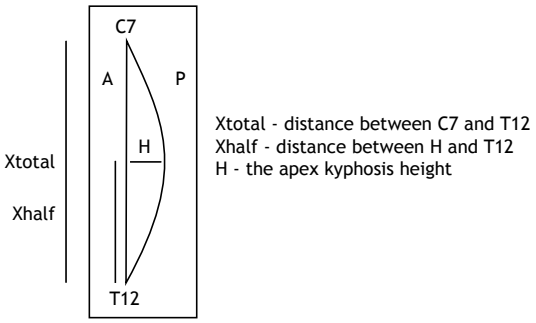

Figure 1. Schematic illustration of thoracic kyphosis measurement with the flexicurve ruler. A: anterior region; and P: posterior region. Source: Teixeira et al.[13]

Statistical analysis

A sample size spreadsheet was used in order to calculate sample size. Sample size calculation was based on a pilot study involving 10 COPD patients with thoracic hyperkyphosis and 10 COPD patients without thoracic hyperkyphosis, the difference in diaphragmatic mobility between the two groups of patients being assumed to be 20.29 mm. For a standard deviation of 20.54 (the largest standard deviation), a type I error of 0.05, and a study power of 0.80, the required sample size was calculated to be 34 (17 per group). Loss to follow-up was estimated at 10%.

Data were analyzed with the IBM SPSS Statistics software package, version 20.0 for Windows (IBM Corporation, Armonk, NY, USA) and described as mean and standard deviation for all variables. Normality of the data was tested by the Shapiro-Wilk test. The Student's t-test (for parametric data) or the Mann-Whitney test (for nonparametric data) was used in order to compare the parameters between the two groups. Pearson's and Spearman's correlation coefficients were used for parametric and nonparametric data, respectively. The level of significance was set at 5% ($p < 0.05$).

RESULTS

A total of 58 patients were initially evaluated. Of those, 24 were excluded from the final analysis: 17 because COPD was not their primary diagnosis and 7 because they did not complete all tests. Of those 7 patients, 3 were excluded because they were unable to perform one or more of the required tests (either because they were unable to understand the instructions or because they were uncooperative) and 4 were excluded because they dropped out during the evaluation period. Therefore, 34 COPD patients were included in the final analysis. Of those, 18 (53%)

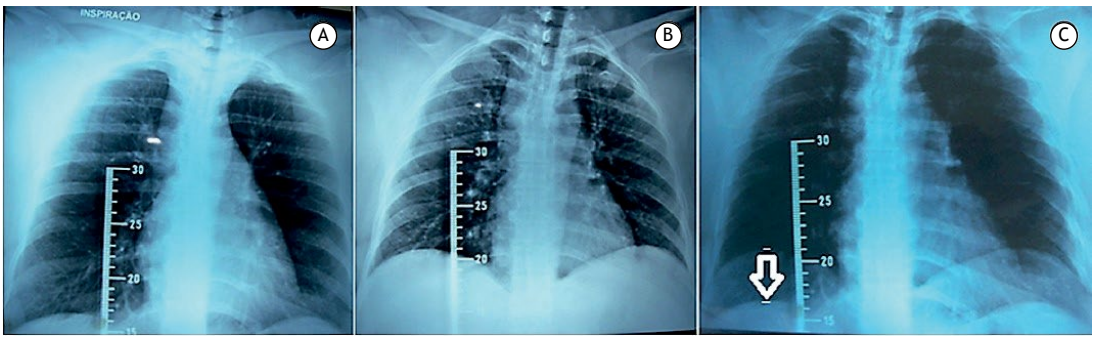

Figure 2. Chest X-rays showing diaphragmatic mobility. In A, chest X-ray taken during a maximal inspiratory maneuver. In B, chest X-ray taken during a maximal expiratory maneuver. In C, superimposition of the two aforementioned images (i.e., the image in B superimposed onto the image in A), the image of the radiopaque ruler being used as reference. Source: Saltiel et al.[15]

were male and 16 (47%) were female. The patients were divided into two groups: COPD with thoracic hyperkyphosis (n = 17) and COPD without thoracic hyperkyphosis (n = 17). The groups were matched for age, weight, height, and BMI.

Table 1 shows the characteristics of the two groups of COPD patients and a comparison of the study variables between the two. There were no statistically significant differences between the two groups regarding lung function or respiratory muscle strength variables.

Diaphragmatic mobility was significantly lower in the group of COPD patients with thoracic hyperkyphosis than in that of those without it (34.76 ± 14.18 mm vs. 53.37 ± 18.27 mm; p = 0.002; Figure 3).

Although the thoracic kyphosis angle correlated negatively with diaphragmatic mobility (r = −0.47; p = 0.005), it did not correlate with lung function or respiratory muscle strength variables in the sample as a whole (Table 2).

In the sample as a whole, there were statistically significant differences between males and females regarding body weight, height, and thoracic kyphosis angle. There was no significant difference in diaphragmatic mobility between males and females (Table 3).

DISCUSSION

In the present study, diaphragmatic mobility was found to be lower in the group of COPD patients with thoracic hyperkyphosis than in that of those without it. It has been shown that a decrease in diaphragmatic mobility is associated with an increased sensation of dyspnea and impaired exercise capacity in patients with COPD.[3] It is also associated with body posture changes in COPD patients. Martinez et al.[16] noted that ineffective diaphragmatic function leads to an apical breathing pattern that is due to a compensatory increase in rib cage and accessory respiratory muscle activity. This can result in increased muscle activity (e.g., increased sternocleidomastoid muscle activity), which results in muscle shortening, decreased muscle flexibility, and head position changes, as well as in shoulder girdle, pelvic girdle, and thoracic spine compensations,[17] all of which can cause thoracic hyperkyphosis.

In the present study, a negative correlation was found between diaphragmatic mobility and thoracic kyphosis, a greater thoracic kyphosis translating to a lower diaphragmatic mobility. This supports the hypothesis that there is an interaction between the two aforementioned variables. However, because of the sample size, it was impossible to determine the influence of those variables on one another, a larger sample being required in order to determine that.

We believe that diaphragmatic impairment plays a role in increasing thoracic kyphosis; however, other COPD-related factors also play a role in that process, including an increased anteroposterior chest diameter,[7] horizontally oriented ribs,[6] and excessive recruitment of accessory muscles.[16]

It is extremely important to investigate the relationship among the aforementioned factors because advanced-stage COPD and increased thoracic kyphosis can further reduce diaphragmatic mobility and affect lung function, which is reduced in patients with COPD.

According to Loubresse et al.,[18] an increased thoracic kyphosis angle can affect lung function. According to Libby et al.,[19] thoracic kyphosis angles greater than 65° characterize thoracic hyperkyphosis; in the present study, the mean thoracic kyphosis angle was 55.92°. Therefore, given that none of the patients in the present study had severe thoracic kyphosis, lung function results were similar between the groups of COPD patients with and without thoracic hyperkyphosis.

Table 1. Demographic, anthropometric, and functional characteristics of the groups studied (n = 34).[a]

Variable	Group		p
	COPD with hyperkyphosis (n = 17)	COPD without hyperkyphosis (n = 17)	
Demographic and anthropometric data			
M/F gender, n/n	6/11	12/5	-
Age, years	67.6 ± 6.1	65.9 ± 7.9	0.489
Body weight, kg	71.6 ± 14.1	75.2 ± 15.9	0.492
Height, cm	164.00 ± 8.30	167.65 ± 6.17	0.162
BMI, kg/m^2	26.6 ± 4.8	26.6 ± 4.9	0.974
Lung function			
FEV_1/FVC, L	0.54 ± 0.12	0.59 ± 0.10	0.168
FEV_1, % predicted	46.8 ± 17.6	56.2 ± 19.6	0.109
FVC, % predicted	66.2 ± 12.7	72.5 ± 20.3	0.283
Respiratory muscle strength			
MIP, % predicted	77.8 ± 26.0	67.6 ± 20.7	0.216
MEP, % predicted	116.1 ± 27.4	107.7 ± 32.1	0.417
DM, mm	34.8 ± 14.2	53.4 ± 18.3	0.002*
Thoracic kyphosis angle	65.3 ± 6.9	46.3 ± 5.2	< 0.001*

M: male; F: female; BMI: body mass index; and DM: diaphragmatic mobility. [a]Values expressed as mean ± SD, except where otherwise indicated.

There was no significant difference between the groups of COPD patients with and without hyperkyphosis regarding respiratory muscle strength. In addition, no correlation was found between the thoracic kyphosis angle and MIP or MEP, possibly because MIP and MEP are not discriminatory variables. It is possible that mobility is more closely related to parameters such as dynamic and transdiaphragmatic pressures than to maximal static respiratory pressures. Our results are consistent with those of Rennó et al.,[20] who studied elderly females with thoracic hyperkyphosis and found no significant correlations between increased thoracic kyphosis and MIP or MEP.

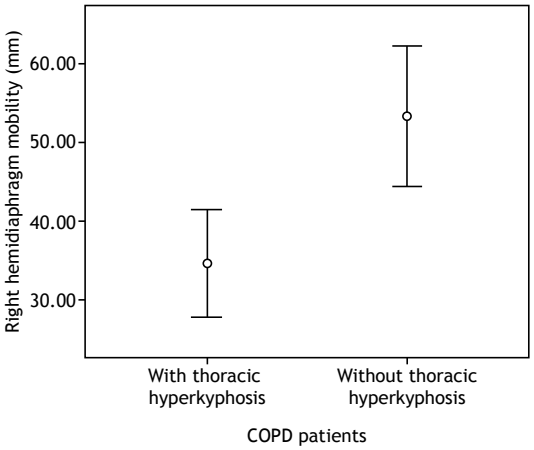

Figure 3. Comparison of diaphragmatic mobility between COPD patients with and without thoracic hyperkyphosis (n = 34). *p = 0.002

Table 2. Relationship of thoracic kyphosis angle with diaphragmatic mobility, lung function, and respiratory muscle strength in the study sample (n = 34).

Variable	Correlation coefficient*	p
DM	−0.470	0.005
FEV_1/FVC, L	−0.170	0.338
FEV_1, % predicted	−0.223	0.206
FVC, % predicted	−0.142	0.423
MIP, % predicted	0.204	0.247
MEP, % predicted	0.086	0.629

DM: diaphragmatic mobility. *Pearson's or Spearman's correlation coefficient.

Body weight and height were lower in females than in males, whereas the thoracic kyphosis angle was greater in females than in males. This might be due to postural changes resulting in markedly reduced height because of excessive kyphosis and a forward head posture.[20]

Our results are similar to those of a study conducted by Katzman et al.,[21] showing greater thoracic kyphosis in females than in males. Poor postural alignment is associated with spinal extensor muscle weakness and estrogen deficiency.[22] In a study of premenopausal and postmenopausal women, the prevalence of kyphosis was 35%, and kyphosis was found to be associated with age, although only in postmenopausal women.[23] After 40 years of age, the thoracic kyphosis angle might increase more rapidly in females than in males (a mean angle of 43° in females in the 55- to 60-year age bracket and of 52° in females in the 76- to 80-year age bracket).[24]

In our sample as a whole, diaphragmatic mobility was found to be similar between males and females. Our results are consistent with those obtained by Saltiel et al.,[15] Grams et al.,[25] Pedrini,[26] and Leal et al.,[27] who also found no difference in diaphragmatic mobility between males and females. However, Boussuges et al.[28] and Kantarci et al.[29] found differences in diaphragmatic mobility between males and females. This might be due to the sample size, given that the aforementioned studies by Boussuges et al.[28] and Kantarci et al.[29] had a large number of participants (210 and 164, respectively), whereas

Table 3. Comparison of lung function, respiratory muscle strength, diaphragmatic mobility, and thoracic kyphosis between males and females in the study sample (n = 34).[a]

Variable	Group		p
	Males (n = 18)	Females (n = 16)	
Demographic and anthropometric data			
Age, years	67.8 ± 8.2	65.7 ± 5.5	0.386
Body weight, kg	79.4 ± 12.5	66.7 ± 14.9	0.011
Height, cm	170.3 ± 5.9	160.8 ± 5.5	< 0.001
BMI, kg/m^2	27.3 ± 4.1	25.8 ± 5.5	0.353
Lung function			
FEV_1/FVC, L	0.56 ± 0.13	0.57 ± 0.10	0.822
FEV_1, % predicted	50.0 ± 20.9	53.0 ± 17.2	0.666
FVC, % predicted	66.5 ± 17.6	72.5 ± 16.3	0.317
Respiratory muscle strength			
MIP, % predicted	70.6 ± 25.6	75.1 ± 22.0	0.596
MEP, % predicted	103.7 ± 26.8	121.1 ± 30.9	0.088
DM, mm	47.89 ± 18.62	39.77 ± 18.35	0.210
Thoracic kyphosis angle	52.06 ± 8.91	60.22 ± 12.68*	0.036

BMI: body mass index; and DM: diaphragmatic mobility. [a]Values expressed as mean ± SD.

the aforementioned studies by Saltiel et al.,[15] Grams et al.,[25] Pedrini,[26] and Leal et al.[27] had smaller sample sizes (of approximately 40 individuals). It is of note that all of the aforementioned studies involved healthy individuals; we found no studies comparing diaphragmatic mobility between male and female patients with COPD.

One of the strengths of the present study is its methodological rigor in performing the required tests. However, the study has some limitations. Given that neither symptoms nor exercise capacity were evaluated, it was impossible to extrapolate our data on diaphragmatic mobility to the aforementioned outcomes. Given that we had no access to a whole-body plethysmograph, it was impossible to evaluate air trapping and correlate it with diaphragmatic mobility. Further studies are needed in order to investigate the clinical implications of our findings with regard to dyspnea, exercise capacity, and air trapping.

The topic of diaphragmatic mobility in COPD patients with and without thoracic hyperkyphosis is relevant because of the relationship between an increased thoracic kyphosis angle and advancing age. Thoracic hyperkyphosis can further impair diaphragmatic mobility and lung function in COPD patients, whose diaphragmatic mobility and lung function are affected by COPD-related pathophysiological factors.

Because of the cross-sectional nature of the present study, it was impossible to establish a cause-and-effect relationship between an increased thoracic kyphosis angle and a decrease in diaphragmatic mobility. Prospective longitudinal studies are needed in order to demonstrate the real influence of these variables on patients with COPD. Nevertheless, the results of the present study provide important information regarding thoracic kyphosis and diaphragmatic mobility in patients with COPD.

In summary, diaphragmatic mobility is lower in COPD patients with thoracic hyperkyphosis than in those without it; however, lung function and respiratory muscle strength are similar between the two groups of patients. There is a negative relationship between thoracic kyphosis angle and diaphragmatic mobility, and the results of the present study suggest that a greater thoracic kyphosis translates to a lower diaphragmatic mobility. In comparison with male patients with COPD, female patients with COPD have a significantly increased thoracic kyphosis angle.

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ORIGINAL ARTICLE

Factors associated with asthma expression in adolescents

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ABSTRACT

Objective: To evaluate risk factors associated with asthma symptoms in adolescents in the 13- to 14-year age bracket. **Methods:** This was a cross-sectional study involving adolescents enrolled in randomly selected public schools in the city of Belo Horizonte, Brazil, and conducted with the use of the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire and its supplementary module for risk factor assessment. The ISAAC questionnaire was completed by the students themselves, whereas the supplementary questionnaire was completed by their parents or legal guardians. Variables showing $p \leq 0.25$ in the univariate analysis were included in the multivariate analysis. Stepwise regression with backward elimination was used for variable selection. **Results:** We evaluated 375 adolescents, 124 (33.1%) of whom had asthma symptoms. The final multivariate analysis model revealed that asthma symptoms were associated with birth weight < 2,500 g ($p < 0.001$), day care center or nursery attendance ($p < 0.002$), maternal history of asthma ($p < 0.001$), contact with animals during the first year of life ($p < 0.027$), current contact with animals outside the home (dogs, cats, or farm animals; $p < 0.005$), and more than 20 cigarettes per day smoked by parents or other household members ($p < 0.02$). **Conclusions:** Exposure to animals in and outside the home is associated with asthma symptoms, as is environmental tobacco smoke exposure. Families, health professionals, and administrators of health care facilities should take that into account in order to prevent asthma and reduce asthma morbidity.

Keywords: Asthma; Risk factors; Adolescent.

INTRODUCTION

Asthma is multicausal and is determined by genetic, epigenetic, and environmental factors.[1] Epidemiological studies have shown that the prevalence of asthma symptoms has increased among adolescents, although only slightly; however, the prevalence of asthma symptoms among adolescents in Latin America has been reported to have increased significantly.[2,3]

Risk factors for childhood asthma include changes in maternal diet, increased fetal growth, reduced family size, reduced prevalence of infant infection, increased use of antibiotics, and increased immunizations; however, none of the aforementioned factors can, in and of itself, explain the increased prevalence of childhood asthma.[4] It is likely that the aforementioned socioeconomic and environmental changes have caused the infant immune system to be shifted toward a Th2 immune response, which is observed in atopic individuals.[5,6]

Given that environmental factors play an important role in the prevalence of asthma, the objective of the present study was to evaluate risk factors associated with asthma symptoms in adolescents, in order to propose measures to reduce the risk of asthma or reduce asthma morbidity in this population.

METHODS

This was a cross-sectional study involving adolescents enrolled in public schools in the city of Belo Horizonte, Brazil, and conducted between May and December of 2012 with the use of the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire. The ISAAC questionnaire was designed to determine the prevalence and severity of symptoms of asthma, allergic rhinitis, and atopic eczema,[7] and was complemented by another questionnaire, which included known and potential risk factors for asthma.[8]

According to the ISAAC protocol, the study population should comprise at least 3,000 students in the 13- to 14-year age bracket. In order to achieve the required sample size, a total of 14 elementary schools were randomly selected from a list provided by the Belo Horizonte Municipal Department of Education and including the number of enrolled students per school and grade. In order to facilitate the operationalization of the study, only schools in which there were at least 200 students in the aforementioned age bracket were considered for participant recruitment. The schools were randomly selected from a list that was randomly generated in the program Epi Info, version 6.04.

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The supplementary questionnaire had previously been translated to Portuguese and adapted for use in Brazil on the basis of phase II of the ISAAC and consists of 33 questions regarding factors that might be associated with asthma, including birth weight and prematurity; breastfeeding; number of siblings; day care center/nursery attendance; family history of asthma (having a parent with a diagnosis of asthma); vaccination; household exposure to pets (dogs, cats, and other furry animals, as well as birds); contact with animals outside the home (including dogs, cats, and farm animals); maternal smoking during pregnancy; passive exposure to tobacco smoke (presence of smokers in the home); exposure to household mold and moisture; nutrition; and area of residence (i.e., urban, suburban, or rural residence).[9]

Sample size

Sample size was calculated by the following formula:

$$n = \frac{N}{1 + \frac{N - 1}{PQ}\left(\frac{d}{Z_{\alpha/2}}\right)^2}$$

where N is the total population size (i.e., 3,000 students); PQ represents population variability; d is the margin of error; a is the level of significance (5%); and $z_{\alpha/2}$ is the value in the standard normal table (1.96).

Population variability was considered to be unknown, the maximum variability (i.e., 0.25, with P and Q = 0.50) therefore being used. For a collected population of 3,000 students and a sample of 375 students, the estimation error margin is 4.8% within a 95% confidence interval. This means that if 100 surveys were conducted simultaneously by the same methods, the results of 95 would be within the estimated margin of error (i.e., 4.8%).

Subgroups were randomly selected, and the parents or legal guardians of 200 adolescents classified as having active asthma (i.e., those who answered "yes" to the question "Have you had wheezing or whistling in the chest in the past 12 months?") and 400 controls (i.e., those who answered "no" to the aforementioned question) received the supplementary questionnaire to be completed at home and returned to the researchers on a pre-scheduled day.

Definitions

The study population was divided into two subgroups, namely, active asthma, which comprised individuals who had had wheezing in the past 12 months, and control, which comprised individuals who had had no wheezing in the past 12 months.

Inclusion and exclusion criteria

Students in the 13- to 14-year age bracket and enrolled in the selected schools were included in the study provided that they had completed the standard questionnaire; in the subsequent phase of the study, the parents or legal guardians of those students completed the supplementary questionnaire.

Statistical analysis

Univariate and multivariate analyses were performed in order to identify factors associated with asthma symptoms. Variables showing $p \leq 0.25$ in the univariate analysis were included in the multivariate analysis. Stepwise regression with backward elimination was used for variable selection. The Wald test was used in order to determine whether any given factor had, in and of itself, an effect on the observed response (presence or absence of wheezing). Only the variables with a value of $p < 0.05$ remained in the final model. Data were analyzed with the use of the Statistical Package for the Social Sciences, version 14.0 (SPSS Inc., Chicago, IL, USA).

Ethical considerations

The research project was approved by the Research Ethics Committee of the Federal University of Minas Gerais on January 18, 2006 (Protocol no. 237) and by the Belo Horizonte Municipal Department of Education. After permission was granted by all 14 school boards, written informed consent was obtained from all participating adolescents and their parents or legal guardians.

RESULTS

The study sample consisted of 3,325 adolescents. A total of 592 adolescents were included in the analysis of risk factors associated with asthma symptoms. After participants had been subdivided into two groups (i.e., with and without wheezing in the past 12 months) and after their parents or legal guardians had completed the supplementary questionnaire, 217 questionnaires were excluded because they had been incorrectly completed or had missing information. Therefore, the final study sample consisted of 375 adolescents, who were divided into two groups: active asthma (n = 124) and control (n = 251).

Of the adolescents in the active asthma group, 42.7% were 13 years of age and 57.3% were 14 years of age; of those in the control group, 48.6% were 13 years of age and 51.4% were 14 years of age.

Table 1 shows the variables that were significantly associated with asthma symptoms in the study sample. Table 2 shows the results of the multivariate analysis. After adjustment by the multivariate logistic regression model, the following variables remained associated with asthma symptoms: birth weight < 2,500 g; day care center or nursery attendance; maternal history of asthma; contact with animals during the first year of life; current contact with animals outside the home; and presence of household smokers smoking more than 20 cigarettes per day.

DISCUSSION

The present study showed that the following factors were associated with wheezing in adolescents: birth weight < 2,500 g; day care center or nursery

Table 1. Univariate analysis: variables associated with wheezing in the 12 months prior to the administration of the two questionnaires and showing p ≤ 0.25.

Variable	p
Birth weight (up to 2,499 g)	0.014
Day care center or nursery attendance	< 0.001
Maternal history of asthma	< 0.001
Current presence of birds in the home	0.021
Current presence of other animals in the home	0.108
Presence of pets in the home in the first year of life (dogs, cats, other furry animals, or birds)	0.047
Current contact with farm animals	0.187
Contact with animals outside the home (dogs, cats, or farm animals)	0.004
Contact with animals outside the home in the first year of life	0.038
Current maternal smoking	0.065
Smoking in the home by parents or other household members	0.194
Number of cigarettes smoked in the home by parents or other household members (> 20 cigarettes/day)	0.003
Current absence of windows in the bedroom	0.116
Current use of bedspreads/blankets as bed linen	0.118
Use of other materials as bed linen in the first year of life	0.105
Current area of residence (suburban residence with parks or urban residence without parks)	0.147

Table 2. Final multivariate analysis model of factors associated with wheezing in the past 12 months.

Variable	Coefficient	Wald c^2	OR (95% CI)	p
Intercept	−1.664	70.978	-	< 0.001
Birth weight < 2,500 g	1.055	14.539	2.9 (1.7-4.9)	< 0.001
Day care center/nursery attendance	0.738	9.194	2.1 (1.3-3.4)	0.002
Maternal history of asthma	0.949	10.456	2.6 (1.5-4.6)	0.001
Contact with animals in the first year of life (dogs, cats, other furry animals, or birds)	1.152	4.871	3.2 (1.1-8.8)	0.027
Current contact with animals outside the home (dogs, cats, or farm animals)	1.145	7.886	3.1 (1.4-7.0)	0.005
Number of cigarettes smoked in the home by parents or other household members (> 20 cigarettes/day)	1.288	5.434	3.6 (1.2-10.7)	0.020

attendance; maternal history of asthma; contact with animals during the first year of life; current contact with animals outside the home; and more than 20 cigarettes per day smoked in the home.

There is controversy in the literature regarding low birth weight. Although many authors have postulated that low birth weight indicates an unfavorable intrauterine environment resulting in impaired lung growth and reduced airway caliber,[10-12] others have found no such association, the fact that associated prematurity is not excluded being often cited as a bias.[1,13] In the present study, this issue was addressed by the question "Was your child born on the due date?" This might have played a role in minimizing the importance of that finding. In addition, the possibility of recall bias on the part of the parents or legal guardians was increased by the fact that our study involved adolescents in the 13- to 14-year age bracket.

Day care center or nursery attendance is known to be associated with recurrent wheezing or asthma depending on age. It increases the risk of recurrent wheezing in children who are 2 years of age or younger and in those in the 4- to 5-year age bracket.[14,15] However, in 7-year-olds, no association has been found between asthma and day care center attendance.[16,17] In children in the 5- to 14-year bracket, asthma has been found to be inversely associated with attending a day care center.[18] According to Ball et al., attending a day care center in the first years of life is a risk factor for wheezing associated with lower respiratory tract infections in infants and also a protective factor for atopic wheezing later in life; this is probably due to Th2 response inhibition caused by infections that elicit a Th1 response at a stage that is crucial in the expansion and maturation of Th2 memory cells.[19] Therefore, the findings of the present study should be taken into consideration despite the fact that they do not fit any of the aforementioned hypotheses. In this context, possible explanations include the presence of one or more risk factors (e.g., family history) strongly influencing clinical progression[20]; the number of children attending the same day care center[20]; and time spent in day care center environments. Cheng et al. found that spending more than 37.5 hours per week in day care center environments was associated with a reduced risk of asthma (OR = 0.6).[21] Therefore, early exposure to infections through day care center attendance can be a risk factor or a protective factor for allergic diseases such as asthma (including atopic

and nonatopic asthma), although this relationship remains unclear.[22]

Burke et al. analyzed studies conducted in more than 20 countries in all geographical regions of the world and found a consistent association between a family history of asthma and an increased risk of developing asthma, with ORs of 1.5-9.7 in cases of first-degree relatives with a history of asthma.[23] The present study confirmed the aforementioned association, a maternal history of asthma being found to be a risk factor for asthma symptoms in adolescents (OR = 2.6; 95% CI: 1.5-4.6). Lima et al. studied 3,069 adolescents in the 13- to 14-year age bracket using the same methodology as that used in the present study and confirmed the association between a family history of asthma and an increased risk of developing asthma (OR = 2.72) in the city of São Luís, Brazil.[24] In a recent study by Valadares et al., the aforementioned association was demonstrated by lung function changes in 30.3% of the children whose mothers had been diagnosed with asthma, an obstructive pattern being observed in 14%.[25] Therefore, a family history of asthma, particularly a maternal history of asthma, warrants preventive environmental measures, such as reducing exposure to aeroallergens and combating passive and active smoking. In addition, it assists in establishing a diagnosis of asthma.[23]

The relationship between exposure to animals and allergic disease is controversial. On the one hand, exposure to animal allergens can result in allergic disease[26]; on the other hand, it can confer protection against it by promoting tolerance and by modulating the immune system via bacterial endotoxins or different microbial agents.[27] In addition, families in which there is a history of atopy tend to avoid having pets in the home.[28] In the present study, contact with animals in the first year of life and current contact with animals outside the home were found to be associated with asthma symptoms in adolescents. In Brazil, two studies involving adolescents and employing the same methodology examined the aforementioned association. In the city of Taubaté, Toledo et al. analyzed 807 adolescents, 55.6% of whom kept furry animals, birds, or both types of animals as pets, which were kept in the home in 34% of the cases.[29] The authors found no significant correlation between "wheezing in the past 12 months" and the presence of pets (p = 0.9), speculating on the role of antigenic load and duration of antigen exposure.[29] In the city of Cuiabá, Jucá et al.[30] found that currently keeping pets in the home constituted a risk factor for active asthma and emphasized the importance of factors influencing this association, including the time at which the pet was owned, child age at exposure, number of animals, allergen load in the home, and family history of atopy. Therefore, the aforementioned factors might modulate the expression of sensitization to animal allergens.[31]

According to the World Health Organization, approximately half of the children in the world are exposed to tobacco smoke, primarily in their own homes.[32] Environmental tobacco smoke exposure has adverse effects on the health of children from conception to adolescence; it is estimated that children living with smoking parents passively smoke 30-150 cigarettes per year.[33] Tanaka et al. found that current heavy passive smoking was related to an increase in the prevalence of wheezing and asthma, particularly in children with a family history of allergy[34]; other authors have reported that there is an increase in respiratory symptoms such as nocturnal cough,[35] exercise-induced wheezing,[36] and nocturnal awakenings caused by wheezing, especially if more than 10 cigarettes per day are smoked in the home (OR = 2.02).[37] The present study found a trend toward an association between wheezing and smoking more than 20 cigarettes per day in the home, a finding that is consistent with those of Mitchell et al.,[38] who showed clear evidence of a dose-dependent effect for current maternal smoking on current wheezing and the severity of asthma symptoms in children in the 6- to 7-year age bracket. According to the authors, the more the mother smokes, the greater the risk of severe asthma symptoms (1-9 cigarettes/day: OR = 1.27; 10-19 cigarettes/day: OR = 1.35; and more than 20 cigarettes/day: OR = 1.56).[38] Therefore, cigarette smoke exposure can increase susceptibility to allergic sensitization in genetically predisposed individuals, leading to suppression of Th1-produced IFN-γ.[39] However, questionnaire-based assessment of environmental tobacco smoke exposure can overestimate or underestimate the effects of passive smoking on children. Therefore, biochemical markers such as cotinine can estimate environmental tobacco smoke exposure more accurately, cotinine levels correlating well with the number of cigarettes smoked and the self-reported number of cigarettes smoked.[40]

One strength of the present study is the use of a questionnaire previously validated for use Brazil.[9] Our study sample was representative, and the results can be extrapolated to the general population despite the number of questionnaires that were excluded from the study, given that multivariate analyses should include 10-20 participants per variable. Potential limitations of the present study include those inherent to questionnaire-based clinical research, such as the subjectivity of the answers given by the parents or legal guardians of the participating adolescents. In addition, neither confounding factors (such as gender, socioeconomic status, and objective measures of smoking) nor factors determining the level of allergen exposure were analyzed.

Future studies should include objective measures of pollutant exposure, aeroallergen exposure, and allergic sensitization, such as allergy testing and pulmonary function testing, in order to control for response bias. In addition, in order to avoid recall bias, cohort or case-control studies are preferable to cross-sectional studies.

Knowledge of asthma risk factors can aid families and health professionals in recommending preventive strategies to the community and parents of adolescents

who are at risk of asthma and asthma exacerbation. Given the heterogeneity of the Brazilian population, further studies, conducted in other regions of Brazil, are needed in order to determine the role that the factors studied here, as well as other factors, have in the genesis of asthma.

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ORIGINAL ARTICLE

Diagnostic value of α-enolase expression and serum α-enolase autoantibody levels in lung cancer

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ABSTRACT

Objective: To investigate the diagnostic value of α-enolase (ENO1) and serum ENO1 autoantibody levels in lung cancer. **Methods:** Immunohistochemistry staining and ELISA were performed to detect ENO1 expression in lung tissue and serum ENO1 autoantibody levels, respectively. **Results:** The expression of ENO1 was higher in lung cancer tissues than in benign lung disease tissues ($p < 0.001$). The proportion of lung cancer samples expressing ENO1 was not significantly different among the various pathological classification groups. The proportion of samples expressing ENO1 was higher in lung cancer patients in stages I/II than in those in stages III/IV ($\chi^2 = 5.445$; $p = 0.018$). The expression of ENO1 in lung cancer tissues was not associated with age, gender, or smoking history. Serum ENO1 antibody levels were significantly higher in the lung cancer group than in the benign lung disease and control groups ($p < 0.001$). The differences among the pathological classification groups were not statistically significant. Serum ENO1 antibody levels were also in lung cancer patients in stages I/II than in those in stages III/IV ($p < 0.01$). Serum ENO1 antibody levels were not associated with age, gender, or smoking history in lung cancer patients. The ROC curve representing the diagnosis of lung cancer based on ENO1 antibody levels had an area under the curve of 0.806. **Conclusions:** Our results suggest that high levels of ENO1 are associated with the clinical stage of lung cancer and that ENO1 expression and its serum autoantibody levels show diagnostic value in lung cancer.

Keywords: Phosphopyruvate hydratase/analysis; Enzyme-linked immunosorbent assay; Immunohistochemistry; Lung neoplasms.

INTRODUCTION

Lung cancer is one of the most common malignant tumors. The morbidity and mortality of lung cancer are very high; therefore, an early, accurate diagnosis is key for increasing treatment efficacy.[1] However, early-stage lung cancer is very insidious, and the disease progresses quickly. Currently, there is no effective diagnostic method or indicator for early-stage lung cancer. When the disease is confirmed, more than 70% of patients with lung cancer have already progressed past the ideal time for treatment. Therefore, identifying early-diagnosis markers for lung cancer has important clinical value. One of three subtypes of enolase is α-enolase (ENO1). Researchers have previously detected high levels of ENO1 protein in tumor tissues and peripheral blood in patients with lung cancer,[2] suggesting that ENO1 could be used as a lung cancer marker. However, the mechanism underlying the effects of ENO1 on the occurrence and development of lung cancer remains unclear, and ENO1 expression and its autoantibody levels for the diagnosis of lung cancer have yet to be clarified. The objective of the present study was to investigate the diagnostic value of ENO1 expression and serum ENO1 autoantibody levels in lung cancer in order to determine whether there is a possibility of using those as lung cancer markers.

METHODS

In the present study, tissue and blood samples were collected from untreated patients with suspected lung cancer. We initially determined the expression of ENO1 in tumor tissues and serum ENO1 autoantibody levels in lung cancer patients in a pairwise fashion and analyzed the correlation between serum ENO1 antibody levels and tissue ENO1 expression.

Pathological tissue specimens

A total of 132 pathological tissue samples from 132 patients with suspected lung cancer were collected in our hospital between January of 2012 and May of 2013. Pathological diagnosis confirmed that there were 72 cases of lung cancer and 60 cases of benign lung diseases (chronic inflammation, bullous lung disease, inflammatory pseudotumor, atypical hyperplasia, and fibroma). Given that palliative radiotherapy and chemotherapy are the major types of treatment for advanced lung cancer patients, there were only 21 patients (29.2%) with confirmed lung cancer in stages III and IV (Table 1).

Serum specimens

A total of 141 serum specimens from 72 patients with lung cancer and 69 patients with benign lung diseases

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were collected. In addition, 70 serum samples from healthy individuals who underwent physical examination during the study period were used as a control group (Table 1).

Sample collection and storage

Tissue specimens were fixed in 10% neutral formalin solution, embedded in paraffin, sectioned into 4-μm sections, and stored at 4°C. Peripheral blood samples (3 mL) were collected and centrifuged at 3,500 rpm for 5 min, and serum samples were collected, aliquoted, and stored at −20°C.

Reagents

The reagents used were rabbit anti-ENO1 monoclonal antibody (Abcam Biotechnology Co. Ltd., Cambridge, UK), an immunohistochemistry reagent kit (Maixin, Fuzhou, China) and an ENO1 antibody ELISA reagent kit (HuaAn, Hangzhou, China).

Detection of tissue ENO1

Immunohistochemistry using the streptavidin-peroxidase staining method was performed according to the manufacturer's instruction manual. For the interpretation of the results, five random fields from each section were selected and examined under a high-power microscope, 100 tumor cells being counted per field. Cells were considered to be positive when ENO1 was localized in the cytoplasm, cell membrane, or cell nucleus as yellow or brownish yellow granules. Samples with a proportion of positive cells ≥ 5% were considered to be positive, whereas those with a proportion < 5% were considered negative.[3]

Detection of serum ENO1 antibody

The ELISA method was performed in accordance with the manufacturer's instruction manual. The concentration of standards provided by the reagent kit and the detected optical density values were used to plot a standard curve. The optical density values of the samples were introduced into the equation to calculate the concentration of samples and to calibrate differences among the plates.

Statistical methods

Data were processed using the IBM SPSS Statistics software package, version 19.0 (IBM Corporation, Armonk, NY, USA) for statistical analysis. Categorical variables were described as absolute and relative frequencies, whereas continuous variables were presented as median and interquartile range. We used the nonparametric Mann-Whitney U test to determine differences between two groups and the Kruskal-Wallis test to determine differences among three groups. We used the chi-square test for comparisons of proportions. Statistical significance was set at $p < 0.05$.

RESULTS

The expression of ENO1 in lung cancer tissue samples was mainly distributed in the cytoplasm and occasionally in the cell membrane or the nucleus. Positive signs are visualized as yellow or brownish

Table 1. Clinical data of the specimens.

Parameter	Tissue specimens		Serum specimens	
	Group			
	Lung cancer (n = 72)	Benign lung disease (n = 60)	Lung cancer (n = 72)	Benign lung disease (n = 69)
Gender				
Male	46	35	46	40
Female	26	25	26	29
Age, years				
Median	64	58	64	58
Interquartile range	37-82	28-85	37-82	26-87
Smoking history				
Yes	38		38	
No	34		34	
Pathological type				
Lung adenocarcinoma	38		38	
Lung squamous cell carcinoma	24		24	
Small cell lung cancer	4		4	
Bronchoalveolar carcinoma	4		4	
Small cell lung cancer + adenocarcinoma	1		1	
Small cell lung cancer + squamous cell carcinoma	1		1	
Clinical stage				
I/II	51		51	
III/IV	21		21	

yellow granules. No expression of ENO1 was found in the majority of the samples in the benign lung disease group (Figure 1). The present study analyzed tumor tissue samples from 72 patients with lung cancer. The patients were grouped according to pathological type, clinical stage, age, gender, and smoking history. Comparisons of differences in expression in each group were performed using the chi-square test (Table 2). Table 2 shows that ENO1 expression was significantly higher in the lung cancer group (50.0%) than that in the benign lung disease group (10.0%), the difference being statistically significant ($\chi^2 = 24.137$; $p < 0.001$). However, ENO1 expression among the groups of patients with adenocarcinoma, squamous cell carcinoma, and other types of cancer was not significantly different ($p > 0.05$), suggesting that ENO1 expression in lung cancer tissues was not associated with the pathological types. In addition, the proportion of ENO1-positive samples was higher in the group of patients in stages I and II than in that of those in stages III and IV. This difference was statistically significant ($\chi 2 = 5.445$; $p = 0.018$), suggesting that ENO1 expression in lung cancer tissues was associated with the clinical stage of the disease. However, ENO1 expression was not associated with age, gender, or smoking history ($p > 0.05$).

The data regarding serum ENO1 antibody levels in the three studied groups all showed skewed distributions. The median (interquartile range) was used in order to represent these levels, and the nonparametric Mann-Whitney U test and the Kruskal-Wallis test were used in order to compare the differences among the groups (Table 3).

Table 3 shows that serum ENO1 antibody levels were significantly higher in the lung cancer group than those in the control and in the benign lung disease groups, the differences being statistically significant ($p < 0.001$). Moreover, ENO1 antibody levels in the benign lung disease group were higher than were those in the control group ($p < 0.05$). Among the groups with squamous cell carcinoma, adenocarcinoma, and other types of cancer, ENO1 antibody levels were not significantly different ($p > 0.05$), which suggested that serum ENO1 antibody levels were not associated with the pathological type of lung cancer. In addition, ENO1 antibody levels in the patients in stages I and II were higher than were those in the patients in stages III and IV ($p < 0.01$), suggesting that serum ENO1 antibody levels might be associated with the clinical stage of lung cancer. However, ENO1 antibody levels were not associated with age, gender, or smoking history ($p > 0.05$).

Differences in serum ENO1 antibody levels in patients with positive or negative ENO1 expression in lung cancer tissues were analyzed (Table 4). The results demonstrated that serum ENO1 antibody levels were significantly higher in the lung cancer patients with positive ENO1 expression than in those with negative ENO1 expression ($p = 0.019$). Therefore, there is a correlation between serum ENO1 antibody levels and ENO1 expression in tissue samples.

The ROC curve representing the diagnosis of lung cancer based on ENO1 antibody levels was plotted, and the area under the curve was 0.806. The maximum value of the Youden index (0.533) was selected as the best cut-off point (19.62 ng/mL) for screening.

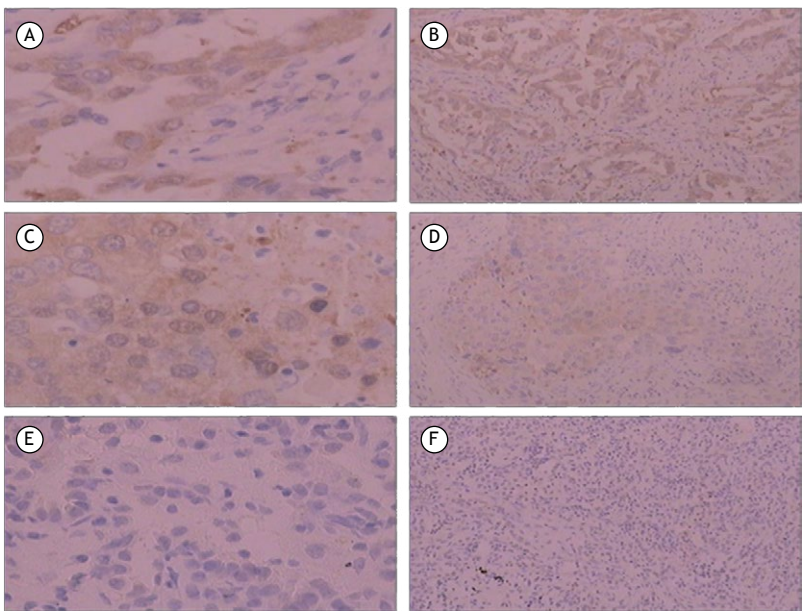

Figure 1. Photomicrographs showing α-enolase (ENO1) expression in lung tissue samples (immunohistochemistry using the streptavidin-peroxidase staining method). Positive signs are visualized as yellow or brownish yellow granules. In A and B, adenocarcinoma tissue samples showing positive ENO1 expression (magnification, ×400 and ×100, respectively). In C and D, squamous cell carcinoma tissue samples showing positive ENO1 expression (magnification, ×400 and ×100, respectively). In E and F, pulmonary inflammatory pseudotumor tissue samples showing negative ENO1 expression (magnification, ×400 and ×100, respectively).

The results showed that the diagnostic sensitivity and specificity of the test were 80.6% and 72.7%, respectively (Figure 2).

DISCUSSION

Enolase is an important metabolic enzyme in the glycolysis pathway. There are three subtypes in mammalian cells: ENO1, β-enolase (ENO3), and γ-enolase (ENO2). ENO1 is extensively distributed in various tissues in the human body, whereas ENO2 and ENO3 expression is tissue specific. ENO2 is also called neuron-specific enolase and is primarily distributed in neurons and neuroendocrine tissues. ENO3 is also called muscle-specific enolase and is mainly present in muscle tissues. ENO1 mainly localizes to the cytoplasm. During glycolysis, ENO1 converts 2-phosphoglycerate into phosphoenolpyruvate. In recent years, in addition to glycolysis, it was discovered that ENO1 has various biological functions. The association of ENO1 with malignant tumors has received increasing attention, and ENO1 has bidirectional functions in the occurrence and development of tumors.[4] ENO1 localized in the nucleus is also called c-myc promoter-binding protein 1

Table 2. α-enolase expression in pathological tissue samples.

Group	Result				χ^2	p
	n	Positive	Negative	Positive, %		
Benign disease tissue sample	60	6	54	10.0	24.137	< 0.001
Lung cancer tissue sample	72	36	36	50.0		
Pathological type						
Adenocarcinoma	38	20	18	52.6		
Squamous cell carcinoma	24	12	12	50.0		
Other types	10	4	6	40.0		
Clinical stage						
I/II	51	30	21	58.8	5.445	0.018
III/IV	21	6	15	28.6		
Age, years						
> 60	50	27	23	54.0	1.047	0.443
≤ 60	22	9	13	40.9		
Gender						
Male	46	21	25	45.7	0.963	0.462
Female	26	15	11	57.7		
Smoking history						
Yes	38	23	15	60.5	3.567	0.098
No	34	13	21	38.2		

Table 3. Comparison of serum α-enolase antibody levels among the three groups studied.

Group	n	α-enolase antibody, ng/mL[a]	p
Control	70	16.5 (10.3-19.6)	< 0.001
Benign lung disease	69	17.5 (15.0-21.3)	
Lung cancer	72	22.8 (19.9-25.1)	
Pathological type			
Squamous cell carcinoma	24	22.8 (20.7-27.2)	0.571
Adenocarcinoma	38	23.5 (20.0-25.0)	
Other types	10	21.2 (18.0 -24.7)	
Clinical stage			
I/II	51	24.2 (20.5-27.3)	0.006
III/IV	21	21.3 (17.5-22.8)	
Age, years			
> 60	50	22.9 (20.7-25.0)	0.456
≤ 60	22	22.3 (17.5-29.2)	
Gender			
Male	46	22.9 (20.0-27.3)	0.376
Female	26	22.4 (19.6-24.5)	
Smoking history			
Yes	38	22.9 (19.8-27.7)	0.573
No	34	22.7 (19.9-24.7)	

[a]Values expressed as median (interquartile range).

and inhibits the transcription of c-myc to inhibit tumor growth.[5] ENO1 localized on the surface of the cell can be used as a receptor for tissue plasminogen activator and plays a role in the invasion and metastasis of tumor cells. ENO1 also strengthens the infiltration ability of monocytes and macrophages, and it can participate in tumor formation by controlling the expression of the c-myc oncoprotein through the Notch signaling pathway.[6,7]

In the present study, immunohistochemistry with the streptavidin-peroxidase staining method was used in order to determine the expression of ENO1 in lung cancer tissues and in benign lung disease tissues. The results showed that the proportion of lung cancer tissues expressing ENO1 (50%) was significantly higher than that of benign lung disease tissues (10%), which is consistent with a previous study.[4] Differences in ENO1 expression among the groups of patients with different cancer types were not statistically significant, suggesting that ENO1 expression was not associated with the pathological type of lung cancer. However, in the subjects included in the present study, adenocarcinoma accounted for 52.8% of the cases, whereas squamous cell carcinoma and other lung cancer types only accounted for 33.3% and 13.9% of the cases, respectively. Therefore, this conclusion should be further validated with an increased number of samples of other pathological types, such as squamous cell carcinoma and small cell lung cancer. The proportion of positive ENO1 expression was higher in patients in stages I and II (58.8%) than in those in stages III and IV (28.6%). It is possible that ENO1 plays different roles in different stages of tumor growth and that it possesses a more active role in energy metabolism processes at an early stage; however, the specific mechanism of action remains unclear. Cheng et al.[3] studied the ENO1 expression in nasopharyngeal cancer tissues and showed that the proportion of ENO1-positive samples exhibited a decreasing trend with an increase in the clinical stage of nasopharyngeal cancer. Other researchers also noted that the proportion of samples with positive ENO1 expression was higher in the early stages of colon cancer than in advanced stages of colon cancer.[3] These results are all consistent with the results in our study. However, the subjects in the present study were all patients who had undergone lung cancer surgery; thus, the proportion of patients in advanced stages of lung cancer was lower, and patients in stages III and IV accounting for only 29.2%. Therefore, this conclusion should be further validated by means of studies involving a greater number of samples and improved detection methods. We also analyzed the association of ENO1 expression in lung cancer tissues with some risk factors for lung cancer, such as age, gender, and smoking history. The results showed that ENO1 expression in lung cancer tissues was not associated with these clinical features, which is in accordance with the study of Hsiao et al.[8]

We used the ELISA method to detect serum ENO1 antibody levels in patients with lung cancer, in those with benign lung disease, and in healthy control individuals. The results showed that ENO1 antibody levels in the lung cancer group were significantly higher than were those in the other two groups. In addition, ENO1 antibody levels in the benign lung disease group were higher than were those in the control group, which might due to an increase in ENO1 antibody levels in patients with diseases such as chronic inflammation.[9] Pairwise comparisons between serum ENO1 antibody levels and pathological subtypes in the groups of patients with adenocarcinoma, squamous cell carcinoma, and other types of lung cancer showed that ENO1 antibody levels were not significantly different among these groups, suggesting that serum ENO1 antibody levels were not associated with the pathological type of lung cancer. However, these levels were higher in the patients in stages I and II of lung cancer than in those in stages III and IV, suggesting that serum ENO1 antibody levels might be associated with the clinical stage of lung cancer. This might be due to the early stage of tumor development, in which the immune surveillance function of the body activates antigen-specific destruction of tumor cells to induce immune responses that produce high titers of autoantibodies. As the tumor progresses, tumor cells and host immune cells interact in the tumor microenvironment to establish an immunosuppressive network, including the transduction of inhibitory signals and the production of immunosuppressive cells to inhibit tumor cells, causing a reduction in autoantibody

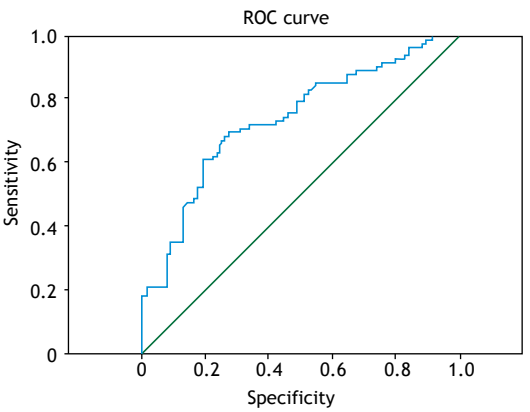

Figure 2. ROC curve showing the sensitivity and specificity of serum α-enolase antibody levels for the diagnosis of lung cancer.

Table 4. Correlation between α-enolase expression and serum α-enolase antibody levels in the lung cancer group.

α-enolase expression	n	α-enolase antibody, ng/mL[a]	p
Positive	36	24.1 (21.3-33.3)	0.019
Negative	36	21.7 (18.9-24.6)	

[a]Values expressed as median (interquartile range).

levels.[9] We also studied the association of serum ENO1 antibody levels with age, gender, and smoking history. The results showed that ENO1 antibody levels were not associated with these risk factors for lung cancer. Furthermore, the analysis of the relationship between serum ENO1 antibody levels and ENO1 expression demonstrated a positive correlation between them. Therefore, the quantification of serum ENO1 antibodies, which is a simple, efficient, and minimally invasive method, might be of great clinical significance in the diagnosis of lung cancer.

The ROC curve of the diagnosis of lung cancer based on ENO1 antibody levels was plotted, and the maximum value of the Youden index was used as the best cut-off point for screening. The results showed that the sensitivity of the method for the diagnosis of lung cancer was 80.6%, and its specificity was 72.7%. Various studies have confirmed that tumor markers, such as CYFRA21-1, ENO2, CEA, and SCC, play an important role in the diagnosis of lung cancer.[10,11] However, these markers usually have low sensitivity, and their positive frequencies vary greatly in different pathological types of lung cancer, which can cause misdiagnoses and might not be conducive to an early diagnosis of lung cancer.[10,11] The ENO1 autoantibody presents a more stable titer in the peripheral blood of early-stage lung cancer patients, which points to its value for the early diagnosis of lung cancer.

In summary, our data support that ENO1 has an important value in the diagnosis of lung cancer and can be used as a lung cancer marker. The quantification of serum ENO1 antibody has as advantages the easiness of sample collection and minimal invasiveness, and it seems to have a high value in the early diagnosis of lung cancer. Further studies should be carried out in order to confirm our conclusion.

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ORIGINAL ARTICLE

Complexity of autonomic nervous system function in individuals with COPD

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ABSTRACT

Objective: To evaluate autonomic modulation in individuals with COPD, compared with healthy controls, via recurrence plots (RPs) and linear heart rate variability (HRV) indices. **Methods:** We analyzed data on 74 volunteers, who were divided into two **groups:** COPD (n = 43) and control (n = 31). For calculation of HRV indices, heart rate was measured beat-by-beat during 30 min of supine rest using a heart-rate meter. We analyzed linear indices in the time and frequency domains, as well as indices derived from the RPs. **Results:** In comparison with the control group, the COPD group showed significant increases in the indices derived from the RPs, as well as significant reductions in the linear indices in the time and frequency domains. No significant differences were observed in the linear indices in the frequency domains expressed in normalized units or in the low frequency/high frequency ratio. **Conclusions:** Individuals with COPD show a reduction in both sympathetic and parasympathetic activity, associated with decreased complexity of autonomic nervous system function, as identified by RPs, which provide important complementary information in the detection of autonomic changes in this population.

Keywords: Pulmonary disease, chronic obstructive; Autonomic nervous system; Nonlinear dynamics; Recurrence; Heart rate; Sympathetic nervous system.

INTRODUCTION

COPD, which is characterized by chronic airflow obstruction or limitation that is not fully reversible,[1] affects three million individuals worldwide,[2] ranks fourth among the leading causes of death globally,[3] and is associated with numerous complications, chief among which are changes in the autonomic nervous system (ANS).[4,5]

The ANS is an example of a system with nonlinear dynamics[6] that has an influence on heart rate and blood pressure to ensure the proper functioning of bodily organs so that their actual needs are met. This system can be evaluated via heart rate variability (HRV) and reflects the ability of the heart to respond to autonomic changes over time.[7]

Studies evaluating the ANS in COPD via HRV primarily use linear indices in the time and frequency domains for this analysis and report that COPD patients show a decrease in these indices at rest when compared with controls of the same age group.[8] The few studies that have used nonlinear methods in this population find a reduction in short-term heart rate fractal correlation properties[9] and a reduction in beat-by-beat RR interval dispersion on electrocardiogram, as determined by analysis of Poincaré plots,[4] indicating lower HRV in individuals with COPD.

Analysis of HRV by nonlinear methods have garnered increasing interest, since there is evidence that the mechanisms involving cardiovascular regulation are likely to interact with each other nonlinearly.[10] One of the methods used for this purpose is the recurrence plot (RP), which was originally developed by Eckmann et al.[11] as a graphical tool for revealing hidden fluctuations and periodicities in the temporal evolution that go undetected by other methods[12]; the RP allows one to obtain measures that are primarily based on diagonally oriented lines in the plot, such as recurrence rate (REC), determinism (DET), and entropy.[12,13]

Traditional nonlinear methods are limited to long stationary signals, a condition that is rarely seen in biology,[14] whereas the RP was developed to locate non-stationary, structural changes[11] and may be a more sensitive tool for detecting physiological changes[15]

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and contribute to the surveillance and monitoring of individuals with COPD.

In view of these facts, the present study is intended to evaluate autonomic modulation in individuals with and without COPD, by analyzing RP indices as well as HRV indices in the time and frequency domains. We hypothesize that individuals with COPD will show a reduction in autonomic modulation and that the RP will be found to be a sensitive tool for identifying this condition.

METHODS

Study population

This was a prospective case-control study. For the purposes of the present study, we recruited 74 volunteers, who were divided into two groups: COPD (n = 43), as defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria[1]; and control (n = 31).

The COPD group included former smokers who had a physician diagnosis of COPD, which was confirmed by an obstructive pattern on pulmonary function testing and by reproducible curves, and who had not had a COPD exacerbation in the last two months. The control group included nonsmokers of the same age group who did not have a diagnosis of COPD, which was confirmed by a normal pattern on pulmonary function testing and by reproducible curves.

Neither group included individuals who had at least one of the following characteristics: being an alcoholic; being on medications that could affect autonomic modulation; and having cardiac and/or metabolic diseases.

The study procedures were approved by the Research Ethics Committee of the São Paulo State University School of Science and Technology (CAAE no. 15922813.9.0000.5402-306.419), located in the city of Presidente Prudente, Brazil, and all volunteers were fully informed about the procedures and purposes of the study. Upon agreement to participate in the study, subjects signed a written informed consent form.

Experimental protocol

The experimental protocol involved two steps. The first consisted of an initial evaluation to collect participant's identification data, perform anthropometric measurements, and assess pulmonary function. In the second step, conducted 24 h later, each participant's heart rate was measured beat-by-beat during 30 min using a heart-rate meter (Polar S810i; Polar Electro, Kempele, Finland) for subsequent calculation of HRV indices.

Initial evaluation

Participants were identified by name, age, and medication use; underwent anthropometric measurements (body mass and height); and were assessed for pulmonary function. Body mass was measured with an electronic digital scale (Lumina MEA-02550; Plenna, São Paulo, Brazil), and height was measured with a stadiometer (Personal Caprice; Sanny, São Bernardo do Campo, Brazil) with subjects being barefoot and standing erect. From the data obtained, we calculated the body mass index (BMI) using the following formula: BMI = weight/height^2 (kg/m^2).[16]

For pulmonary function assessment, participants underwent spirometry with a Spirobank spirometer (MIR, Rome, Italy).[17,18] Three acceptable and two reproducible curves were obtained, after a maximum of eight attempts. Obstructive lung disease was defined according to GOLD guidelines.[1]

Assessment of autonomic modulation

Autonomic modulation was assessed 24 h after completion of the first step. For this assessment, participants were instructed not to consume alcohol or any drinks that could stimulate the ANS, such as coffee, tea, soft drinks, and chocolate milk, and not to perform any vigorous exercise in the 24 h preceding the test.

For the assessment of autonomic modulation, heart rate was measured beat-by-beat, in the morning (from 8:00 to 11:00), in a quiet environment with a room temperature between 21°C and 24°C and a relative humidity between 40% and 60%.

Heart rate was measured with a chest strap, which was placed on the distal third of the sternum, and a heart-rate meter (Polar Electro), which was worn on the wrist; this equipment has been previously validated for measuring heart rate beat-by-beat and for use in the calculation of HRV indices.[10] Participants were instructed to remain silent, awake, and at rest and to breathe spontaneously for 30 min in the supine position on a stretcher. After this assessment, participants were released.

For calculation of HRV indices, we used 1,000 RR intervals obtained from the most stable part of the tracing. The series of RR intervals initially underwent filtering, using the standard filter in the Polar ProTrainer 5 (version 5.41.002) software (Polar Electro),[19] using a moderate filter (median protection zone of six heartbeats), and, subsequently, a visual inspection of the temporal series of RR intervals on the computer screen was performed, which showed no artifacts that could affect HRV analysis. Only series showing more than 95% of sinus beats were included in the study.[10]

HRV indices in the time and frequency domains were calculated using Kubios HRV version 2.0 software (Kubios Oy; Kuopio, Finland), whereas RP indices were calculated using Visual Recurrence Analysis version 4.9 software (Eugene Kononov, Springfield, MA, USA).

In the time domain, we calculated the following indices: the standard deviation of the NN interval (SDNN), representing all normal RR intervals; and the root mean square of successive differences (RMSSD), which corresponds to the square root of the mean squared differences between successive RR intervals over a given time period.[10]

In the frequency domain, we used low-frequency (LF; 0.04-0.15 Hz) and high-frequency (HF; 0.15-0.40 Hz) spectral components, in ms^2 and in normalized units (nu), as well as the ratio of these two components (LF/HF). Spectral analysis was performed using the fast Fourier transform algorithm.[10]

RPs were analyzed qualitatively and quantitatively. Qualitative analysis was based on visualization of plots, and quantitative analysis was based on the following indices: REC; DET; Shannon entropy (SE); laminarity (LAM); trapping time (TT); and maximum line length (MaxLine). The parameters used in creating the RPs were as follows: embedding dimension = 10; time delay = 1; radius = 70; line length = 2[20]; and color scheme in gray.

RPs visualize the behavior of trajectories in phase space and show the times at which a dynamic system repeats itself.[11] RPs are defined as a symmetric matrix consisting of ones and zeros, and RP(i,j) is 1 if the vector ξi on the trajectory is closed for the vector ξj.[21]

$$PR(i, j) = \begin{cases} 1 \text{ se } d(\xi i - \xi j) < r, \\ 0 \text{ se cc}, \end{cases}$$

where $d(\xi i - \xi j)$ is the Euclidean distance, r is a fixed threshold, and o/w stands for "otherwise".

Based on this matrix, vectors are calculated by reconstruction of the space, and the sum of these vectors enables the determination of Euclidean distance values. The Euclidean distance values are compared with the r value, and this enables the construction of a plot. If the distance between the vectors ξi and ξj on the reconstructed trajectory is smaller than r, a black dot is placed at location (i,j) in the matrix; otherwise, the location is left blank (white).[22]

REC is the probability of similar states occurring within a given system.[23] DET is the proportion of recurrent points that form diagonal lines through which systems with similar or equal phase spaces remain in the same regions over a given time period.[23] LAM is represented by the radius between recurrent points that form vertical lines, determining the occurrence of laminar states in the system.[24] The number and length of vertical lines are defined as TT.[24] MaxLine is defined as the length of the longest diagonal line in the RP.[25] And, finally, we calculate entropy, defined on the basis of the frequency distribution of the diagonal line lengths.[15] The term entropy refers to the SE of the probability $p(l) = P(l)/N_l$ to find diagonal lines corresponding to given line lengths l ($N_l = \Sigma_{l \geq l\,min} P(l)$), where l is the number of diagonal lines, Ni is the total number of diagonal lines, and P is probability.

Data analysis

The sample was characterized with descriptive statistics, and the results are expressed as mean, median, and minimum-maximum value. For comparison of anthropometric variables, age, spirometric values, and HRV indices between groups, data were tested for normality by using the Shapiro-Wilk test; for data showing a normal distribution (age, weight, height, FVC, FEV_1/FVC, REC, TT, SE, SDNN, LF/HF), the Student's t-test for unpaired data was used, whereas for data with a non-normal distribution (BMI, FEV_1, DET, LAM, MaxLine, RMSSD, LF [ms^2], HF [ms^2], LF [un], and HF [un]), the Mann-Whitney test was used. Statistically significant differences were defined as those with p values > 0.05.

RESULTS

Table 1 presents the characteristics of the volunteers in the two groups studied. Significant differences were observed between the groups for height, FVC, FEV_1, and FEV_1/FVC.

The linear HRV indices analyzed in the time and frequency domains are presented in Table 2. Lower values for SDNN, RMSSD, LF (ms^2), and HF (ms^2) were observed in the COPD group as compared with the control group ($p < 0.05$). No statistically significant differences were found between the groups for LF (un), HF (un), or the LF/HF ratio.

Table 3 presents the indices derived from the RCs of the groups studied. Increases in all indices derived from the RCs were observed for the COPD group ($p < 0.05$).

Figure 1 shows a representative example of the visual analysis of RPs. The presence of more points in a given configuration state (black dots) is observed in the COPD group as compared with the control group.

DISCUSSION

The results of the present study suggest that individuals with COPD exhibit decreased complexity of ANS function, associated with reductions in both sympathetic and parasympathetic activity. In addition, there were increases in all indices derived from RPs in the COPD group as compared with the control group.

REC and DET were associated with the complexity of cardiac autonomic modulation.[21] According to Webber et al.,[15] periodic systems show high REC values as compared with nonperiodic systems, and structured deterministic systems show high DET values. Because structured periodic systems are less complex, high REC and DET values indicate lower complexity of autonomic modulation, which can be observed in the COPD patients analyzed in the present study.

According to Javorka et al.,[6] lower TT and LAM values translate to higher complexity of a dynamic system. In our study, we observed that COPD patients showed an increase in TT and LAM values as compared with controls, again suggesting lower complexity in the former.

Regarding SE, low values appear to be associated with stochasticity, whereas high values are associated with a more deterministic behavior.[21] In the present study, we observed that the individuals in the COPD group showed higher SE values, which indicates a more

Table 1. Characteristics of the study volunteers in the control and COPD groups.[a]

Variable	Group		p
	Control (n = 31)	COPD (n = 43)	
Age, years	63.25 ± 7.13 (63.00) [52.00-79.00]	66.37 ± 8.27 (66.00) [48.00-83.00]	0.080
Weight, kg	68.83 ± 16.26 (65.00) [46.00-113.00]	69.74 ± 13.88 (71.00) [35.30-106.50]	0.802
Height, cm	155.45 ± 7.52 (155.00) [140.00-173.00]	161.84 ± 8.76 (162.00) [144.00-176.00]	0.001
BMI, kg/m^2	29.83 ± 9.49 (29.00) [19.00-67.00]	26.41 ± 4.67 (26.00) [18.00-38.72]	0.071
FVC, L	2.95 ± 0.62 (2.79) [2.00-4.24]	2.52 ± 0.85 (2.27) [1.03-4.38]	0.015
FVC, % of predicted	104.70 ± 18.03 [72.00-146.00]	82.41 ± 23.93 [36.00-137.00]	< 0.001
FEV_1, L	2.36 ± 0.47 (2.30) [1.63-3.50]	1.31 ± 0.52 (1.10) [0.54-2.45]	< 0.001
FEV_1, % of predicted	105.03 ± 16.90 [75.00-145.00]	54.79 ± 21.04 [21.00-106.00]	< 0.001
FEV_1/FVC, %	80.35 ± 5.28 (79.00) [72.00-93.00]	51.70 ± 11.74 (51.60) [29.00-71.00]	< 0.001

BMI: body mass index. [a]Values expressed as mean ± SD (median) [minimum – maximum].

Table 2. Linear heart rate variability indices in each group.[a]

Index	Group		p
	Control	COPD	
SDNN	34.48 ± 12.51 (32.50) [17.30-58.60]	28.04 ± 12.18 (26.60) [8.20-63.00]	0.031
RMSSD	21.71 ± 11.60 (19.90) [8.70-60.70]	13.80 ± 7.19 (12.90) [3.10-30.70]	0.001
LF, ms^2	339.25 ± 299.40 (213.00) [72.00-1.138.00]	205.93 ± 219.79 (141.00) [7.00-1.193.00]	0.013
HF, ms^2	161.19 ± 145.38 (115.00) [24.00-606.00]	74.02 ± 74.92 (42.00) [1.00-282.00]	0.001
LF, nu	67.72 ± 10.93 (69.00) [38.60-83.20]	72.43 ± 18.165 (75.70) [28.30-97.20]	0.061
HF, nu	32.25 ± 10.92 (31.00) [16.80-61.40]	27.56 ± 18.165 (24.30) [2.80-71.70]	0.061
LF/HF	2.44 ± 1.16 (2.22) [0.62-4.97]	5.72 ± 6.94 (3.11) [0.39-34.22]	0.062

SDNN: standard deviation of the NN interval (i.e., standard deviation of all normal RR intervals), expressed in milliseconds; RMSSD: root mean square of successive differences between adjacent normal RR intervals, expressed in milliseconds; LF: low frequency; HF: high frequency; and nu: normalized units. [a]Values expressed as mean ± SD (median) [minimum – maximum].

deterministic system and, therefore, lower complexity of ANS function in these individuals.

Finally, we observed that the individuals with COPD showed higher MaxLine values as compared with controls. MaxLine is the longest diagonal line in the RP[25] and is known to correspond to the persistence of the state over a given time interval[22]; therefore, higher MaxLine values translate to less chaotic systems,[26] which again indicates lower complexity of autonomic modulation in the COPD group.

Qualitative analysis based on visualization of RPs also demonstrates that individuals with COPD exhibit lower complexity of ANS function as compared with healthy individuals. In individuals with COPD, the presence of more points in a given configuration state (black dots) is noted, unlike what is found in individuals without COPD, in whom the presence of a greater number of points in different configuration states (white dots) can be observed.

Analysis of the diagonal, horizontal, and vertical lines in the RP enables rapid visual interpretation of the changes in autonomic modulation in individuals with pathological conditions.[21] According to Assmann et al.,[22] diagonal lines indicate similar evolution of different parts of the trajectory, whereas horizontal and vertical lines show that the system does not change for some time. As reported by Ferreira,[21] for time series of healthy subjects, the RP has a diagonal line and fewer apparent squares, which indicates higher HRV. Therefore, we can observe that Figure 1A shows a higher proportion of recurrent points as compared

Table 3. Recurrence plot indices for analysis of heart rate variability, by group studied.

Index	Group		p
	Control	COPD	
REC, %	28.87 ± 5.33 (28.67) [18.74-39.14]	33.20 ± 5.47 (34.20) [15.96-42.23]	0.001
DET, %	98.54 ± 0.81 (98.67) [96.65-99.51]	98.85 ± 0.97 (99.14) [94.95-99.825]	0.017
LAM, %	96.28 ± 3.03 (96.94) [87.25-99.46]	97.09 ± 4.62 (98.38) [71.76-99.89]	0.016
TT	9.99 ± 4.01 (8.82) [4.39-19.65]	12.52 ± 5.17 (12.41) [2.42-23.41]	0.021
SE, bitys	−4.63 ± 0.43 (4.58) [3.76-5.46]	−4.91 ± 0.41 (4.96) [3.82-5.65]	0.008
MaxLine	377.45 ± 279.31 (282.00) [103.00-990.00]	589.11 ± 279.94 (600.00) [106.00-990.00]	0.001

REC: recurrence rate; DET: determinism; LAM: laminarity; TT: trapping time; SE: Shannon entropy; and MaxLine: length of the longest diagonal line in the recurrence plot. [a]Values expressed as mean ± SD (median) [minimum – maximum].

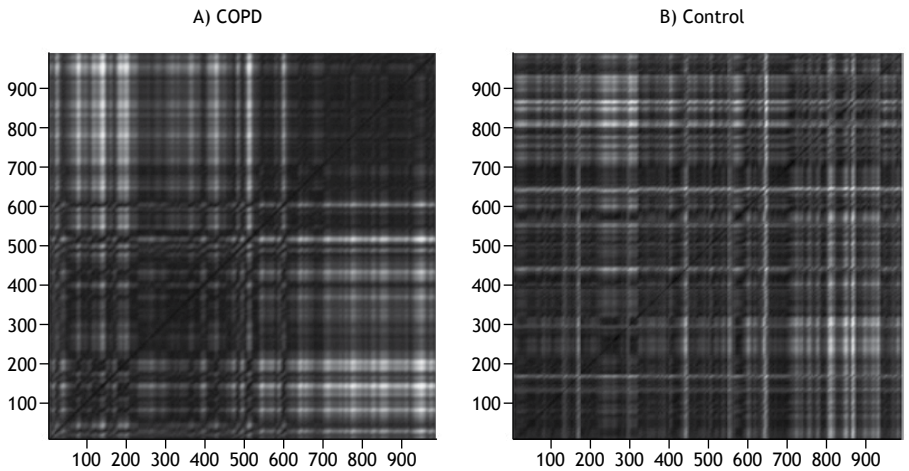

Figure 1. Recurrence plots. In A, a subject in the COPD group (REC = 32.98 and DET = 98.76), and, in B, a subject in the control group (REC = 28.67 and DET = 98.52). REC: recurrence rate; and DET: determinism.

with Figure 1B, indicating a more recurrent and less dynamic system in the COPD group and lower complexity of autonomic modulation in this population.

Detection of autonomic changes by using linear HRV indices has received increasing attention in the literature because of evidence indicating that the mechanisms involved in cardiovascular regulation interact with each other nonlinearly,[10] enabling a better understanding of the complex and dynamic systems of the human body,[27] which provides additional information related to physiological interpretation and prognosis.[28] Carvalho et al.[9] studied the fractal dynamics of heart rate in subjects with and without COPD by measuring short- and long-term fractal exponents and reported a decrease in the short-term fractal correlation properties of heart rate in the COPD group, indicating a reduction in autonomic complexity in these individuals, as was also observed in our study via application of RPs.

Analysis of fractal dynamics differs in some aspects from RP analysis. Fractal dynamics was developed to characterize scale fluctuations, that is, short- and long-term time series,[20] whereas the RP was developed to locate nonstationary structural changes,[11] thus enabling the identification of hidden fluctuations and periodicities in the temporal evolution.[12] Therefore, the use of RPs as a tool for analyzing HRV can provide important complementary information in the detection of autonomic changes in individuals with COPD.

The state of being healthy is characterized by a certain degree of chaos in the ANS, and abnormalities in ANS function cause a decrease in cardiac chaos.[21,29] Changes in autonomic modulation can lead to a marked reduction in the complexity of the dynamics of heart rate fluctuations, making the heart period less adaptable and making the heart less able to cope with a frequently changing environment.[25,30]

Taken together, these data suggest that COPD patients exhibit decreased complexity of autonomic modulation and are consequently subject to poor health status. Decreased complexity of cardiac autonomic modulation is associated with adverse clinical events, such as coronary artery disease with stenosis ≥ 50%,[31] type

I diabetes mellitus,[6] and schizophrenia,[32] as well as with the aging process.[33]

In addition to decreased complexity of ANS function, our findings show a reduction in LF and HF in ms^2, as well as in SDNN and RMSSD, which suggests a decrease in overall variability and in sympathetic and parasympathetic activity.

Carvalho et al.[9] also found reductions in LF and HF in ms^2, as well as in SDNN and RMSSD, when comparing elderly subjects with COPD and controls of the same age group. Geometric indices have also indicated a decrease in vagal activity (standard deviation 1) and overall variability (standard deviation 2; triangular interpolation of NN interval histogram; and triangular index) in COPD patients.[4] Several other studies have corroborated these findings, which indicate a change in cardiac autonomic modulation, demonstrating impairment of this activity in individuals with COPD.[34-38]

In addition, Mazzuco et al.[39] found that greater pulmonary function impairment translates to decreased heart rate dynamics in individuals with COPD, as shown by linear and nonlinear HRV indices. Also according to the same authors, there is in these individuals a negative relationship between DLCO and RR intervals during parasympathetic stimulation (respiratory sinus arrhythmia), which may be related to greater sympathetic stimulation that changes pulmonary capillary tone.

The mechanism by which autonomic modulation is altered in COPD has yet to be well established. Hypotheses are considered relative to predominant tone in such cases, since the hyperinflation that is characteristic of COPD could generate altered vagal impulses.[40] Therefore, linear HRV indices indicate that individuals with COPD exhibit a reduction in both sympathetic and parasympathetic activity, and RP analyses show decreased complexity of ANS function, indicating poorer health status in this population. In addition, our findings contribute new information to the literature with regard to a new effective method that can detect changes related to the ANS in individuals with COPD by locating nonstationary structural changes.

One limitation of the present study is the heterogeneity in the degree of obstruction in the patients included in the COPD group. The COPD group comprised 3 patients classified as GOLD I ($FEV_1 \geq 80\%$ of predicted), 18 patients classified as GOLD II ($50\% < FEV_1 < 80\%$ of predicted), 17 classified as GOLD III ($30\% < FEV_1 < 50\%$ of predicted), and 5 patients classified as GOLD IV ($FEV_1 < 30\%$ of predicted). Although this is a heterogeneous group in terms of the degree of disease severity, Camilo et al.[5] found that this aspect does not significantly affect HRV analysis. Another limitation is the use of bronchodilator medication. However, in our study, subjects were not under the daily effect of this medication during the period of data collection, and, as mentioned previously, none had had a recent COPD exacerbation, a fact that can overcome this limitation.

We therefore conclude that individuals with COPD exhibit decreased complexity of ANS function, as demonstrated by the indices derived from the RPs, associated with a reduction in both sympathetic and parasympathetic activity, as shown by the linear HRV indices.

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Is suicidal ideation associated with allergic asthma and allergic rhinitis?

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ABSTRACT

Objective: To investigate whether there is an association between suicidal ideation (SI) and allergic diseases in adults. **Methods:** This was a comparative cross-sectional study involving individuals ranging from 20 to 50 years of age recruited from a university hospital in the city of Guadalajara, Mexico. We included patients with a confirmed diagnosis of allergic asthma, those with a confirmed diagnosis of allergic rhinitis, and healthy controls. All subjects completed the Beck Depression Inventory-II (BDI-II), which includes an item that evaluates the presence of suicidal thoughts or desires within the last two weeks, in order to identify SI. **Results:** The sample comprised 115 patients with allergic asthma, 111 patients with allergic rhinitis, and 96 healthy controls. The number of individuals identified with SI in the three groups were, respectively, 17 (14.8%), 13 (11.7%), and 8 (8.3%). Regarding the presence of SI, no statistically significant association was found in the allergic asthma group (OR = 1.98; 95% CI: 0.78-4.64; p = 0.154) or in the allergic rhinitis group (OR = 1.46; 95% CI: 0.58-3.68; p = 0.424) when they were compared with the control group. However, the presence of depression was associated with SI in the three groups: allergic asthma (OR = 12.36; 95% CI: 2.67-57.15; p = 0.001); allergic rhinitis (OR = 6.20; 95% CI: 1.66-23.14; p = 0.006); and control (OR = 21.0; 95% CI: 3.75-117.36; p < 0,001). **Conclusions:** In comparison with the control group, no association was found between SI and the groups with allergic diseases. In contrast, there was association between SI and depression in the three groups.

Keywords: Suicidal ideation; Asthma; Rhinitis, allergic; Adult.

INTRODUCTION

The prevalence of suicidal ideation (SI) in the general population is approximately 9%.[1] However, this prevalence seems to be higher in people with chronic diseases, such as diabetes, arthritis, COPD, and asthma.[2-4]

Suicidal behavior is a dynamic process; its initial manifestation is ideation that can lead to suicide intent and ultimately to its consummation. To explain the propensity to suicide, a proposed model includes suicide vulnerability (personal or familial history of suicide); mood disorder vulnerability (presence of major depression or bipolar disorder); and allergy vulnerability (the production of specific IgE against pollens has been reported to be associated with this propensity).[5]

The evidence suggests the existence of an association between SI and allergic respiratory diseases, the majority of these results coming from epidemiological studies,[4,6,7] and one study found no such an association.[8] Therefore, our main objective was to verify whether SI is associated with allergic respiratory diseases in the clinical context of patients attending a university teaching hospital.

METHODS

The present study was carried out at a university hospital that provides health care to the population in the metropolitan area of Guadalajara, Mexico. In this comparative cross-sectional study, the subjects were recruited consecutively from an outpatient immunology and allergy clinic between March of 2013 and February of 2014.

All of the patients underwent clinical and physical evaluation. The diagnosis of asthma was established in accordance with the Global Initiative for Asthma (GINA) [9] criteria and forced spirometry results showing airflow obstruction and significant improvement in FEV_1 (≥ 12% and ≥ 200 mL) after the administration of 400 μg of albuterol.[10] Thereafter, patients were categorized by asthma severity in accordance with the GINA criteria.[9]

Allergic rhinitis was defined as the presence of typical symptoms: nasal congestion and hyaline rhinorrhea, as well as sneezing or nasal pruritus after aeroallergen exposure. The patients were then distributed by their clinical course in accordance with the Allergic Rhinitis

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and Its Impact on Asthma guidelines.[11] The allergic condition of asthma and rhinitis was defined by the presence of at least one positive skin prick test against a regional aeroallergen panel. The interpretation of these tests were carried out by a specialist in allergy who interpreted the results in accordance with recommendations by the European Academy of Allergy and Clinical Immunology.[12]

The patients (20-50 years of age) diagnosed with allergic asthma or allergic rhinitis were divided into two groups. Those with a history of diabetes, hypertension, cancer, rheumatic diseases, or any other chronic disease were excluded. Pregnant or breastfeeding women were also excluded. Healthy blood donors who came to the hospital during the study period and volunteered to participate in the study formed a third group (control). All participants gave written informed consent.

In order to identify SI, all of the subjects from each group completed the Spanish-language version of Beck Depression Inventory-II (BDI-II),[13] a 21-item list of symptoms, with corresponding multiple-choice questions (with a score ranging from 0 to 3). Depression was confirmed if the final score was greater than 13 points. Item 9 of BDI-II evaluates the presence of suicidal thoughts or wishes within the past two weeks and has the following response options: 0) "I don't have thoughts of killing myself;" 1) "I have thoughts of killing myself, but I would not carry them out;" 2) "I would like to kill myself;" and 3) "I would kill myself if I had the chance." SI was defined as any response other than 0 to that item.

The physicians (previously trained by a psychologist) responsible for the medical attention of the patients applied the BDI-II to the patients on the same day they received their diagnosis, as well as to the volunteers when they gave written informed consent.

In order to identify the proportion of depression and SI in the three groups, the relative frequency was calculated; in addition, we used descriptive statistics. To establish the association of SI with atopic respiratory diseases and the association of depression with SI, we calculated the odds ratios with a 95% confidence interval. Any p value smaller than 0.05 was considered significant. The analyses were performed with the use of the IBM SPSS Statistics software package, version 20.0 (IBM Corporation, Armonk, NY, USA).

The present study was supervised and approved by the research ethics committee of the university hospital. During the study period, all the participants who were found to have SI or depression symptoms were sent to a psychologist for specialized attention and care.

RESULTS

The sample comprised 322 individuals, divided into three groups: allergic asthma (n = 115), allergic rhinitis (n = 111), and control (n = 96). The majority of the subjects were in the fourth decade of life (Table 1). A significant predominance of females was found in the two study groups. Alcohol consumption was significantly higher in the control group than in the allergic asthma and allergic rhinitis groups ($p < 0.001$). The proportion of current smokers was higher in the control group than in the allergic asthma group ($p < 0.001$), but it was similar between the allergic rhinitis group and the control group ($p > 0.05$). The BDI-II scores were significantly higher in the allergic asthma and allergic rhinitis groups than in the control group; however, only the subjects with allergic asthma showed a significant higher frequency of depression when compared with the control group ($p < 0.001$). The proportions of subjects presenting with SI in allergic asthma group, allergic rhinitis group, and control group were, respectively, 14.8% (17/115), 11.7% (13/111), and 8.3% (8/96; Table 2). There was no statistically significant difference in the frequency of SI in relation to the severity of allergic diseases ($p > 0.05$; Table 3).

The presence of SI showed no statistically significant difference in the allergic asthma or allergic rhinitis groups (OR = 1.98; p = 0.154; and OR = 1.46; p = 0.424, respectively) when they were compared with the control group (Table 4). However, the presence of SI did show a significant association with the presence of depression in the three groups (Table 5).

Table 1. Clinical characteristics of the population studied.[a]

Variable	Group		
	Allergic asthma (n = 115)	Allergic rhinitis (n = 111)	Control (n = 96)
Age, years	36.2 ± 8.8	32.0 ± 10.4	32.1 ± 9.7
Female sex	100 (87.0)*	82 (73.9)**	37 (38.5)
Current smoking	8 (7.0)*	9 (8.1)	14 (14.5)
Current alcohol consumption	21 (18.3)*	27 (24.3)**	49 (51.0)
Physical activity, active	57 (49.6)*	68 (61.3)	71 (74.0)
Hours of sleep	7.3 ± 1.4	7.1 ± 1.7	7.5 ± 1.2
BMI, kg/m^2	28.2 ± 6.4	26.1 ± 5.7	26.9 ± 3.7
BDI-II score	13.0 ± 8.8*	9.7 ± 8.7*	6.7 ± 7.0
Depression	52 (45.2)*	29 (26.1)	17 (17.7)

BMI: body mass index; and BDI-II: Beck Depression Inventory-II. [a]Values expressed as n (%) or mean ± SD. *p < 0.001 (allergic asthma vs. control). **p < 0.05 (allergic rhinitis vs. control).

DISCUSSION

Our results show no association between SI and allergic respiratory diseases in adults. However, they support the association between depression and SI.

The frequency of SI in the allergic asthma group was 14.8%; this proportion is within the range of the results in two major epidemiological studies, which showed a disagreement in terms of SI prevalence among patients with asthma: Clarke et al.[4] reported a prevalence of SI (without suicidal intent) of 12.1%, whereas Druss et al.[14] reported an SI prevalence of 30.4%. These differences in the prevalence of SI can be partially explained by the way SI and asthma were defined. When the results are obtained from a clinical setting (11.5% to 12.6%),[15,16] the proportion of asthma patients with SI is more consistent with our results. In relation to the prevalence of SI in patients with allergic rhinitis, very few studies are available; our study provides valuable information on that account, since 11.7% of participants had SI, which is similar to the results by Messias et al.,[6] in which 10.5% of the interviewed population were seriously considering to commit suicide.

Previous studies have shown an increase in the risk of SI among patients with asthma. Druss et al.[14] reported that subjects with asthma had an up to two-third increase in the possibility of having SI (OR = 1.69; p = 0.01). In 2003, Goodwin et al.[16] studied patients selected from primary care units and reported that asthma was associated with SI (OR = 1.9; 95% CI: 1.3-3.4; p < 0.05), even after adjusting for other mental conditions. In 2012, Goodwin et al.[7] reported a similar finding, since current asthma was significantly associated with an increased risk of SI (OR = 1.77; 95% CI: 1.97-5.39); however, that same group of researchers partially failed to document this association by means of a population study (OR = 1.09; 95% CI: 0.81-1.45), since they could only find it when SI was accompanied by suicidal intent (OR = 1.98; 95% CI: 1.42-2.76).[4] We consider that the positive association between asthma and SI shown in those previous studies can be a consequence of inadequate diagnostic evaluation and lack of categorization of asthma phenotypes, as well as the absence of chronic disease-free individuals. In our study, no association was found between asthma and SI, even after diagnostic confirmation by means of pulmonary function tests; however, the fact that we included only patients with allergic sensitization might have influenced the results, since atopic patients have a less severe clinical course, are younger, and present with an earlier onset of the disease when compared with nonallergic asthma patients.[17] This circumstance could allow their better coping with and accepting their disease, reducing the possibility of having suicidal thoughts. However, we found no association between asthma severity (in accordance with the GINA criteria)[9] and the frequency of SI; this supports the fact that neither asthma nor atopy is a factor related to SI and that depression is the most likely origin of it. Finally, the use of medications for asthma control has also been implicated in the etiology of SI.[15] This circumstance was beyond the scope of our study, because most of the patients used bronchodilators as the only therapeutic measure (data not shown).

Table 2. Prevalence of suicidal ideation in relation to the type of respiratory disease.

Group	Participants, n	Suicidal ideation	
		n	% (95% CI)
Allergic asthma	115	17	14.8 (8.3-21.3)
Allergic rhinitis	111	13	11.7 (5.7-17.7)
Control	96	8	8.3 (2.8-13.8)

Table 4. Association between atopic respiratory diseases and suicidal ideation in the groups studied.

Group	OR	95% CI	p
Control	1 (reference)	---	---
Allergic Asthma	1.98	0.78-4.64	0.154
Allergic rhinitis	1.46	0.58-3.68	0.424

Table 3. Frequency of suicidal ideation in relation to the degree of severity of the allergic disease.[a]

Group	Symptom	Suicidal ideation		
		Yes	No	p*
Allergic rhinitis (n = 111)	Frequency			
	Intermittent	3 (10.7)	25 (89.3)	0.85
	Persistent	10 (12.0)	73 (88.0)	
	Severity			
	Mild	2 (9.1)	20 (90.9)	0.67
	Moderate/severe	11 (12.4)	78 (87.6)	
Allergic asthma (n = 115)	Severity			
	Mild	8 (18.2)	36 (81.8)	0.70
	Moderate	6 (12.0)	44 (88.0)	
	Severe	3 (14.3)	18 (85.7)	

[a]Values expressed as n (%). *Chi-square test.

Table 5. Association between suicidal ideation and depression in the three groups studied.[a]

Group	OR	95% CI	p
Allergic asthma	12.36	2.67-57.15	0.001
Allergic rhinitis	6.20	1.66-23.14	0.006
Control	21.0	3.75-117.36	0.0005

[a]The comparison group comprised the subjects without depression.

In our study, we were unable to confirm the association between allergic rhinitis and SI. This result differs from those found in another study, in which seasonal allergic rhinitis was statistically related to SI (OR = 1.27; 95% CI: 1.01-1.59) but not with a history of suicide intent (OR = 1.16; 95% CI: 0.89-1.52).[6] However, similarly to asthma, this association must be interpreted with caution, since the clinical behavior of seasonal allergic rhinitis differs from the perennial type; moreover, the intensity of symptoms might be an intervening factor in the risk for SI. In our population with allergic rhinitis, neither severity nor frequency of the symptoms was related to SI; hence, this result further supports the concept that neither asthma nor atopy is the origin of SI.

Comparing the frequencies of SI in our sample with those obtained from a wide epidemiological study carried out in Mexico[18] (from 7.1% to 11.48% according to age group), we can confirm that the results are similar. It would appear that, considering the Mexican population at least, the association of asthma and allergic rhinitis with SI is unlikely and that other factors are the major source of this type of behavior.

The most significant factor associated with SI in patients with allergic respiratory diseases was depression. A similar finding was reported by Botega et al.[19] using a cohort of patients admitted to the infectious diseases, oncology, and hematology departments in a university hospital (OR = 9.1; 95% CI: 6.4-12.9; p = 0.0001). In another study,[20] the results were conflicting, since the research showed that thyroid problems, seizures, syncope, and hepatic diseases were associated with SI regardless of the age of the patients and the presence of depression. However, they found no association between SI and major stroke events (OR = 1.63; 95% CI: 0.78-3.40; p = 0.19), in which depression was the generating factor of SI.[20] Based on the results found in our sample, we believe that the disease in itself is not the most important promoting factor of SI, since we found that depression was the component that explained this behavior; this has been further established, since the subjects in the control group showed this similar finding. Additionally, other factors, such as unemployment, smoking, alcohol consumption, depression, hospitalization, low income, history of financial crisis, chronic pain, history of psychiatric disease, and sleep disorders, among others, must be considered as factors that intervene in the development of SI as well.[1,21-23]

A population-based study carried out in Denmark showed that people with a history of atopic disease were at a higher risk of suicide.[24] Additionally, there are regions in the world where a substantial increase in the number of suicides are reported during spring. A possible explanation of these phenomena has to do with pollen concentrations in the air.[25] However, this is not the case for all types of pollen, and, apparently, it was only observed in women.[26] In addition, a recent study was unable to replicate those findings.[8] To the best of our knowledge, studies regarding the relationship between SI and allergic diseases are scarce, and, in that sense, our study provides relevant information.

From a molecular perspective, there is increasing evidence that various mediators of inflammation play an important role in the physiopathology of major depression and suicidal behavior, since a positive association between suicidal tendencies and serum levels of IL-2, IL-6, IL-8, TNF-α and VEGF has been documented.[27] Neuropeptides, such as the corticotropin releasing factor, neuropeptide VGF, cholecystokinin, substance P, and neuropeptide Y, have also been implicated.[28]

As for the limitations of our study, the identification of SI and depression was not confirmed by means of a precise instrument. We used the BDI-II, which has been validated in multiple occasions; however, this tool only determines the presence of SI within the last two weeks, and this may reflect the presence of triggering psychological factors other than the influence of allergy on SI. With the purpose of not overestimating the frequency of SI, we excluded adolescents and elderly adults from our study, since the reported proportion of SI in these age groups is higher. Therefore, our results must be interpreted with caution regarding age. Similarly, we highlight the fact that the results of this study reflect the behavior of highly selected subjects who were also recruited from a hospital that serves the general population in an area where most patients have a low socioeconomic level. Another limitation was the gender disproportion of the allergic rhinitis and allergic asthma groups when compared with the control group. Other types of variables, such as unemployment, smoking, alcohol consumption, recent loss of loved ones, and sleep disorders, were not considered in the data analysis. Nevertheless, among the strengths of the present study, we must highlight that the diagnosis of allergic asthma was not made based on questionnaires or on the review of medical records; it has been established by clinical history, physical examination, and pulmonary function tests compatible with reversible airway obstruction, whereas atopy was defined by a positive result in a skin prick test against regional aeroallergens.

In summary, our findings contradict the hypothesis of an association between allergic respiratory diseases or their severity and SI; in fact, our results show that SI is another component of the spectrum of depression symptoms.

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ORIGINAL ARTICLE

Soluble urokinase-type plasminogen activator receptor as a measure of treatment response in acute exacerbation of COPD

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ABSTRACT

Objective: To evaluate the value of soluble urokinase-type plasminogen activator receptor (suPAR) in the diagnosis of acute exacerbation of COPD (AECOPD) and in monitoring treatment response, analyzing the relationship between suPAR and fibrinogen in AECOPD. AECOPD leads to increased airway inflammation, contributing to an exaggerated release of inflammatory mediators. **Methods:** We recruited 45 patients with AECOPD and 20 healthy control subjects. Medical histories were taken, and all subjects underwent clinical examination, chest X-ray, pulmonary function tests, and blood gas analysis. On day 1 (treatment initiation for the AECOPD patients) and day 14 (end of treatment), blood samples were collected for the determination of serum suPAR and plasma fibrinogen. **Results:** Serum levels of suPAR were significantly higher in the AECOPD group than in the control group. In the AECOPD patients, there was a significant post-treatment decrease in the mean serum suPAR level. The sensitivity, specificity, and accuracy of suPAR were 95.6%, 80.0%, and 93.0%, respectively. The Global Initiative for Chronic Obstructive Lung Disease stage (i.e., COPD severity) correlated positively and significantly with serum levels of suPAR and plasma levels of fibrinogen. **Conclusions:** Monitoring the serum suPAR level can be helpful in the evaluation of the COPD treatment response and might be a valuable biomarker for determining the prognosis of AECOPD. Because serum suPAR correlated with plasma fibrinogen, both markers could be predictive of AECOPD.

Keywords: Pulmonary disease, chronic obstructive/complications; Pulmonary disease, chronic obstructive/diagnosis; Receptors, urokinase plasminogen activator; Fibrinogen.

INTRODUCTION

Acute exacerbation of COPD (AECOPD) is characterized by deterioration of the respiratory symptoms that is beyond the normal day-to-day variations and leads to a change in medication.[1,2] Although exacerbations are the main determinants of COPD-related morbidity and mortality, their exact incidence remains unknown. Exacerbations have a major impact on the quality of life of COPD patients, resulting in multiple hospitalizations.[3] AECOPD leads to increased airway inflammation, provoking the exaggerated release of numerous inflammatory mediators.[4]

The most commonly used marker of COPD severity is FEV_1. However, FEV_1 does not correlate well with symptoms and other factors that quantify the progression of COPD.[5] It is therefore important to seek other markers of COPD activity.

Urokinase-type plasminogen activator receptor and plasminogen activator inhibitor type 1 are the main urokinase-type plasminogen activators. They are considered important components of the immune system and the inflammatory response.[6,7] Elevated levels of soluble urokinase-type plasminogen activator receptor (suPAR) result from increased stimulation of the immune system by different types of infections or solid tumors. Therefore, serum suPAR levels are believed to indicate the degree of immune activation.[8] There have been many studies reporting elevated suPAR levels in patients with infection, cancer, inflammatory diseases, sepsis, or bacteremia.[9-12]

Determination of the serum level of suPAR is a simple test that is easy to perform and, in comparison with determination of the plasma level of fibrinogen, requires fewer precautions related to sample collection and processing.[13] Determination of the serum level of suPAR and the plasma level of fibrinogen could play an important role in the evaluation of patients with stable COPD.[14] Fibrinogen has come to be a helpful biomarker in COPD and is being considered as a drug development tool for qualification by the U.S. Food and Drug Administration and the European Medicines Agency. Fibrinogen is synthesized in the liver and converted to fibrin by thrombin during blood coagulation; it is considered an acute phase plasma protein.[15]

The objective of this study was to evaluate the value of suPAR as a biomarker in the diagnosis of AECOPD and as a tool for monitoring the treatment response. We also analyzed the relationship between suPAR and fibrinogen in patients with AECOPD.

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METHODS

We enrolled 45 patients with AECOPD and 20 healthy control subjects. The patients were recruited from among those under treatment at the outpatient clinics or in the inpatient wards of the Chest Department of the Tanta University Hospitals, in the city of Tanta, Egypt, between August 2015 and January 2016. The study was performed in accordance with the ethical standards of the Tanta University Hospitals and was approved by the Research Ethics Committee of the Tanta University Faculty of Medicine. All of the participants gave written informed consent.

The diagnosis of COPD was made in accordance with the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria,[16] on the basis of smoking history, clinical manifestations, and pulmonary function test results showing airflow obstruction, with a post-bronchodilator FEV_1/FVC ratio < 0.7. AECOPD was defined as prolonged (≥ 48 h) worsening of dyspnea, coughing, or the production of mucoid or purulent sputum, leading to increased use of rescue and maintenance medications.[17]

Patients who had conditions that could alter their serum level of suPAR[18]—such as bronchial asthma, bronchiectasis, requiring mechanical ventilation, malignancies, liver failure, renal failure, heart failure, and uncontrolled diabetes mellitus—were excluded. Pneumonia was ruled out if a chest X-ray revealed no pulmonary infiltrate.

The patients were admitted and managed with supplemental oxygen at an optimum saturation of 90-92%. Bronchodilators (short-acting β_2 agonists), with or without short-acting anticholinergic agents, were used for the treatment of exacerbations. Prednisolone (40 mg/day for 5 days) was prescribed. Antibiotics were given if there were clinical signs of a bacterial infection, such as purulent sputum.[19] Medical histories were taken, and all patients underwent the following: thorough clinical examination; chest X-rays, in posteroanterior and lateral views, at enrolment (on day 1, when treatment for AECOPD was initiated) and on day 14 (after the end of that treatment); laboratory tests, including a complete blood count, renal function tests, liver function tests, and determination of fasting blood glucose levels; arterial blood gas analysis (arterial blood samples were collected, with sterile, disposable plastic syringes containing heparin, on day 1); pulmonary function tests to determine FEV_1 and the FEV_1/FVC ratio, with a spirometer (CHESTGRAPH HI-101; Chest M.I., Inc., Tokyo, Japan); and determination of the levels of fibrinogen and suPAR in plasma and serum, respectively, peripheral blood samples having been collected on day 1 and on day 14.

Plasma and serum were obtained from peripheral blood samples by centrifugation for 15 min at 1,500 *g*. Plasma and serum samples were stored at ≤ −20°C until analysis. Plasma fibrinogen was measured with a commercial kit (Fibrinogen Human ELISA Kit, ab108842; Abcam/KEMET Medical, Cairo, Egypt), with a typical sensitivity of approximately 0.10 μg/mL, the intra- and inter-assay coefficients of variation being 4.0% and 9.7%, respectively. Serum suPAR was also measured with a commercial kit (Quantikine Human uPAR Immunoassay Kit, DUP00; R&D Systems Europe, Oxon, United Kingdom), with a sensitivity < 33 pg/mL, the intra- and inter-assay coefficients of variation being 4.1% and 5.1%, respectively.

Statistical analysis

We calculated means and standard deviations, to which we applied unpaired Student's t-tests, paired t-tests, and chi-square tests, as well as determining linear correlation coefficients and constructing ROC curves. Data were analyzed with the Statistical Package for the Social Sciences, version 17.0 (SPSS Inc., Chicago, IL, USA). Values of $p < 0.05$ were considered statistically significant.

RESULTS

We included 45 patients diagnosed with AECOPD and 20 healthy, age- and gender-matched control subjects. Patients with AECOPD were treated for 14 days and re-evaluated at the end of treatment. The characteristics of the patients and control subjects are presented in Table 1. The AECOPD patients were stratified according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage of airflow limitation: stage I, in 7 patients (15.5%); stage II, in 16 (35.6%); stage III, in 13 (28.9%); and stage 4, in 9 (20.0%).

The serum levels of suPAR were significantly higher in the AECOPD patients than in the control subjects, on day 1 and day 14 ($p < 0.001$ for both). In the AECOPD group, there was a significant post-treatment decrease in the mean serum suPAR level—from 4,676.8 ± 1,478.9 pg/mL to 3,521.3 ± 1,382.9 pg /mL ($p < 0.001$)—as shown in Figure 1.

The plasma levels of fibrinogen were significantly higher in the AECOPD patients than in the control subjects, on day 1 and day 14 ($p < 0.001$ for both). In the AECOPD group, there was a significant post-treatment decrease in the mean plasma fibrinogen level—from 567.3 ± 216.6 mg/dL to 445.1 ± 190.8 mg/dL ($p < 0.001$)—as shown in Figure 2.

Serum levels of suPAR and plasma levels of fibrinogen increased in proportion to increases in the severity of COPD, being significantly higher in patients with GOLD stage III or IV than in those with GOLD stage I. Table 2 shows the comparison between suPAR and fibrinogen levels, by GOLD stage. The serum suPAR level was found to correlate negatively with FEV_1 (% of predicted), the FEV_1/FVC ratio (% of predicted), PaO_2, and SpO_2, whereas it correlated positively with the GOLD stage, both correlations being significant. Likewise, the plasma fibrinogen level correlated negatively with FEV_1, the FEV_1/FVC ratio, and SpO_2, whereas it correlated positively with the GOLD stage, both correlations also being significant ($p < 0.001$).

There was a significant positive correlation between the serum suPAR level and the plasma fibrinogen level ($r = 0.715$; $p < 0.001$).

The suPAR and fibrinogen cut-off values for the diagnosis of AECOPD were obtained by calculating the maximum sum of sensitivity and specificity. The ROC curves for suPAR and fibrinogen are shown in Figures 3 and 4, respectively. For the diagnosis of AECOPD, the sensitivity, specificity, and accuracy of suPAR were 95.6%, 80.0%, and 93.0%, respectively, compared with 77.8%, 85.0%, and 89.5%, respectively, for fibrinogen.

Of the 45 COPD patients, 9 (20.0%) did not recover from the exacerbation: 1 patient in GOLD stage II; 4 patients in GOLD stage III; and 4 patients in GOLD stage IV. Analyzing those 9 patients together, in comparison with the 36 patients who recovered, we found that the mean serum suPAR on day 1 had been slightly but significantly higher in the former group (5,551.1 ± 1,483.2 pg/mL vs. 4,462.71 ± 1,411.3 pg/mL; $p = 0.046$), as had the plasma fibrinogen levels on day 1 (685.5 ± 271.1 mg/dL vs. 522.5 ± 190.8 mg/dL; $p = 0.048$).

DISCUSSION

In patients with AECOPD, the deteriorating lung function and pronounced systemic inflammation worsen quality of life and reduce survival.[20] In the present study, suPAR and fibrinogen were evaluated as blood biomarkers of AECOPD. In accordance with our results,

Table 1. Baseline characteristics, pulmonary function parameters, stages of COPD, and arterial blood gas analysis results in patients with acute exacerbations and healthy control subjects.

Variable	AECOPD group (n = 45)	Control group (n = 20)	p
Age (years), mean ± SD	56.65 ± 6.48	57.711 ± 5.723	0.510
Male gender, n (%)	13 (65.0)	31 (68.9)	0.758
Current smoker, n (%)	14 (70.0)	32 (71.1)	0.928
Smoking history (pack-years), mean ± SD	31.00 ± 6.15	39.62 ± 9.56	0.003
FEV_1 (% of predicted), mean ± SD	87 ± 4.078	50.44 ± 19.83	< 0.001
FEV_1/FVC ratio (% of predicted), mean ± SD	88.2 ± 8.16	54.53 ± 10.43	< 0.001
pH, mean ± SD	7.38 ± 0.016	7.332 ± 0.043	< 0.001
PaO_2 (mmHg), mean ± SD	75.75 ± 5.18	58.77 ± 4.96	< 0.001
$PaCO_2$ (mmHg), mean ± SD	41.8 ± 3.17	55.40 ± 6.62	< 0.001
SpO_2, mean ± SD	95.75 ± 1.65	88.02 ± 4.25	< 0.001
GOLD stage of COPD, n (%)			
I	7 (15.5)		
II	16 (35.6)		
III	13 (28.9)		
IV	9 (20.0)		

AECOPD: acute exacerbation of COPD; and GOLD: Global Initiative for Chronic Obstructive Lung Disease.

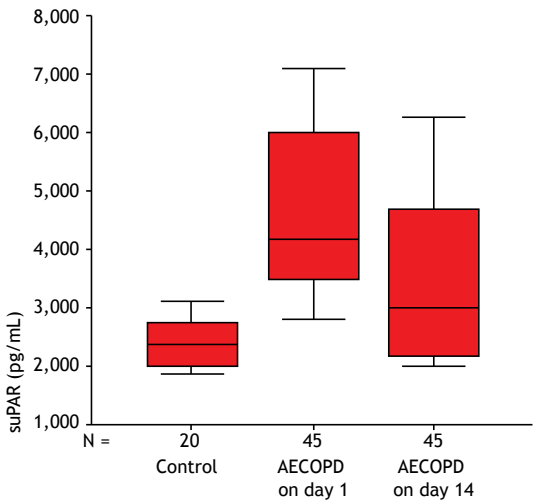

Figure 1. Serum levels of soluble urokinase-type plasminogen activator receptor (suPAR) in the control group, as well as in the acute exacerbation of COPD (AECOPD) group on day 1 and after 14 days of treatment.

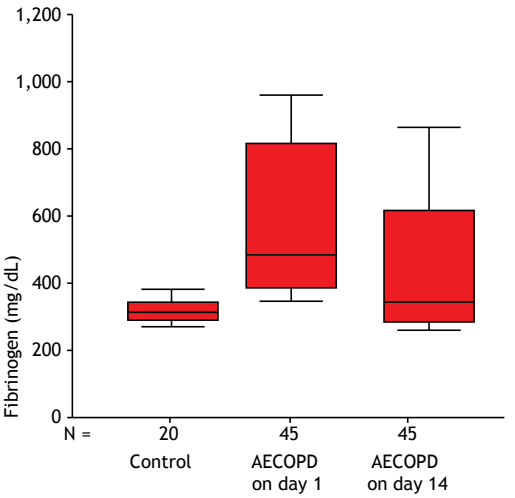

Figure 2. Plasma fibrinogen levels in the control group, as well as in the acute exacerbation of COPD (AECOPD) group on day 1 and after 14 days of treatment.

Table 2. Comparison between serum levels of soluble urokinase-type plasminogen activator receptor and plasma levels of fibrinogen, by GOLD stage, in patients with acute exacerbation of COPD.

Marker	GOLD stage			ANOVA	
	I or II	III	IV		
	Mean ± SD	Mean ± SD	Mean ± SD	F	p
suPAR (pg/mL)					
Day 1	3,504.34 ± 542.53	5,309.23 ± 994.52	6,760.0 ± 502.81	78.232	< 0.001
Day 14	2,558.69 ± 607.38	4,084.61 ± 1,201.23	5,167.77 ± 1,054.14		
Fibrinogen (mg/dL)					
Day 1	443.47 ± 107.98	595.38 ± 229.98	843.33 ± 125.0	21.669	< 0.001
Day 14	337.82 ± 101.88	473.84 ± 201.31	677.77 ± 125.07		

GOLD: Global Initiative for Chronic Obstructive Lung Disease; and suPAR: soluble urokinase-type plasminogen activator receptor.

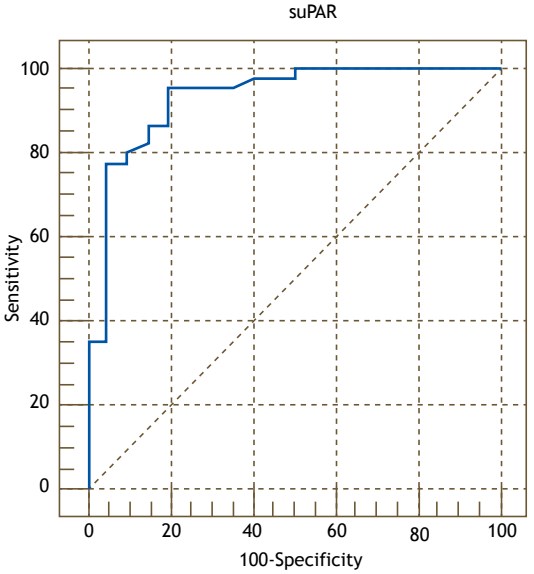

Figure 3. ROC curve of the accuracy of soluble urokinase-type plasminogen activator receptor (suPAR) in identifying acute exacerbation of COPD, with an area under the curve of 0.93 (p <0.001). The curve was constructed by calculating the sensitivity versus the specificity for the different possible suPAR cut-off points.

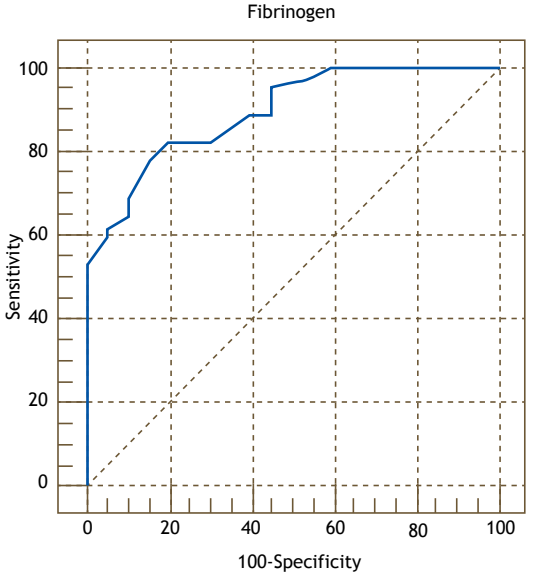

Figure 4. ROC curve of the accuracy of fibrinogen in identifying acute exacerbation of COPD, with an area under the curve of 0.89 (p < 0.005). The curve was constructed by calculating the sensitivity versus the specificity for the different possible fibrinogen cut-off points.

other studies have reported fibrinogen levels to be significantly higher in COPD patients than in control subjects.[21-23] Similarly, Portelli et al.[23] found that levels of serum suPAR were higher in patients with asthma or COPD than in control subjects. In another recent study,[14] fibrinogen was found to be higher in AECOPD patients than in healthy subjects. Therefore, determining the serum levels of suPAR and fibrinogen could be helpful in the evaluation of patients with stable COPD.[24]

The presence of C-reactive protein and fibrinogen indicates systemic inflammation, and the levels of both of those markers increase during AECOPD.[25] In contrast, suPAR has been shown to be an independent marker of inflammation, because it is very stable and its serum concentration is unaffected by circadian changes.[26]

In our study, serum suPAR levels were higher in the AECOPD patients than in the control subjects, and the difference was statistically significant. Our finding that serum suPAR levels were significantly higher before treatment than after is in agreement with the findings of another recent study[27] in which the suPAR levels of patients with stable COPD were compared with those of control subjects and were found to be significantly higher in the former, suggesting that there are inflammatory processes in stable COPD.

One recent study of patients with stable COPD[14] reported that serum suPAR levels were significantly higher on day 7 of treatment than on the day before treatment, and that levels of suPAR were higher in COPD patients than in healthy control subjects. Despite the fact that we measured serum suPAR after 14 days of treatment for AECOPD, that is in agreement with our results. Assessment of serum suPAR levels could play an important role in the evaluation of the inflammatory process in COPD. An increase in the serum suPAR level

has been associated with GOLD stages III and IV,[18] which is also in agreement with our results.

Many studies have reported that fibrinogen levels are higher in COPD patients than in healthy control subjects.[28-32] As in our study, Gumus et al.[24] found a significant positive correlation between serum suPAR and fibrinogen. Those authors concluded that suPAR should be considered a marker of acute inflammation.

In the present study, a significant negative correlation was found between serum suPAR levels and FEV_1 (% of predicted), which indicates the degree of airflow obstruction. That is in accordance with the findings of previous studies evaluating the relationship between inflammatory markers and lung function.[16,33,34] On the basis of these findings, suPAR can be considered an inflammatory marker in AECOPD.

Plasma fibrinogen appears to be an important blood biomarker of systemic inflammation. In COPD exacerbations, steroids might alter plasma fibrinogen through an effect on the inflammatory response, an effect not seen in patients with stable COPD.[15]

Our study also showed a decrease in plasma fibrinogen and serum suPAR levels after 14 days of treatment for AECOPD. Analysis of the area under the ROC curve showed that suPAR was superior to fibrinogen in identifying patients with AECOPD on day 1 and day 14, which is in agreement with the findings of Gumus et al.,[24] despite the fact that those authors evaluated their patients at 7 days of treatment.

We conclude that the determination of serum suPAR levels can be helpful in the follow-up of AECOPD and in the monitoring of the treatment response, potentially making suPAR a valuable biomarker in the prognosis of AECOPD. Because serum suPAR levels correlated with plasma fibrinogen levels, both markers have the potential to predict AECOPD. There is a need for further clinical studies including more patients in order to evaluate the diagnostic value of serum suPAR in comparison with that of other known markers of AECOPD.

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ORIGINAL ARTICLE

Evaluation of smoking cessation treatment initiated during hospitalization in patients with heart disease or respiratory disease

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ABSTRACT

Objective: To evaluate the effectiveness of a smoking cessation program, delivered by trained health care professionals, in patients hospitalized for acute respiratory disease (RD) or heart disease (HD). **Methods:** Of a total of 393 patients evaluated, we included 227 (146 and 81 active smokers hospitalized for HD and RD, respectively). All participants received smoking cessation treatment during hospitalization and were followed in a cognitive-behavioral smoking cessation program for six months after hospital discharge. **Results:** There were significant differences between the HD group and the RD group regarding participation in the cognitive-behavioral program after hospital discharge (13.0% vs. 35.8%; p = 0.003); smoking cessation at the end of follow-up (29% vs. 31%; p < 0.001); and the use of nicotine replacement therapy (3.4% vs. 33.3%; p < 0.001). No differences were found between the HD group and the RD group regarding the use of bupropion (11.0% vs. 12.3%; p = 0.92). Varenicline was used by only 0.7% of the patients in the HD group. **Conclusions:** In our sample, smoking cessation rates at six months after hospital discharge were higher among the patients with RD than among those with HD, as were treatment adherence rates. The implementation of smoking cessation programs for hospitalized patients with different diseases, delivered by the health care teams that treat these patients, is necessary for greater effectiveness in smoking cessation.

Keywords: Smoking; Smoking cessation; Hospitalization; Respiratory tract diseases; Heart diseases.

INTRODUCTION

Although the prevalence of smoking in Brazil has been declining in recent decades, with a rate of 12.1% in 2013 in Brazilian state capitals and the Federal District of Brasília, there remains a high prevalence of smokers who are hospitalized.[1,2] These rates range from 15% to 22% in public hospitals[3-5] and are usually associated with tobacco-related diseases, which provides a window of opportunity for smoking cessation interventions.[6-8]

Specific strategies can increase adherence, reduce health care costs, and, most importantly, improve patient quality of life.[8,9] Studies have shown that smoking cessation treatment is effective when initiated at hospital admission and continuing for one month after hospital discharge,[10] which also results in a reduction in readmission costs for tobacco-related diseases when the hospital has a smoking cessation program for inpatients.[9]

Despite scientific evidence of the benefits of smoking cessation treatment initiated during hospitalization, there are few health care facilities in Brazil that provide the necessary treatment resources.[8] For functioning of this in-hospital service, there is a need for integration of a qualified team into routine care in hospitals, to approach patients who smoke, together with provision of pharmacological and behavioral treatment. In addition, it is recommended that patients receive post-discharge follow-up for maintenance of cessation.[8] However, few studies in Brazil have described this in-hospital intervention or have reported results regarding smoking cessation for different tobacco-related chronic diseases in hospitalized patients. Therefore, the objective of the present study was to evaluate the effectiveness of a smoking cessation program, delivered by trained health care professionals, in patients hospitalized for respiratory disease (RD) or heart disease (HD).

METHODS

We evaluated a total of 393 patients—246 and 147 patients hospitalized for HD and RD, respectively—at the Botucatu School of Medicine *Hospital das Clínicas*, located in the city of Botucatu, Brazil, between March 2012 and June 2014. We included patients ≥ 18 years of age. The

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group of patients with HD was classified according to the primary diagnosis during hospitalization: acute myocardial infarction, in 166 patients; unstable angina, in 65; and heart failure, in 15. The RD group was also classified according to the primary diagnosis: COPD, in 58 patients; other causes (dyspnea), in 52; pulmonary thromboembolism, in 28; interstitial lung disease, in 5; and pneumonia, in 4. All patients who reported current smoking (at least one cigarette/day in the previous week) at admission were classified as active smokers. Patients who had ceased using tobacco products for more than 30 days before hospitalization were considered former smokers. The exclusion criteria were the impossibility of evaluating patients because of their unstable clinical condition, such as the requirement for mechanical ventilation, hemodynamic instability, or coma, and a lack of understanding on the part of patients regarding the objectives of the protocol.

The study was approved by the Research Ethics Committee of the Botucatu School of Medicine (Protocol no. 3403-2009), and all participating patients gave written informed consent.

All participants were evaluated by clinical history taking and underwent a thorough physical examination. They also completed a specific questionnaire addressing demographic characteristics, smoking history (including current smoking status), smoking habits in social activities, age at smoking initiation, and number of cigarettes smoked per day. In addition, all participants were administered the Hospital Anxiety and Depression scale,[9] the Fagerström Test for Nicotine Dependence,[10] and the stages-of-change model for smoking cessation devised by Prochaska & DiClemente.[11]

Patient status as a smoker or former smoker during treatment was confirmed by measuring exhaled carbon monoxide (CO) levels (Micro CO; Micro Medical Ltd, Rochester, England), and exhaled CO levels ≥ 7 ppm were considered significantly indicative of recent smoking.[12,13]

Smoking cessation protocol

All smoking cessation treatment (during hospitalization and after discharge) was conducted by one trained health care professional. All patients underwent two 15-min sessions of individual counseling during hospitalization. Smoking cessation medications were used at the physician's discretion, in accordance with smoking cessation guidelines,[7,14] that is, all patients with a dependence score ≥ 5 or who experienced withdrawal symptoms during hospitalization were prescribed smoking cessation medications (nicotine replacement therapy, bupropion, or varenicline).[7,14] Pharmacological treatment was not prescribed for patients who did not experience withdrawal symptoms and/or did not want to use medications. Educational material containing information about nicotine dependence and behavioral counseling was distributed to all participants. All of the material was developed by the smoking cessation group at the Botucatu School of Medicine *Hospital das Clínicas*.

At hospital discharge, all patients were referred for continuing treatment in a cognitive-behavioral smoking cessation treatment program, attending 2-h weekly sessions in the first month. In the second month, patients returned every 15 days for a session; and, from the third month onward, they returned once a month until they completed six months of follow-up. In addition, patients were contacted via telephone before the scheduled reevaluations, in order to improve adherence to treatment. For the purposes of data analysis, participants who did not complete follow-up were considered to have experienced treatment failure and to be active smokers. Readmissions and outpatient visits were analyzed.

Statistical analysis

The study sample size was calculated based on a population estimate. The proportion of smokers among patients hospitalized with HD or RD and treated at the Botucatu *Hospital das Clínicas* was unknown. In addition, we considered a confidence interval of 90% and a maximum estimation error of 5%. On this basis, the sample size was set at 271 patients.

Descriptive statistics are presented as mean and standard deviation or as median and interquartile range for variables with normal and non-normal distribution, respectively. The difference between the groups was assessed using the chi-square test for categorical variables and using the t-test or the Mann-Whitney test for continuous variables according to their parametric or non-parametric distribution, respectively. All analyses were performed with SPSS Statistics, version 22.0 for Windows (IBM Corporation, Armonk, NY, USA), and values of $p < 0.05$ were considered significant.

RESULTS

We evaluated 393 hospitalized patients, of whom 227 were active smokers and were included in the study: 146 in the HD group and 81 in the RD group (Figure 1). Compared with the RD group, the HD group had a significantly higher number of males (72.6% vs. 32.1%; $p < 0.001$); a higher monthly income (in Brazilian reals [R$]: R$1,150 [R$677-2,000] vs. R$677 [R$360-1,040]; $p = 0.02$); a higher mean body weight (77.4 ± 17.1 kg vs. 68.7 ± 20.0 kg; $p < 0.002$); and greater height (1.65 ± 0.10 m vs. 1.60 ± 0.10 m; $p < 0.001$). Conversely, tobacco consumption (in pack-years) was greater in the RD group patients than in the HD group patients (55.6 ± 36.0 pack-years vs. 53.4 ± 25.1 pack-years; $p = 0.62$), although that difference was not significant (Table 1).

The causes of hospitalization among smokers in the RD group were, in decreasing order: other causes (dyspnea), in 34 patients; COPD, in 31; pulmonary thromboembolism, in 13; interstitial lung disease, in 2; and pneumonia, in 1. In the HD group, the causes of hospitalization among smokers were, also in decreasing order: acute myocardial infarction, in 112 patients; unstable angina, in 25; and heart failure, in 9.

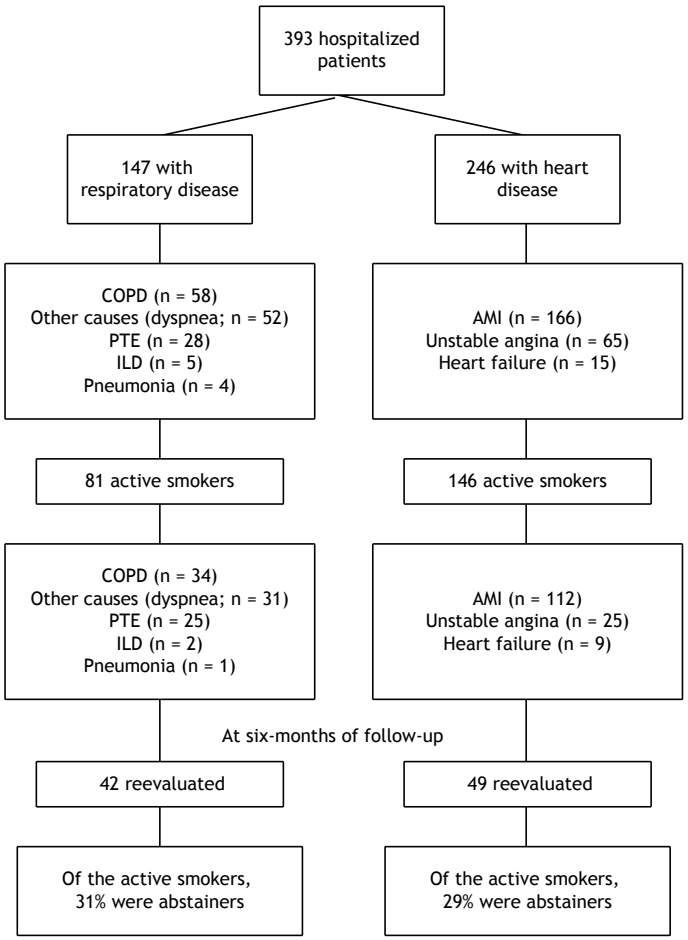

Figure 1. Flowchart of study participants. PTE: pulmonary thromboembolism; ILD: interstitial lung disease; and AMI: acute myocardial infarction.

The Fagerström Test for Nicotine Dependence scores were "high" among active smokers in the HD group and the RD group (54.1% vs. 46.9%; p = 0.29). The proportion of patients who were in the "action" stage of change in the HD group and the RD group was also similar (55.5% vs. 44.4%; p = 0.17). We also did not find statistically significant differences between the HD group and the RD group regarding the Hospital Anxiety and Depression Scale scores: "probable anxiety" (22.0% vs. 18.5%; p = 0.83) and "probable depression" (9.7% vs. 14.9%; p = 0.20).

Of the total number of active smokers at hospital discharge, only 19 patients (13.0%) in the HD group and 29 (35.8%) in the RD group participated in the cognitive-behavioral smoking cessation intervention (p = 0.003). Nicotine patch use occurred in 3.4% and 33.3% of the patients in the HD group and the RD group, respectively (p < 0.001), whereas bupropion use occurred in 11.0% and 12.3%, respectively (p = 0.92). Varenicline was used in 0.7% of the patients in the HD group.

At six months after hospital discharge, 42 patients in the RD group and 49 patients in the HD group were reevaluated. The proportion of abstainers was higher in the RD group than in the HD group (Figure 2).

There were 35 deaths within six months after hospital discharge: 18 in the RD group (13 patients still smoked) and 17 in the HD group (14 patients still smoked; p = 0.003). The primary cause of death was undetermined in 23.6% and 28.0% of the patients in the HR group and the RD group, respectively; followed by septicemia, in 23.6% and 11.1%; pneumonia, in 11.7% and 16.7%; and acute respiratory failure; in 11.7% and 16.7%. We observed that 19 (12.3%) and 27 (10.9%) of the patients in the RD group and the HD group, respectively, had further hospitalizations over the follow-up period, and most of them were active smokers (89% and 92% in the RD group and the HD group, respectively).

During the follow-up period, 75% of the total of 81 active smokers with RD and 78% of the total of 146 active smokers with HD had at least one outpatient visit with a medical specialist (pulmonologist or cardiologist, respectively).

DISCUSSION

The objective of the present study was to evaluate the rate of smoking cessation in patients hospitalized

Table 1. Characteristics of smoking participants by study group.[a]

Variable	Respiratory disease (n = 81)	Heart disease (n = 146)	p*
Male gender	26 (32.1)	106 (72.6)	< 0.001
Age, years	59.7 ± 13.0	57.3 ± 17.1	0.13
Income, R$[b]	677 (360-1.040)	1150 (677-2.000)	0.02
Weight, kg	68.7 ± 20.0	78.4 ± 17.1	0.002
Height, m	1.60 ± 0.10	1.65 ± 0.10	< 0.001
BMI, kg/m^2	26.9 ± 7.6	28.1 ± 5.9	0.27
Level of education			
< 9 years of schooling	45 (55.6)	84 (57.5)	0.29
Age at smoking initiation, years	14.1 ± 7.6	14.1 ± 5.9	0.79
Smoking history, pack-years	55.6 ± 36.0	53.4 ± 25.1	0.62
Exhaled carbon monoxide, ppm	3.6 ± 4.6	2.1 ± 1.8	< 0.001
Level of dependence			
High	38 (46.9)	79 (54.1)	0.29
Low	43 (53.1)	67 (45.9)	
Motivational stage			
Precontemplation	14 (17.3)	13 (8.9)	
Contemplation	31 (38.3)	52 (35.6)	0.17
Action	36 (44.4)	81 (55.5)	
Anxiety scale			
Improbable	45 (55.5)	78 (53.4)	
Possible	21 (26.0)	36 (24.6)	0.83
Probable	15 (18.5)	32 (22.0)	
Depression scale			
Improbable	52 (64.1)	110 (75.3)	
Possible	17 (21.0)	22 (15.0)	0.20
Probable	12 (14.9)	14 (9.7)	

BMI: body mass index. [a]Values expressed as n (%) or as mean ± SD, except where otherwise indicated. [b]Values expressed as median (interquartile range). *Chi-square test, t-test, or Mann-Whitney test

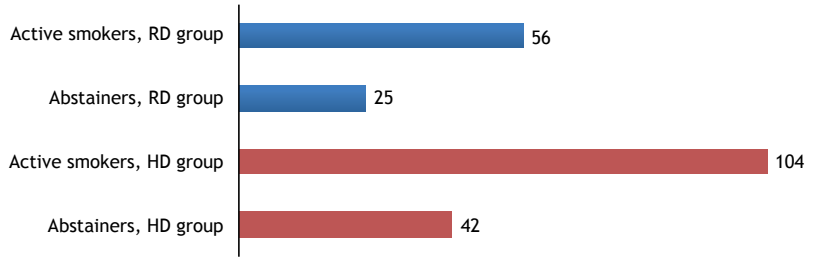

Figure 2. Number of patients in each group by smoking status at six months after hospital discharge. RD: respiratory disease; and HD: heart disease. p < 0.001.

for HD or RD. At six months after discharge, the rates of smoking abstinence were 29% and 31% in the HD group and the RD group, respectively. In addition, we found that the highest proportion of patients adhering to the post-discharge smoking cessation protocol (35.8%) was seen in the RD group, as was the highest proportion patients using the medications provided through the protocol (23.3%).

Our study showed a similar rate of smoking cessation in the RD group at six months after hospital discharge similar to that reported in the literature. An early study,[15] in which 74 hospitalized patients with RD were randomized into a control or intervention group, showed that the rate of smoking cessation in the intervention group was 33.3% at six months after hospital discharge. The intervention group subjects were provided with 15- to 20-min smoking cessation counseling sessions every two days, whereas the control group subjects were simply advised to quit smoking.[15] Unlike our findings, those of a recent study conducted at three public hospitals in Australia showed that the sustained smoking cessation rate for a cohort of 600 patients hospitalized for different tobacco-related diseases was 11.6% at six months of follow-up.[16] In contrast, when the rate of smoking cessation in the group of patients with RD is compared with data from outpatient treatment of patients with RD, we observe that the rate found in

our study was lower than those reported in two previous studies (40.5% and 52%, respectively).[17,18]

A systematic review has shown that the effectiveness of smoking cessation interventions in hospitalized patients with RD did not differ by type of treatment, and none of the treatments studied had any significant effect.[19] However, in the present study, the rate of smoking cessation was higher in the RD group than in the HD group, and the rate of abstinence in the HD group was lower than that reported in the literature (range, 21.3-25.0%).[20-24]

Our study showed a high prevalence of active smokers among patients hospitalized for RD or HD (57.8%), which is consistent with the literature showing that smoking is associated with 51.5% of hospitalizations.[4,14] A previous study conducted at our institution demonstrated that, of 348 patients hospitalized for tobacco-related diseases, 41% were active smokers.[3] Therefore, on the basis of treatment recommendations for hospitalized smokers,[25] our study showed that post-discharge treatment adherence was poor, being in contrast with a study showing that only 33% of patients were noncompliant with the recommended cognitive-behavioral intervention during follow-up.[26] Similarly, in a recent study of 109 participants who received pharmacological smoking cessation treatment with outpatient follow-up for four weeks, the dropout rate was 33.1%.[27]

In our study, the RD group showed greater adherence to the post-discharge smoking cessation protocol compared with the HD group; this appears to be associated with the development of a relationship between patients and respiratory care professionals. The protocol required that the smoking cessation treatment always be provided by the same health care professional, even after hospital discharge. The better treatment adherence the RD group might have reflected the fact that, during hospitalization, respiratory care professionals directly assess smoking withdrawal symptoms on a daily basis, which was not true for the cardiac care team. These findings confirm that counseling and follow-up by the team treating smokers with non-respiratory, tobacco-related diseases are essential.[6,28,29]

The rates of additional hospitalizations and mortality were comparable between the RD and HD groups, being low in both groups. Our study showed that 12.3% of the patients with RD were hospitalized again during the follow-up period, and most of them were still smoking. One recent study reported a 27.7% rate of hospital readmission at six months after hospital discharge among patients who received smoking cessation treatment, a rate higher than that found in our study.[20] In line with those findings, a study of 254 patients with coronary disease reported that 30% of the patients who continued smoking had a higher number of comorbidities and a higher hospital readmission rate,[30] which increases hospitalization rates and health care expenditures.[1] With regard to reducing costs, the study by Berndt et al.[31] showed that the costs of hospital readmissions for smokers were lower when these smokers received a combined approach of usual smoking cessation treatment and telephone or face-to-face counseling.

The rate of medication use to control nicotine withdrawal symptoms was low in the total sample (14.5%); however, nicotine replacement therapy use was more common in the RD group compared with the HD group. Our finding is similar to those reported by Barreto et al.[4] and Regan et al.,[32] who found rates of use of these medications of 28.1% and 37.6%, respectively. In contrast, there have been studies showing a greater frequency of use of pharmacological treatment in hospitalized patients. Simon et al.[33] showed that 48% of smokers hospitalized with HD used smoking cessation medications. Similarly, Rigotti et al.[34] reported the use of medications in 67% of all patients hospitalized with tobacco-related diseases. The limited use of medications in the present study may have influenced the low smoking cessation rate at six months after hospital discharge.

Maintaining patient motivation depends on professionals working constantly and multidisciplinarily.[2] However, the lack of knowledge and training of health care professionals is an important factor in treatment failure. In contrast, a study conducted in Greece showed that 76.7% of health care professionals believed they provided effective smoking cessation counseling/aids for their patients.[35] In our study, the lack of qualified health care professionals made it impossible to assess the effectiveness of the intervention in patients with other tobacco-related diseases; in fact, it is necessary that all patients who smoke receive treatment. A study of surgeons showed that most of them (60.9%) reported advising their patients to quit smoking. At the surgeon's advice, 95.3% of the patients agreed to quit smoking before surgery, 53.6% would quit after surgery, and 70.6% had already quit smoking.[36] Thorndike et al.[37] evaluated physician practices regarding the counseling of patients to quit smoking, between 1991 and 1995, and found that, at 65% of visits, physicians asked patients about their smoking status; at 29%, they counseled patients to quit smoking; and, at only 1.3%, they prescribed a specific smoking cessation treatment.

The demographic data in the present study revealed a low level of education and a low per capita income in both groups; however, the RD group had a lower median monthly per capita income compared with the HD group. These data are similar to those found previously at our facility, where 61% of the outpatient smokers had not completed high school and 66% had a monthly income of less than two times the national minimum wage.[38] Studies have associated increased smoking prevalence with lower economic and educational levels, and poor motivation and a lack of resources are also believed to be associated with smoking cessation failure.[39] Therefore, continuous formulation of smoking prevention and control strategies remains a major challenge for developing countries.[2,40]

The present study observed a low rate of smoking cessation during the follow-up period in both groups. The proportion of patients who were lost to follow-up was high, and the rate of medication use to aid in smoking cessation was low in both groups. Nevertheless, most of the patients were monitored by a specialist during outpatient follow-up. It is certainly essential to maintain smoking cessation programs for hospitalized smokers to prevent complications of tobacco-related chronic diseases and to improve overall aspects of health.

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Association between the display of cigarette packs at the point of sale and smoking susceptibility among adolescents in Brazil

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ABSTRACT

This was a cross-sectional study aimed at determining the association between exposure to tobacco displays at the point of sale and susceptibility to smoking in schoolchildren in the 14- to 17-year age bracket. Of the participating students, 69.0%, 21.3%, and 9.7% were classified as never smokers, experimenters, and smokers, respectively. Of the participants who were classified as being exposed to smoking, 18.9% were susceptible to smoking. Of the participants who were classified as being unexposed to smoking, 12.9% were susceptible to smoking (OR = 1.56; 95% CI: 1.04 -2.35; p = 0.029). Exposure to point-of-sale tobacco displays is associated with smoking susceptibility in Brazilian adolescents.

Keywords: Tobacco products; School health; Adolescent health.

Smoking is the most common cause of preventable death in the world, given that it increases the risk of death from diseases such as cancer, ischemic heart disease, and COPD.[1] In Brazil, the prevalence of smoking in the adult population has decreased in recent decades.[2,3] Data collected by the Brazilian National Ministry of Health Department of Health Surveillance using telephone-based survey methods show a reduction in the prevalence of adult smokers in Brazil, from 15.6% in 2006 to 11.3% in 2013.[3]

This downward trend in the prevalence of smoking among adults in Brazil has not been observed in young Brazilians.[4] The *Pesquisa Nacional de Saúde do Escolar* (PeNSE, Brazilian National Adolescent School-Based Health Survey), conducted over several years, showed that the prevalence of young individuals who reported having smoked in the 30 days preceding the survey had not decreased, having remained at approximately 6.0%.[4]

In Brazil, several strategies have been implemented to reduce tobacco supply and demand, including public policies toward tobacco advertising, promotion, and sponsorship, as well as toward health warnings, passive smoking, smoking cessation treatment, illegal tobacco trade, prices, and taxes.[2,5] With regard to laws aimed at protecting the population from exposure to tobacco advertising, Federal Law no. 10,167/2000[6] banned the advertising of tobacco products in magazines and newspapers, as well as on television, radio, and billboards. It also banned Internet-based tobacco advertising, indirect advertising, and advertising in stadiums, at race tracks, on stages, and in other similar places; in addition, as of 2003, it banned tobacco-company sponsorship of international sporting events and cultural events. Federal Law no. 12,546/2011, regulated by Decree no. 8,262/2014, banned the advertising of tobacco products at the point of sale, representing a significant advance in the national legislation; however, the display of tobacco products at the point of sale is still allowed in the country.[7,8]

The tobacco industry has implemented several strategies to counter tobacco advertising bans, including increasingly sophisticated tobacco displays, attractive packaging, and preferred positions in displays at the point of sale, i.e., near products that are attractive to children and young individuals.[9]

In this context, the objective of the present study was to determine the association between the display of cigarette packs at the point of sale and smoking susceptibility among Brazilian adolescents.

We conducted a cross-sectional study involving a sample of high school students who were in the 14- to 17-year age bracket and who attended state public schools in the morning in any of five Brazilian capitals (i.e., Brasília, São Paulo, Manaus, Curitiba, and Salvador). All of the students who met the inclusion criteria and who attended class on the day assigned for data collection were invited to participate in the study. Data were collected by means of an anonymous self-administered questionnaire that was completed under the supervision of a trained field team.

The study variables were as follows: gender; age; high school grade level; parental smoking; respondent smoking status; exposure to smoking; susceptibility

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to smoking in the year following study participation; and exposure to tobacco displays and advertising at the point of sale (including bakeries, minimarkets, convenience stores, and supermarkets).

Nonsmoking schoolchildren who reported that they would probably or definitely start smoking in the following year were classified as susceptible to smoking.[10,11] Schoolchildren who reported that they frequented at least one of the aforementioned points of sale and saw cigarette packs displayed there were classified as being exposed to smoking. Schoolchildren who reported that they did not frequent any of the aforementioned points of sale or see cigarette packs displayed there were classified as being unexposed to smoking. Schoolchildren who reported having smoked at least once in the 30 days preceding the survey were classified as smokers.

We used Pearson's chi-square test in order to identify associations among independent variables, values of $p < 0.05$ being considered statistically significant.

The study was approved by the Research Ethics Committee of the Federal University of Santa Catarina, located in the city of Florianópolis, Brazil (Ruling no. 552,940), and by the Johns Hopkins School of Public Health Institutional Review Board, located in the city of Baltimore (MD) USA (Protocol no. 00005015).

We interviewed 11,086 schoolchildren, 5,964 (53.8%) of whom were female. The participating students were classified as never smokers, experimenters, or smokers. The proportions of never smokers, experimenters, and smokers in the study sample were 69.0%, 21.3%, and 9.7%, respectively.

The prevalence of smoking in the present study (9.7%; 95% CI: 9.4-10.5) was higher than that in the 2012 PeNSE,[12] in which 5.1% (95% CI: 3.9-6.2) of students in 27 Brazilian capitals (including the Federal District of Brasília) were identified as being regular smokers. This difference in the prevalence of smoking might be due to methodological differences between the present study, which included public high school students in the 14- to 17-year age bracket, and the PeNSE, which included 9th-grade students at public and private schools in Brazil.[12]

A total of 3,407 students (30.7%) responded in the affirmative to the question "Have you ever tried or experimented with cigarette smoking, even one or two puffs?" Of the students who were classified as experimenters or smokers, 10.3% had smoked their first full cigarette before the age of 10 years.

Questions regarding the habit of frequenting points of sale showed that the vast majority of students (98.9%) had frequented at least one of the aforementioned points of sale during the study period, virtually all of the participants (99.2%) having reported viewing point-of-sale tobacco displays (Table 1).

Of the male participants, 67.9% had never smoked, 21.3% had tried cigarettes, and 10.8% were smokers. Of the female participants, 69.9% had never smoked, 21.1% had tried cigarettes, and 9.0% were smokers (Table 2).

Of the participants who were classified as being exposed to smoking, 18.9% were susceptible to smoking. Of the participants who were classified as being unexposed to smoking, 12.9% were susceptible to smoking. A significant association was found between exposure to point-of-sale tobacco displays and smoking susceptibility (OR = 1.56; 95% CI: 1.04-2.35; p = 0.029).

In a study conducted in the United Kingdom in 2008 and involving young individuals in the 11- to 16-year age bracket, Mackintosh et al.[13] reported that the proportion of individuals who were exposed to tobacco displays was high (i.e., 81.0%), having also found a significant association between exposure to point-of-sale tobacco displays and smoking susceptibility (OR = 1.77; 95% CI: 1.15-2.73; p = 0.029).

Other studies have found that children and adolescents who are exposed to point-of-sale tobacco displays are more likely to be susceptible to smoking.[14-16] In a recently published systematic review aimed at examining the relationship between promotion of tobacco products at the point of sale and susceptibility to smoking, the authors concluded that current evidence supports a positive association between the two.[16]

One limitation of the present study is that it is representative of adolescents who attended state public schools in the morning in any of five Brazilian capitals and who attended class on the day assigned for data collection.

In conclusion, exposure to point-of-sale tobacco displays is associated with smoking susceptibility in Brazilian adolescents. The findings of the present study reinforce the importance of banning tobacco displays at the point of sale.

Table 1. Numbers and proportions of schoolchildren classified as never smokers, experimenters, or smokers on the basis of their answers to questions regarding visits to tobacco points of sale and exposure to tobacco displays at the point of sale. Brazil, 2014.

Smoking status	Questionnaire item			
	Frequents at least one tobacco point of sale		Frequents a tobacco point of sale and sees tobacco displays there	
	n	%	n	%
Never smokers	7,561	98.9	7,561	100.0
Experimenters	2,317	99.3	2,278	98.8
Smokers	1,076	98.1	1,051	97.9
TOTAL	10,954	98.9	10,961	99.2

Table 2. Numbers and proportions of schoolchildren, by gender, grade, age, and smoking status. Brazil, 2014.

Variable	Smoking status						Total	
	Never smoker		Experimenter		Smoker			
	n	%	n	%	n	%	n	%
Male gender	3,285	67.9	1,030	21.3	520	10.8	4,835	100.0
Female gender	4,143	69.9	1,247	21.1	533	9.0	5,923	100.0
High school grade level								
1	4,267	70.5	1,175	19.4	607	10.0	6,049	100.0
2	2,115	67.0	710	22.5	332	10.5	3,157	100.0
3	1,052	66.5	399	25.2	132	8.3	1,583	100.0
Age, years								
14	375	73.5	69	13.5	66	12.9	510	100.0
15	2,491	74.0	612	18.2	263	7.8	3,366	100.0
16	2,474	67.3	804	21.9	398	10.8	3,676	100.0
17	2,069	64.5	797	24.8	343	10.7	3,209	100.0

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BRIEF COMMUNICATION

Between-occasion repeatability of fractional exhaled nitric oxide measurements in children

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Study carried out in the Department of Epidemiology, School of Medicine in Katowice, Medical University of Silesia, Katowice, Poland.

ABSTRACT

The aim of the study was to assess short-term repeatability of measurements of fractional exhaled nitric oxide (F_ENO) and its correlates in children in the 6- to 9-year age bracket participating in a respiratory epidemiological survey. F_ENO was measured in two sessions one week apart in 101 children. Participants were divided into three **groups:** asymptomatic (n = 76); symptomatic (n = 14); and asthma (n = 11). Absolute and relative differences between the measurements, as well as concordance correlation coefficients, were used in order to assess repeatability. The two F_ENO measurements were strongly correlated (0.98). Although intragroup comparisons of the two measurements were not significantly different (p = 0.2), intergroup comparisons were. F_ENO measurements are reproducible in children in epidemiological settings.

Keywords: Nitric oxide; Exhalation; Asthma.

The measurement of fractional exhaled nitric oxide (F_ENO) is recognized as a useful method in the clinical assessment and management of respiratory disease, including asthma.[1-3] Little is known about its role in respiratory epidemiological studies, although F_ENO is recommended as a supplemental outcome for observational studies.[3] Inclusion of F_ENO in population-based studies on pediatric asthma could be helpful in the characterization of asthma phenotypes and chronic respiratory symptoms in children. This type of application requires that the test is standardized and that its repeatability is known and acceptable. Validation studies on F_ENO measurement have shown a very small intra-measurement variability as well as diurnal variation that—in children—is likely to range from 1 ppb to 2 ppb, on average.[4,5] Little is known about the repeatability of F_ENO measurement assessed on independent occasions in healthy, symptomatic, and asthmatic children examined in the field setting. Against this background, we performed a study on the short-term variability of F_ENO levels in a sample of elementary school children participating in a respiratory epidemiological survey. The objectives of the study were to assess the repeatability of F_ENO measured in that group of children on two occasions (one week apart) and to analyze its anthropometric and respiratory correlates. The study was performed in the voivodship of Silesia, Poland.

The subjects were 104 elementary school children, between 6 and 9 years of age, randomly selected in the town of Tychy. Respiratory symptoms were assessed using the translated version of the International Study of Asthma and Allergies in Childhood questionnaire,[6] which was completed by the parents. Informed consent was obtained from the parents or legal guardians of all participants included in the study. The study protocol was approved by the Research Ethics Committee of the Medical University of Silesia (Protocol no. KNW/0022/KB1/37/I/14).

All measurements were obtained in local schools. Anthropometric variables (age, height, and body mass) were measured before F_ENO and spirometry tests. F_ENO was measured with the child in a sitting position using a specific device (NIOX MINO®; Aerocrine, Solna, Sweden). The test consisted of a maximum of five attempts until one acceptable measurement was obtained. The second F_ENO measurement was performed one week after the first examination. Spirometric variables, including FVC, FEV_1, FEV_1/FVC ratio, $FEF_{25\%}$, $FEF_{50\%}$, and $FEF_{75\%}$, were obtained in accordance with the American Thoracic Society/European Respiratory Society recommendations, with the use of a spirometer (EasyOne®; ndd Medizintechnik AG, Zurich, Switzerland), being expressed in absolute values. Spirometry was performed after F_ENO measurement.

Statistical analyses were performed with the Statistical Analysis System, version 9.2 (SAS Institute Inc., Cary, NC, USA). The difference in FeNO levels between the two occasions was determined by subtracting the second measurement from the first one. The mean absolute value was calculated as the mean of the individual differences between the first and second measurements. The mean relative value was obtained by the following formula: first measurement − second measurement, expressed as %. Statistical significance of between-group differences in quantitative variables was assessed by the nonparametric Kruskal-Wallis test, and that of within-group differences was assessed by the Wilcoxon paired signed-rank test. Repeatability of F_ENO measurements was assessed by calculating the concordance correlation coefficient (r_{CC}). Statistical significance of between-group differences in qualitative variables was assessed by the chi-square test or Fisher's exact test. McNemar's test and Cohen's kappa

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test were used in order to assess the agreement of two qualitative results of F_ENO levels (cut-off point of 35 ppb). The correlates of within-subject variability of F_ENO were assessed using linear regression analysis, the relative F_ENO difference being used as the dependent variable. Simple and multivariate models were used in order to examine effects of gender, age, body mass index, respiratory status, and lung function variables. Interpretation of the results was based on the $p < 0.05$ criterion.

All subjects included in the study were examined in their schools on a Monday morning, and tests were applied after instructions. Two children were unable to perform the tests, and one child was unable to perform repeated F_ENO measurements. As a result, the analyses involved data obtained from 101 children (boys, 63%). The sample was divided into three groups: asymptomatic—no physician-diagnosed asthma, bronchitis, allergic diseases, or asthma symptoms (n = 76); symptomatic—no physician-diagnosed asthma but presenting with symptoms of wheezing (unrelated to having a cold) or dyspnea in the last year (n = 14); and asthma—physician-diagnosed asthma (n = 11). No significant differences were found among the groups regarding mean age (7.1 ± 0.7 years), height (128.3 ± 7.3 cm), or weight (26.7 ± 6.4 kg).

Table 1 shows the mean results of F_ENO obtained from the two measurements separately, as well as its between-occasion variability. In the sample as a whole, the mean absolute value was 1.4 ppb (11.7%). Intragroup comparisons between the two measurements were not significantly different (p = 0.2) and were strongly correlated (r_{CC} = 0.98; 95% CI: 0.98-0.99). The occurrence of F_ENO levels > 35 ppb showed very good repeatability (no discordant pairs). However, intergroup comparisons were significantly different regarding F_ENO levels (Tables 1 and 2). The mean values were the lowest in the asymptomatic group and the highest in the asthma group. The variability among the groups was similar regarding the mean absolute values (0.9-1.8 ppb) and the mean relative values (7.5-12.8%). No statistically significant differences were found in the means between the two measurements in the asymptomatic, symptomatic, and asthma groups (p = 0.6; p = 0.5; and p = 0.7, respectively). The groups showed strong correlations between the measurements: asymptomatic group (r_{CC} = 0.96; 95% CI: 0.94-0.97); symptomatic group (r_{CC} = 0.99; 95% CI: 0.99-0.99); and asthma group (r_{CC} = 0.99; 95% CI: 0.98-0.99). Table 2 shows the measurements divided into different ranges of F_ENO levels for the sample as a whole and for each group. F_ENO levels > 35 ppb were 100% reproducible on both measurements in each group (no discordant pairs). The correlates of within-subject variability of F_ENO levels were assessed using linear regression analysis,

Table 1. Results of two measurements of fractional exhaled nitric oxide and differences in between-occasion measurements in children by their respiratory status (quantitative variables).[a]

Variable		Total sample	Group			p*
			Asymptomatic	Symptomatic	Asthma	
		(N = 101)	(n = 76)	(n = 14)	(n = 11)	
F_ENO, ppb	Measurement 1	15.1 ± 13.5 [10 (7)]	12.6 ± 7.9 [10 (5.5)]	17.3 ± 19.7 [9 (17)]	29.1 ± 24.4 [21 (40)]	0.08
	Measurement 2	15.6 ± 14.0 [10 (8)]	13.0 ± 8.1 [10 (7)]	17.7 ± 19.5 [10 (14)]	30.6 ± 25.8 [23 (41)]	0.03
Between-occasion measurement difference	Mean absolute value, ppb	1.4 ± 1.5	1.4 ± 1.5	0.9 ± 0.9	1.8 ± 1.8	0.4
	Mean relative value, %	11.7 ± 14.2 [9.0 (18.1)]	12.8 ± 15.5 [10.0 (19.5)]	8.8 ± 10.0 [8.0 (11.1)]	7.5 ± 6.8 [7.0 (6.7)]	0.5
	Mean difference	−0.50 ± 2.01	−0.39 ± 2.08	−0.35 ± 1.27	−1.45 ± 2.02	0.1

F_ENO: fractional exhaled nitric oxide. [a]Values expressed as mean ± SD or [median (Interquartile range)]. *Kruskal-Wallis test.

Table 2. Results of two measurements of fractional exhaled nitric oxide and differences in between-occasion measurements in children by their respiratory status (qualitative variables).[a]

Variable		Total sample	Group			p*
			Asymptomatic	Symptomatic	Asthma	
		(N = 101)	(n = 76)	(n = 14)	(n = 11)	
Measurement 1, range in ppb	0-19	81	66	10	5	0.006
	20-35	14	8	3	3	
	> 35	6	2	1	3	
Measurement 2, range in ppb	0-19	82	67	10	5	0.004
	20-35	13	7	3	3	
	> 35	6	2	1	3	
Relative difference > 10%		44	37	5	2	0.1
Relative difference > 20%		19	15	3	1	0.8

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

the relative difference being used as the dependent variable. Neither simple nor multivariate models showed any association of the relative difference with gender, age, height, body mass index, respiratory status, or spirometric variables.

Our findings showed very good repeatability of F_ENO measurements in our sample. Moreover, the repeatability was found to be equally good in healthy children and in children with chronic respiratory symptoms or in children with asthma, a finding that corroborates the evidence concerning diurnal variation observed in healthy and asthmatic children.[4,5] In our study, short-term variability of F_ENO levels measured over one week was independent of demographic or lung function variables. Between-test differences in F_ENO levels could be confounded by the contents of fat, antioxidants, and nitrates in food or by physical exercise.[3,7] Exposure to outdoor air pollution was also found to increase short-term variability of F_ENO levels.[8] We did had control for the aforementioned factors, and our study was performed under conditions that are common in respiratory surveys in children.

The results support a view that F_ENO as measured by portable devices is a well-accepted noninvasive method for the assessment of eosinophilic airway inflammation in respiratory epidemiology. Another interesting finding of our study is a convincing between-group gradient of F_ENO levels that reflects the respiratory status of children as identified by a questionnaire, a relationship that seems to add to the reliability of our measurements.

Few studies have addressed the issue of repeatability of F_ENO measurements in children. However, the published evidence is mostly pertinent to diurnal variation; recent studies reporting FENO repeatability in young subjects have primarily examined small groups of children (especially children with asthma) in a hospital setting with F_ENO measurements obtained during one visit.[4,5,9,10] Although our study involved a relatively small group of subjects, it is distinct because of its real-epidemiology protocol and because of the fact that the measurements were made in two different sessions, one week apart. The results of our study show that F_ENO measurement is stable under epidemiological conditions, corroborating the slight day-to-day variations found in another study.[11]

In conclusion, our findings demonstrate that F_ENO measurements performed with a portable device in a field setting are highly reproducible and seem to support a view that F_ENO measurement is a valuable tool in respiratory health surveys in children and, perhaps, in asthma screening programs for that age group.

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REVIEW ARTICLE

Lung cancer in Brazil

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ABSTRACT

Lung cancer is one of the most incident types of cancer and a leading cause of cancer mortality in Brazil. We reviewed the current status of lung cancer by searching relevant data on prevention, diagnosis, and treatment in the country. This review highlights several issues that need to be addressed, including smoking control, patient lack of awareness, late diagnosis, and disparities in the access to cancer health care facilities in Brazil. We propose strategies to help overcome these limitations and challenge health care providers, as well as the society and governmental representatives, to work together and to take a step forward in fighting lung cancer.

Keywords: Lung neoplasms/epidemiology; Lung neoplasms/therapy; Lung neoplasms/diagnosis; Biomarkers; Brazil.

INTRODUCTION

Lung cancer is the most common malignancy worldwide, accounting for 13% of all new cancer cases.[1] According to the Global Burden of Disease Study 2015, lung cancer is also the leading cause of cancer mortality—over 1.7 to 1.8 million deaths every year and the highest age-standardized death rate (26.6 deaths per 100,000 population) among cancers.[2] In Brazil, the *Instituto Nacional de Câncer* (INCA, Brazilian National Cancer Institute) estimated a total of 596,000 new cancer cases in 2016, 28,220 (4.7%) of which were primary lung malignancies.[3] Lung cancer is the second most incident cancer among men and the fourth most incident cancer among women in the country (Figure 1).[3]

As in most countries, lung cancer is the major cause of cancer mortality in Brazil. The age-standardized 5-year survival rate in the country is 18%, which is concordant with global rates, ranging from 10% to 20%.[4] Lung cancer age-standardized mortality rates in 2012 were 16.5 deaths/100,000 population and 8.6 deaths/100,000 population in men and women, respectively.[5] In Brazil, mortality increased from 10.6 deaths/100,000 population to 31.1 deaths/100,000 population in men and from 3.0 deaths/100,000 population to 5.4 deaths/100,000 population in women from 1979 to 2004.[6] Mortality rates (both crude and age-adjusted) among men and women differed in magnitude in all periods (1980-2007), with a more significant relative increase among females than among males (78.4% vs. 8.2%), which was probably related to differences in smoking prevalence (Figure 2). Moreover, age-specific mortality rates increased among men aged 65 years or older and among women across all age groups.[7]

The Brazilian health care system is divided into private and public coverage (27% and 73%, respectively).[8] As will be discussed later in the present analysis, significant discrepancies in the availability of health care resources and patient outcomes are evident between these two different settings.

RISK FACTORS AND TOBACCO EXPOSURE

Trends in lung cancer mortality in Brazil reflect the epidemiological model of tobacco-related mortality. Tobacco use increased during the 1950s and the 1960s,

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Prostate	61,200	28.6%		Breast	57,960	28.1%
Lung & bronchus	**17,330**	**8.1%**		Colon & rectum	17,620	8.5%
Colon & rectum	16,660	7.8%		Uterine cervix	16,340	7.9%
Stomach	12,920	6.0%		**Lung & bronchus**	**10,890**	**5.3%**
Oral cavity	11,140	5.2%		Stomach	7,600	3.7%
Esophagus	7,950	3.7%		Uterine corpus	6,950	3.4%
Urinary bladder	7,200	3.4%		Ovary	6,150	3.0%
Larynx	6,360	3.0%		Thyroid	5,870	2.9%
Leukemias	5,540	2.6%		Non-Hodgkin lymphoma	5,030	2.4%
Central nervous system	5,440	2.5%		Central nervous system	4,830	2.3%

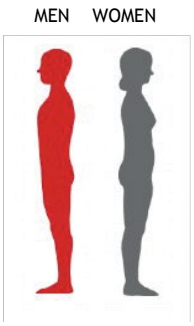

Figure 1. Brazilian National Cancer Institute estimate for new cancer cases in 2016 by gender. Adapted from Instituto Nacional de Câncer José Alencar Gomes da Silva.[3]

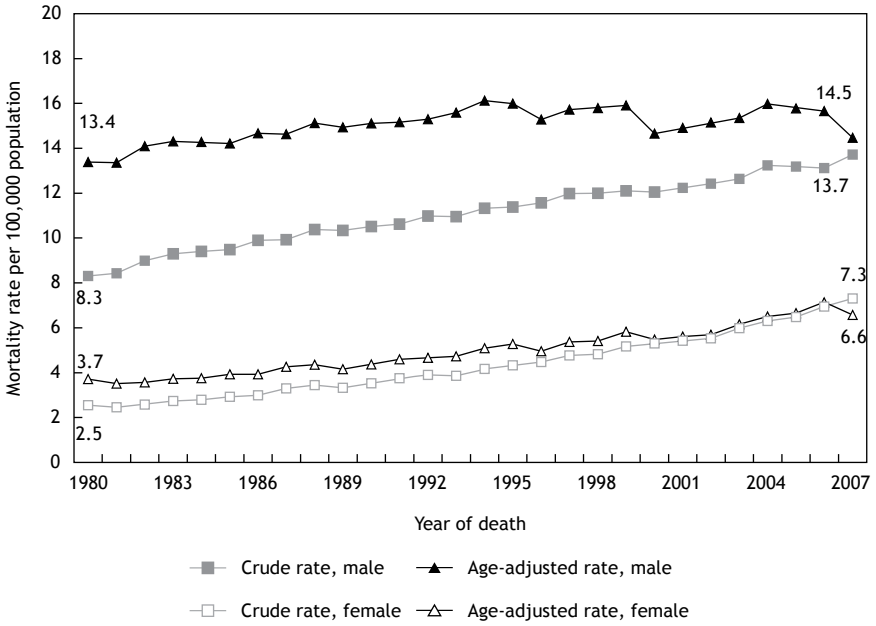

Figure 2. Crude and age-adjusted lung cancer mortality rates by gender. Brazil, 1980-2007.[7]

peaking in the 1970s. Notably, strong public health policies in Brazil have led to a subsequent reduction in tobacco consumption, which may serve as an example for other low- and middle-income countries. Brazilian national studies indicate that smoking prevalence has diminished approximately 50%, as have tobacco-related deaths.[9] Data from a nationwide surveillance study of risk factors and protective factors for chronic diseases carried out by telephone inquiries showed that 12,7% of men and 8.0% of women aged 18 years or older were smokers in 2016[10]; those proportions were 43.3% and 27.0% in 1989, respectively.[11]

The major components of Brazilian anti-tobacco policies include prohibition of smoking in public places, higher taxes for tobacco products, and health-warning labels on cigarette packages. Despite this decline in tobacco consumption, national surveys involving children in Brazil still show a significant prevalence of smokers among the young population in various cities.[12] Moreover, smoking-related illnesses remain a major economic health burden. It has been estimated that, by 2020, the population-attributable fraction of the lung cancer burden associated with smoking in Brazil will be 83.3% among men and 64.8% among women.[13] These data are relevant to reinforce the role of local tobacco control. Data on the prevalence of lung cancer related to other risk factors, such as asbestos exposure, residential wood smoke exposure, and radon exposure, are lacking.

DIAGNOSIS AND STAGING

Data on how lung cancer is diagnosed and staged are relatively scarce in Brazil; however, some datasets have been published in the past 15 years. Similarly to what occurs in developed countries, non-small cell lung cancer (NSCLC) is usually diagnosed in advanced stages and has poor survival rates in Brazil. Overall, approximately 70% of the patients present with either

locally advanced or metastatic disease (stages III and IV, respectively). According to a large cancer registry database in the state of São Paulo, Brazil, only 8.8% of the 20,850 lung cancer patients registered in the system between 2000 and 2010 had stage I disease.[14] These proportions are in contrast with the higher frequencies of 15.4% and 14.5% reported for a similar period in the USA and in the United Kingdom, respectively.[15,16] A Brazilian lung cancer screening trial was conducted in order to address the effectiveness of screening in the country.[17] Between January of 2013 and July of 2014, 790 participants volunteered to participate, following the same eligibility criteria applied in a USA national lung screening trial. NSCLC was diagnosed in 10 participants (prevalence of 1.3%), most of whom were classified as stage I.[17]

Several retrospective series have been published reporting single institution data on lung cancer histology, staging, and outcomes (Table 1).[18-26] Interestingly, it seems that squamous cell histology is more prevalent in public health care services, whereas adenocarcinoma predominates in private institutions. In the USA, squamous cell carcinoma and small cell lung carcinoma (SCLC) rates declined after the 1990s, and adenocarcinoma rates rose in the period between 2006 and 2010 among every racial/ethnic/sex group.[27] A major cancer center in the state of São Paulo reviewed data collected between 1997 and 2008 from 1,887 lung cancer patients.[18] A decline in the proportion of SCLC was reported in two different time periods (1997-2002 and 2003-2008), although no significant changes occurred in the NSCLC histological subgroups.[18] However, in an epidemiological study evaluating case registry data from 35,018 patients diagnosed with NSCLC in the states of Rio de Janeiro and São Paulo between 2000 and 2011, a shift was observed towards a prevalence of adenocarcinoma histology over squamous cell carcinoma (43.3% vs. 36.5%) in recent years.[28]

DIAGNOSTIC PROCEDURES

Delay in the diagnosis of cancer in general and of lung cancer in particular is one of the major challenges faced in Brazil. Information on the timeframe for an individual with suspicious symptoms to receive a diagnosis of lung cancer, to visit a tertiary health care facility, and to initiate therapy is lacking. Nonetheless, the high rate of late-stage diagnoses, the low frequency of patients receiving curative-intent therapy, and the large number of patients not receiving any disease-directed treatment reflect a significant delay and inefficiency in the diagnostic workflow, at least in the public health care scenario.[21,29] In general, access to diagnostic imaging is limited in many regions. A retrospective study from two institutions showed that 89% of the patients were diagnosed with cancer via chest X-ray, whereas only 20% were diagnosed via CT.[21] Moreover, access to invasive diagnostic procedures is limited, with few facilities performing bronchoscopy or transthoracic biopsies.

In a 2005 survey, the rate of CT scanners per one million population was 4.9 and 30.8 in the public and private health care settings in Brazil, respectively.[30] These rates underscore the difficulties in the access to adequate diagnostic evaluation in the public health care system, whereas the rates described in private health care facilities are similar to those in developed countries, such as the USA and Japan (31.5 and 32.2, respectively). There is also a geographic disproportion of technology distribution, with higher numbers of diagnostic facilities in the southeast and south regions and lower numbers in the north and northeast regions.[30] In 2010, the agency that regulates the private medical sector—*Agência Nacional de Saúde Suplementar* (National Health Insurance Agency)—approved the use of positron emission tomography (PET) for lung cancer staging; however, the public health care system—*Sistema Único de Saúde* (Brazilian Unified Health Care System)—incorporated the technology only in 2014. The number of facilities providing PET has increased sharply in the country, reaching 124 scanners and 15 cyclotrons in 2014, distributed in 21 of the 26 states of Brazil and the Federal District of Brasília (personal communication). The lower availability of the technology in the public health care system is noteworthy.

Reports on the Brazilian experience with invasive diagnostic procedures are also scarce or outdated. The *Sociedade Brasileira de Pneumologia e Tisiologia* mailed 576 questionnaires to physicians—mostly pulmonologists—addressing their experience

Table 1. Lung cancer distribution by histology and staging.

Author	N	Type of facility	NSCLC, %	SCC/Ad ratio	III-IV, %
Ismael et al.[18]	1,887	Public	89	0.93	71
Younes et al.[19]	737	Public	100[a]	1.20	74
Westphal et al.[20]	352	Public	91	2.54	66
Barros et al.[21]	263	Public	87	1.96	94
Novaes et al.[22]	240	Public	80	1.25	72
Araujo et al.[23]	566	Private	100[a]	0.33	80
Caires-Lima et al.[26]	232	Public	92	0.48	93
Mascarenhas et al.[24]	338	Private	83	0.38	78
Freitas et al.[25]	93	Private	100[a]	0.33	88

NSCLC: non-small cell lung cancer cases; SCC: squamous cell carcinoma cases; Ad: adenocarcinoma cases; and III-IV: patients in stages III or IV. [a]Studies including only NSCLC cases.

with bronchoscopy.[31] Of the respondents, 111 (19.2%) declared being familiar with both flexible and rigid bronchoscopy, the majority of those (n = 63; 56.7%) performing at least 100 fiberoptic bronchoscopies per year, which is in line with international recommendations.[32,33] In 2007, experts at INCA reported their experience with bronchoscopy-guided transbronchial needle aspiration, which is considered a safe and effective procedure.[34] Samples were deemed satisfactory in 57% of the cases, 81% of those allowing a definitive diagnosis.[34] Some groups have also developed expertise in CT-guided transthoracic fine-needle aspiration, showing high diagnostic yield, accuracy, and safety.[35] After 2010, endobronchial ultrasound was introduced in a few large institutions, and the initial experience with 50 cases has been reported.[36,37] In most cases, endobronchial ultrasound was recommended for diagnostic purposes (76%), yielding adequate specimens in 74% of the cases.[36] In general, these data suggest that referral centers have adequate expertise, but it is unknown what proportion of patients has access to these.

MOLECULAR TESTING

The introduction of molecular testing in lung cancer is key to improving therapeutic results. Unfortunately, access, affordability, and incorporation strategies remain significant challenges in low- and middle-income countries.[38] Access to molecular testing is limited in Brazil, and data on the frequency of clinically useful mutations is still scarce, especially in the public health care system. Unpublished information (personal communication) on approximately 1,700 cases obtained from a marketing survey conducted in the first half of 2014, suggests that, overall, fewer than half of the patients are tested for *EGFR* mutations in Brazil. Approximately two thirds of the tests are performed in the private sector, and only one third is performed in public health care institutions. These rates are likely to be lower for anaplastic lymphoma kinase (*ALK*) gene testing.[39] The major issues regarding molecular genotyping are as follows: 1) reimbursement and logistics; 2) access to targeted therapy; 3) patient and medical information (i.e., unawareness); and 4) limited laboratory infrastructure for molecular testing (restricted to a few large centers or cities). Pharmaceutical companies involved in distributing EGFR tyrosine kinase inhibitors (TKIs) have provided most of the molecular testing that has been performed in the past few years. Regulatory agencies have recently approved *EGFR* testing and the reimbursement of its costs by private health insurance companies. The development of local guidelines, the definition of test algorithms, and the application of comprehensive policies that associate testing with personalized treatment are essential to enable a functional process to make targeted therapy a reality for a larger proportion of patients.[39]

Some efforts have been made to compile data on the frequency of molecular abnormalities in Brazilian patients (Table 2).[40-48] Overall, the data suggest that the frequency of *EGFR* mutations is lower in Brazil (approximately 25%) than in Asia but higher than in White populations in North America and Europe (Figure 3), confirming findings from other Latin American countries.[49] It has been speculated that the ethnic background could be responsible for the distinct molecular profile seen in these instances, perhaps due to the characteristic genetic admixture seen in Brazilians, inherited from European, African, and Native American ancestors. The frequency of *ALK* translocations has been reported to range from 3% to 4%.[48,50,51] To explore these points in a better way, two multicenter studies have been initiated, led by the Brazilian National Clinical Cancer Research Network and the Latin American Cooperative Oncology Group. These consortiums are supported by pharmaceutical companies, as well as by North American societies, such as the American Society of Clinical Oncology and the American Association for Cancer Research.

TREATMENT

Surgery

Precise data on the number of surgical procedures performed to treat lung cancer are unavailable. According to the Brazilian Technology Information Department of the SUS—a public health care system database that covers approximately 75% of the Brazilian population—a median of 964 pulmonary lobectomies and segmentectomies were performed yearly between 2007 and 2014.[52] However, this number has some potential flaws, though, since lobectomies and segmentectomies could have been performed for diseases other than lung cancer; the database is restricted to the public health care system, and the quality of the data is questionable.

Only a limited proportion of patients undergo curative-intent surgery. Data suggest that approximately 25% of the patients undergo surgical treatment.[19,22,23] Access to curative surgery is likely influenced by socioeconomic differences, performance status scores, presence of comorbidities, advanced age, and geographic distribution.[22] According to the São Paulo State Department of Health, patients with a lower educational level are less likely to undergo surgery.[14] Currently, there are 763 thoracic surgeons in Brazil, concentrated in the south and southeast regions of the country.[53] In a survey promoted by the *Sociedade Brasileira de Cirurgia Torácica* (Brazilian Society of Thoracic Surgery), 51% of the respondents stated that they worked in cities with more than one million inhabitants.[54] Therefore, although the absolute number of thoracic surgeons is adequate, their distribution is a cause for concern. Medium-sized cities and highly populated regions in central, northern, and northeastern Brazil are underserved in terms of thoracic surgery.

Video-assisted thoracic surgery is rapidly growing in the country. The 30-day mortality rates in the two largest surgical case series reported, which included

Table 2. Frequency of *EGFR* mutations and clinical characteristics in Brazilian cohorts.

Author	N	*EGFR* mutation, %	NS, %	Female, %	non-SCC, %	Setting
Pontes et al.[40]	3,371	25	NR	58	100	Clinical
Yen et al.[45]	417	25	34	57	100	Clinical
Saito et al.[46]	395	26	27	51	91	Clinical
Domingues et al.[43]	288	27	26	56	95	Clinical
Bacchi et al.[41]	207	30	54	58	82	Clinical
Gomes et al.[48]	162	33	32	48	100	Clinical
Melo et al.[42]	157	22	15	47	68	Research
De Sa et al.[44]	100	28	NR	NR	100	Clinical

NS: never smoker; non-SCC: non-squamous cell carcinoma; and NR: not reported.

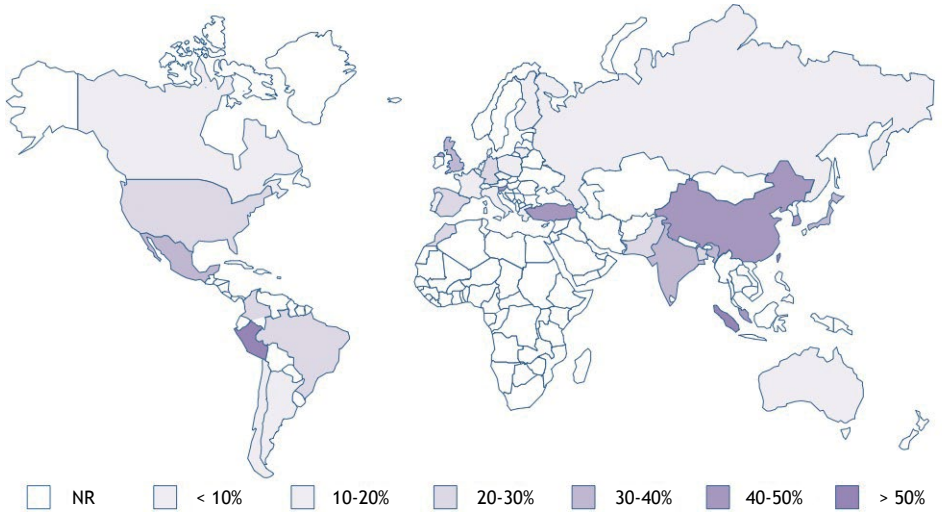

Figure 3. Prevalence of *EGFR* mutations around the world. *EGFR* mutations are in general more prevalent in Asian countries, whereas Latin American countries tend to have an intermediate prevalence between Asia and Europe/North-America. NR: not reported. Adapted from Werustky et al.[49]

patients who underwent lobectomy due to lung cancer, were 2.9% and 4.3%.[55,56] Large international case series published in the 2000s showed a somewhat lower mortality rate (of approximately 1%).[57] These numbers suggest that there is room for improvement in lung cancer surgery in Brazil. The dissemination and availability of new techniques, such as video-assisted and robotic surgery, will hopefully speed up this process.

Radiation therapy

According to the *Comissão Nacional de Energia Nuclear* (Brazilian National Commission of Nuclear Energy), there 224 radiation therapy (RT) facilities (65% of which are public) are currently available in Brazil, but they are unequally distributed across the country (2 of the 26 states lack RT facilities).[58] These facilities have approximately 250 linear accelerators that can provide treatment for more than 150,000 cancer patients per year. The World Health Organization recommends one megavoltage machine for every 600,000 inhabitants in order to provide adequate treatment availability. With an estimated population of 200 million inhabitants, Brazil needs approximately 335 megavoltage machines. This corresponds to a deficiency of nearly 100 RT devices to provide full treatment coverage for approximately 100,000 untreated patients per year.[59]

Approximately 550 radiation oncologists work in Brazil, mostly in the southeastern region, where the majority of the linear accelerators (124/235 units; 52.7%) are centralized.[60] There are long waiting lists to start treatment (mean waiting time, 113 days) mainly in public health care centers, with a potential impact on patient outcome. In order to minimize this problem, the government has implemented different strategies.[60] The most recent and outstanding one was the acquisition of 80 linear accelerators that are able to deliver high-quality therapy, including three-dimensional conformal RT and potential for upgrades to deliver intensity-modulated RT. At the same time, 39 of the already existing RT facilities are intended to be expanded, and 41 RT facilities are to be created, the federal government investing more than 250 million US dollars. As a result, it is expected that all geographic areas in the country should be properly served in the near future, avoiding patient migration for treatment. Nevertheless, the backlog of patients requiring therapy and the need to train qualified human resources remain as critical challenges in need of urgent measures.

According to a survey sent to all RT services registered with the *Sociedade Brasileira de Radioterapia* (Brazilian Society of Radiotherapy), approximately 25% of all RT procedures are performed in lung cancer patients. Among these, approximately half are submitted to palliative treatment only, and very few are in early stages (I or II). Few centers have stereotactic body RT or stereotactic ablative RT to treat localized disease, only one of them providing care via the public health care system. Among the 13 centers that provide this technology, only 10 use it for lung cancer treatment. The preliminary experience (21 patients; mean age, 81 years) with stereotactic body RT in a private health care institution showed that the treatment was mostly recommended for elderly or clinically inoperable patients. With a median follow-up period of 12 months, local control was achieved in 95% of the patients, and the complication rate was very low.[61]

There is a lack of well-annotated outcome data on locally advanced NSCLC in Brazil. Although chemoradiation therapy is the standard of care in most facilities, treatment protocols are quite diverse. For instance, in a retrospective analysis of 171 elderly patients with unresectable, locally advanced NSCLC, the treatment offered was best supportive care, in 39%; definitive RT alone (at least 40 Gy), in 32%; and combined chemoradiation therapy, in only 29%.[62] In order to improve the description of the results regarding this issue in Brazil, the Latin American Cooperative Oncology Group and the *Grupo Brasileiro de Oncologia Torácica* are coordinating a multicenter study to collect data on locally advanced NSCLC from 7 referral centers for cancer in the country.

The Brazilian experience with palliative RT demonstrates high rates of symptom control (70-84%) and a median overall survival (OS) of approximately 3 months following hypofractionated regimens.[63,64] Regimens based on fewer RT fractions can be very convenient in centers with long waiting lines. High dose-rate brachytherapy is also available in approximately half of the centers, although reimbursement in public health care services is limited to gynecological cancers.[65] The endobronchial procedure is used mostly for palliative purposes and in very few centers (11/59 surveyed), only 1 belonging to the public health care system. The overall symptom relief rate was 70% in a national case series involving 78 patients.[66]

Systemic therapy

In comparison with developed countries, the incorporation of systemic therapies and technologies for lung cancer diagnosis and treatment suffers from significant delays in Brazil. More importantly, inequities in the access to drugs and molecular testing between public and private health care systems are striking. For instance, standard third-generation chemotherapy agents, such as taxanes and gemcitabine, were only incorporated into the public health care system in the late 2000s, and pemetrexed is still unavailable. Targeted therapies, such as monoclonal antibodies (bevacizumab) and first-generation EGFR TKIs, are available only for patients with private health care coverage. Although EGFR TKIs were included in the public health care system in 2015, both mutation testing and medications are neither adequately available nor routinely provided to patients yet. The first ALK inhibitor approved for use in Brazil was crizotinib in February of 2016, whereas ceritinib is still being evaluated. The delay in the approval of crizotinib was estimated to result in over 700 patients dying prematurely from their disease as a consequence of the lack of access to this effective agent.[67]

In a large retrospective review, Younes et al. collected data from 2,673 metastatic NSCLC patients treated in two cancer centers in the city of São Paulo between 1990 and 2008.[68] Notably, 49% of the patients had a Karnofsky performance status of 70% or less, reflecting the late access of the patients to specialized cancer centers. The majority (57.9%) of the patients were treated with first-line chemotherapy, whereas second- and third-line chemotherapy was offered to 23.4% and 8.0% of the patients, respectively. A platinum-based regimen as the first-line treatment was used in 61% of the patients (median OS, 8.0 months).[68] Naime et al. reviewed the heterogeneity of systemic regimens employed in a cohort of 564 metastatic NSCLC patients, also in the city of São Paulo, between 1990 and 2003.[69] Again, 47% of the patients had an Eastern Cooperative Oncology Group performance status scale score of 2-3; chemotherapy was used in 59% of the patients, 47 different regimens being used. Although most (83.5%) of the patients received a platinum salt, only 57.3% were treated with a platinum doublet regimen. Taxanes and gemcitabine were offered to only 19.0% and 15.8% of patients, respectively. The median OS was 8.3 months.[69] Araujo et al. reported the results of palliative chemotherapy given to 339 NSCLC patients treated in a private health care institution in the city of Rio de Janeiro between 1998 and 2010.[23] Most patients received a first-line platinum-based regimen, its combination with paclitaxel being the most common, in 31%; followed by pemetrexed, in 21%; and gemcitabine, in 17%. The median OS was 12.2 months.[23] These and other studies are summarized in Table 3.

Given the relatively high rate of patients being diagnosed late and having advanced disease and poor performance status, Brazilian investigators established a national research infrastructure to explore the best approach to manage fragile patients. In a multi-institutional phase III trial, Zukin et al. compared a carboplatin plus pemetrexed regimen with the use of pemetrexed alone in 205 metastatic NSCLC patients with a performance status of 2.[70] Notably, the authors confirmed the benefit of the platinum-doublet regimen, showing improved overall response rate, progression-free survival, and OS in the group receiving the combined therapy. In parallel, Pereira et al. demonstrated the feasibility of a cisplatin plus vinorelbine regimen for elderly patients with NSCLC in a prospective phase II trial.[71]

Several groups have reported their experience with targeted therapies in Brazil, especially regarding their local experience with EGFR TKIs. Caires-Lima et al. reported the efficacy and safety of erlotinib in patients with advanced adenocarcinoma harboring sensitizing *EGFR* mutation.[72] In that single-center experience in the city of São Paulo, 49 consecutive cases treated between 2010 and 2013 were evaluated; of those, 22% were treated with a first-line regimen, and 63% and 14% were treated with second-line and third-line regimens, respectively. Treatment was well tolerated and led to a clinical benefit rate of 64%. One-year OS rate was 94%, and the median survival had not been reached at the time of publication.[72] Domingues et al. described the outcomes of 32 *EGFR* mutant cases treated with EGFR TKIs in the city of Rio de Janeiro.[43] The median OS was an impressive 62.9 months.[43] Freitas et al. reported the outcomes of 61 patients treated with a TKI (from a cohort of 115 metastatic NSCLC patients with an *EGFR* mutation) in another cancer institution in the city of São Paulo between 2010 and 2014.[73] The median progression-free survival was 13.9 months and 11.4 months in the patients using first-line and the second-line regimens, respectively. The median OS was not different between those two groups (36.3 months vs. not reached; p = 0.61).[73] These data confirm the benefit of selecting patients locally and reinforce the importance of correct identification of *EGFR* mutant cases for targeted therapy.

Given that these medications have only recently been approved, there is still no information regarding the use of immunotherapy in the country.

CLINICAL RESEARCH AS AN OPPORTUNITY

The participation of patients in international, industry-sponsored clinical trials has been significant in various academic institutions in Brazil and has facilitated access to novel therapies. For instance, Zylberberg et al. reported the experience involving 97 consecutive patients with advanced NSCLC enrolled in clinical trials at INCA.[74] Half of the patients were initially enrolled in a first-line regimen trial; of those patients, 31% also participated in a subsequent trial using a second-line regimen or a later-line regimen. Notably, all patients eventually received a contemporary standard treatment, as follows: taxanes, in 49% of the patients; pemetrexed, in 30%; gemcitabine, in 31%; and TKIs, in 37%. This highly selected group had a median OS of 17.2 months, which is higher than are the historical data outside of a clinical trial.[74] As more trials are open nationally, the participation of community-based institutions tends to increase, making research an option for more patients. Clinical research in Brazil faces a number of challenges, including the slow and lengthy regulatory process that reduces and significantly limits the opportunities to participate in clinical trials. The mean time for regulatory approval of a research protocol in Brazil is three times longer than that in the USA and other leading countries in research, having an impact on the availability of studies and reducing the timeframe for patient accrual.

PERSPECTIVES

Investing in epidemiological research and evidence-based lung cancer care should be a strategic priority for the Brazilian health care system. Important steps have been undertaken to improve case registry data; however, those available still cover only a small proportion of the population, and the quality of data collection is often questionable. Lung cancer control certainly faces significant challenges in Brazil (Chart 1). Collecting high-quality data on epidemiology and health economy will help understand the current scenario and will contribute

Table 3. Summary of the most relevant studies on non-small cell lung cancer palliative systemic treatment in Brazil.

Author	Design	N	Study period	PS ≥ 2, %	Type of facility	mOS, months
Chemotherapy						
Younes et al.[68]	Re	2,673	1990-2008	49[a]	Private	8.0
Naime et al.[69]	Re	564	1990-2003	47	Private	8.3
Araujo et al.[23]	Re	339	1998-2010	11	Private	12.2
Leite et al.[75]	Re	163	2006-2013	NA	Public	NA
Zukin et al.[70]	Pro	205	2008-2011	100	Public	5.3/9.3[b]
Pereira et al.[76]	Re	82	2007-2011	NA	Private	26.4/16.4[c]
Jardim et al.[77]	Re	56	2006-2011	7.2	Private	14.8
Pereira et al.[71]	Pro	44	1996-1998	50[a]	Public	7.5[d]
EGFR TKI						
Caires-Lima et al.[72]	Re	49	2010-2013	NA	Public	NR[e]
Domingues et al.[43]	Re	32	2011-2014	NA	Public	62.9
Freitas et al.[73]	Re	61	2010-2014	NA	Private	36.3/NR[f]

PS: Eastern Cooperative Oncology Group performance status score; mOS: median overall survival; Re: retrospective; Pro: prospective; NA: not available; NR: not reached; and TKI: tyrosine kinase inhibitor. [a]Karnofsky performance status ≤ 70%. [b]Survival for single-agent and doublet-agent arms, respectively. [c]Survival for bevacizumab-based and pemetrexed-based protocols, respectively. [d]Only elderly patients (≥ 70 years of age) were included. [e]Survival not reached after a median follow-up of 14 months. [f]Survival among patients receiving an EGFR TKI as first- or second-line treatment, respectively.

Chart 1. Summary of the current scenario and proposed actions to improve lung cancer control in Brazil.

Current scenario	Action
Lung cancer is a leading cause of cancer death in Brazil. Smoking-related lung cancer remains a major health burden. Data on lung cancer diagnosis, staging, therapy, and outcomes are scarce. There is a deficiency in radiation therapy machines to provide full treatment coverage in the country. There is a significant delay in the approval of systemic therapies by local regulatory agencies. Inequities in the access to diagnosis, therapy, and molecular testing between public and private health care systems are remarkable. A lengthy clinical research approval process limits access to clinical trial opportunities.	Reinforce the role of tobacco control, and stimulate programs directed to the entire population, particularly teenagers. Collect high-quality data on epidemiology and health economy aiming at describing diagnosis, staging, access to therapy, and outcomes. Strengthen, bring together, and stimulate productive dialogue among medical societies, advocacy groups, government, pharmaceutical companies, and regulatory agencies. Propose and implement programs to positively impact on prevention, diagnosis, and access to therapy. Increase local funding for lung cancer prevention, diagnosis, and treatment research. Stimulate the development of research units and participation in clinical trials. Stimulate and implement international collaborations.

to the process of defining strategic plans. Promising examples include local studies showing favorable cost-effectiveness ratios that support the incorporation of PET-CT for lung cancer staging in the public health care system, as well as chemotherapy doublets in the first-line treatment of metastatic NSCLC patients with a performance status of 2. Bringing together community representatives, health care providers, pharmaceutical companies, tax payers, researchers, and government officials is an important strategy to enable the definition and implementation of programs that will have impact on the areas of prevention, diagnosis, and access to standard therapies. The participation of oncology societies and workgroups will be key to orchestrating such efforts. These strategies should involve international collaboration and strongly focus on decreasing health care discrepancies.

FINAL CONSIDERATIONS

This comprehensive review addresses the current landscape and emphasizes various weaknesses in the management of lung cancer in Brazil. Specific data are often scarce or absent in various instances, which should motivate concentrated efforts to address these topics in the near future. Anti-tobacco legislation and education campaigns should be continued and intensified, particularly focusing on the younger population. Programs to increase public awareness on lung cancer, stimulate smoking cessation, shorten the time to diagnosis, and improve access to specialized health care facilities are among the most relevant needs to tackle lung cancer and improve therapeutic results.

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Sleep characteristics in an adult with sleep complaints in three cities at different altitudes

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ABSTRACT

Sleep studies conducted at an altitude that is different from the home altitude can yield misleading results regarding the severity of obstructive sleep apnea (OSA). The objective of the present study was to determine the sleep characteristics of a patient undergoing polysomnography (PSG) in three Colombian cities at different altitudes (Bogotá, at 2,640 m above sea level [ASL]; Bucaramanga, at 959 m ASL; and Santa Marta, at 15 m ASL). The patient was an obese man with diabetes and suspected OSA. All PSG recordings were scored and interpreted in accordance with American Academy of Sleep Medicine criteria. In Bogotá, PSG revealed moderate OSA (an apnea-hypopnea index [AHI] of 21 events/h); in Bucaramanga, PSG revealed increased upper airway resistance (an AHI of 2 events/h); in Santa Marta, PSG revealed mild OSA (an AHI of 7 events/h). The reduction in the AHI was predominantly a reduction in hypopneas and obstructive apneas. The respiratory events were shorter in duration in the city at an intermediate altitude. Given that the AHI varied widely across cities, we can assume that the patient is normal or has moderate OSA depending on the city where he is. Central apneas were found to have no influence on the AHI.

Keywords: Sleep apnea, obstructive; Polysomnography; Altitude.

INTRODUCTION

Sleep disorders have a substantial impact on the quality of life of patients and on their work performance.[1] The prevalence of sleep complaints in Colombia is 59.6%.[2,3] Among sleep disorders, sleep-disordered breathing has the most serious and deleterious health consequences, and studies have shown substantial increases in its prevalence.[4,5]

Multiple studies have shown that as the altitude increases, so does the possibility of disorders. These disorders have been associated with decreased PaO_2 resulting from changes in altitude, although in some cases evidence suggests that they are more closely related to hypoxic changes than to reduced atmospheric pressure (AP).[6] However, what is the effect of altitude descent on sleep-disordered breathing? Could it be explained by changes in three atmospheric variables, namely air density (and therefore viscosity through a critically narrowed upper airway), oxygen content, and barometric pressure or external compressive effect?[7] In an attempt to answer these questions, we conducted three polysomnographic studies on a patient residing in the city of Bogotá, Colombia. Each study was conducted in a different city in Colombia, namely Bogotá (at 2,640 m above sea level [ASL]), Bucaramanga (at 959 m ASL), and Santa Marta (at 15 m ASL), the recordings being scored and interpreted in accordance with American Academy of Sleep Medicine criteria.[8]

CASE REPORT

We report the case of a 57-year-old male public health official originally from Bogotá and undertaking extensive domestic and international travel. His relevant medical history included diet-controlled diabetes mellitus—he had been diagnosed with diabetes mellitus 10 years prior—and tonsillectomy during childhood. At this writing, the patient was a current smoker (with a smoking history of 6 pack-years). In addition to having reported no medication use, he reported being unable to have a regular diet during his travels, his diet usually consisting of sandwiches and soup. He reported drinking alcohol only on special occasions.

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The patient reported snoring, daytime sleepiness, fatigue, and morning headaches. Before the three polysomnographic recordings, he described his sleep as being generally very good. Upon physical examination, the patient was noted to be 1.74 m tall, his weight, body mass index, waist circumference, and neck circumference being 94 kg, 31.04 kg/m^2, 110 cm, and 47 cm, respectively. The remainder of the physical examination was unremarkable. His Epworth Sleepiness Scale score was 11.

The polysomnographic study conducted in Bogotá showed a sleep latency of 4 min and a sleep efficiency of 82%. There was an increase in non-rapid eye movement (NREM) stage 1 sleep (to 24% of total sleep time) and a decrease in rapid eye movement (REM) sleep (to 18% of total sleep time). The apnea-hypopnea index (AHI) was 21 events per hour of sleep, indicating moderate supine-dependent sleep apnea. Respiratory events included primarily hypopneas, which were more frequent during NREM sleep. The longest event lasted 25 s. Snoring was observed. Only 6 central apneas without periodic breathing were observed (Table 1). The patient had no significant periodic leg movements in sleep. Most arousals were related to respiratory events, with a rate of 3 per hour. Mean waking oxygen saturation was 86%, having decreased to 74% during events.

The polysomnographic study conducted in Bucaramanga showed a slightly prolonged sleep latency (of 26 min) and a decreased sleep efficiency (of 75%). There was an increase in NREM stage 1 sleep (to 20% of total sleep time). REM sleep accounted for 23% of total sleep time. The AHI was 2 events per hour of sleep. There were respiratory effort-related arousals and flattening of the respiratory curve, indicating airflow limitation (Table 1). Snoring was observed. No central events were observed. The patient had 10 arousals per hour. The longest event lasted 18 s. There were no periodic leg movements in sleep. Mean waking oxygen saturation was 94%, having decreased to 86% during sleep.

The polysomnographic study conducted in Santa Marta showed a sleep latency of 11 min and a sleep efficiency of 81%. There were increases in NREM stage 1 sleep (to 19% of total sleep time) and REM sleep (to 35% of total sleep time). There were 6 central apneas without periodic breathing (Table 1). The AHI was 7 events per hour of sleep, indicating mild, predominantly supine-dependent sleep apnea. Respiratory events included primarily obstructive apneas, predominantly during NREM sleep. Snoring was observed. The longest event lasted 23 s. The patient had no significant periodic leg movements in sleep. Mean waking oxygen saturation was 94%, having decreased to 88% during respiratory events. The patient had 4 arousals per hour.

DISCUSSION

Although we expected a linear relationship between sleep apnea and altitude, we found that the city in which the patient showed the lowest AHI was at an intermediate altitude (i.e., Bucaramanga, at 959 m ASL). In Bogotá, which is the city at the highest altitude (2,640 m ASL) and where the patient resided at this writing, polysomnography (PSG) showed moderate

Table 1. Summary of the results.

Variable	City (altitude)		
	Bogotá (2,640 m ASL)	Bucaramanga (959 m ASL)	Santa Marta (15 m ASL)
	Date		
	February 17, 2014	October 14, 2014	August 5, 2014
Weight, kg	94	94	94
Sleep efficiency, %	82	75	81
Sleep latency, min	4	26	11
REM sleep latency, min	64	53	94
NREM stage 1 sleep, %	24	20	19
NREM stage 2 sleep, %	46	46	40
NREM stage 3 sleep, %	12	11	6
REM sleep, %	18	23	35
Central apneas, n	6	0	6
Obstructive apneas, n	37	11	26
Mixed apneas, n	0	0	0
Hypopneas, n	69	3	6
AHI, events/h	21	2	7
Supine AHI, events/h	39	2	12
Arousal index, events/h	3	10	1
SpO_2, %	74-86	86-94	88-94
Heart rate, bpm	66-91	67-74	66-70

ASL: above sea level; REM: rapid eye movement; NREM: non-rapid eye movement; and AHI: apnea-hypopnea index.

sleep apnea (an AHI of 21 events/h). This could be explained by the acclimatization process, whereby the number of central apneas might decrease and obstructive events might occur. In Bucaramanga, the patient showed increased upper airway resistance, whereas in Santa Marta—the city at the lowest altitude (15 m ASL)—he showed mild sleep apnea (an AHI of 7 events/h). The highest AHI was found in the city at the highest altitude, a finding that is consistent with those of the literature. However, the effect of altitude descent on the AHI in the present study contrasts with that reported by Patz et al.,[7] who studied 11 patients and found a reduction in the AHI on descent. They found that the reduction in the AHI was predominantly a reduction in central apneas and hypopneas, which decreased by 70% and 49%, respectively.[7] In our patient, the reduction in the AHI was due to fewer hypopneas and obstructive apneas, which decreased by 85% and 71%, respectively. This reduction in hypopneas on altitude descent is consistent with the findings of Patz et al.[7]

Our results could be explained by our particular climatic conditions. It has been reported that patients with sleep-disordered breathing exhibit an increased AHI with increasing altitude, and it has been postulated that hypoxic changes are the triggers of this phenomenon, more so than reductions in AP.[6] In a sleep study conducted at 60 m ASL, the AHI was found to be altered by changes in weather-related AP.[6] The authors of that study concluded that small changes in AP due to weather systems might play an important role in the pathophysiology and diagnosis of obstructive sleep apnea.[6]

Unlike Patz et al.,[7] we found no significant association between longer lasting events and lower altitudes. In our patient, the duration of the events was similar between the study conducted at the highest altitude and the study conducted at the lowest altitude (25 s vs. 23 s), being shortest (18 s) in the study conducted at an intermediate altitude. We expected that, at a lower altitude, it would have taken longer to reach the threshold SaO_2 to trigger arousal, leading to a longer apnea.[7]

With regard to hypoxemia, we found an inverse linear trend with altitude; values of 82%, 86%, and 88% were found for the highest to lowest altitudes, being similar to those described in the literature. In Bogotá, we found that oxygen saturation remained below 90% 80% of the time, whereas in the other two cities it remained below 90% only 0.4% of the time. This finding is very important because of the proposed association between desaturation time and the development of neoplastic lesions in the long term,[9] as well as because of the development of pulmonary hypertension.[10]

In all three cities, our patient spent more time in superficial sleep stages (24% of total sleep time in Bogotá, 20% of total sleep time in Bucaramanga, and 19% of total sleep time in Santa Marta), showing a downward trend with altitude. Air conditioning was not used in any of the cities, and our country has no seasons. The patient traveled to Bucaramanga on the same day on which PSG was performed and to Santa Marta one day before PSG.

The polysomnographic studies conducted in Santa Marta and Bogotá showed central events without periodic breathing. The types of events observed in our patient (with a predominance of obstructive apneas in Santa Marta and of hypopneas in Bogotá) are similar to those described previously.[11] In a study of sleep disorders in immigrants with and without chronic mountain sickness, hypopnea was found to be the most common event.[11]

Our patient had 4 arousals per hour of sleep in Santa Marta, 3 in Bogotá, and 10 in Bucaramanga. It has been reported that an increased AHI does not cause more frequent arousals at high altitudes.[12] This finding is similar to those of the present study. Although our patient showed an arousal rate within normal limits in two cities, this does not rule out the possibility that daytime functioning might be affected. It has been reported that respiratory disorders not accompanied by arousals could impact the quality of sleep and impair reparative processes associated with sleep more than previously believed.[13]

Studies examining the presence of sleep apnea at different altitudes have shown decreased oxygen saturation, increased AHI, and decreased slow wave sleep at higher altitudes. Our finding of decreased oxygen saturation is consistent with the literature.[14]

From a physiological standpoint, increased sensitivity to CO_2 below eupnea leads to $PaCO_2$ levels below the threshold for apnea and causes breathing to stop until $PaCO_2$ rises above the apnea threshold.[15] Given that capnography was unavailable, we were unable to observe that in our patient.

Although no statistically significant differences have been found between high and low altitudes regarding specific sleep stage duration, sleep quality, total sleep time, and sleep efficiency, the number of arousals has been found to have doubled at a high altitude.[16] No changes in the frequency of periodic breathing have been reported, with the exception of isolated central events and a lower mean oxygen saturation at a high altitude.[16]

It is of note that the polysomnographic study that we conducted in Bucaramanga showed upper airway resistance syndrome in our patient. This finding is noteworthy because of the ongoing debate regarding this condition and the diagnostic approach to, health implications of, and therapeutic options for it.[17-20] Further comparative studies are needed, especially in Colombia and other countries with similar geographic characteristics, barometric pressure, and climate, in order to provide a better understanding of the characteristics of sleep disorders, improve detection programs, correct disturbances, and provide more treatment options tailored to each individual.

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Extracorporeal membrane oxygenation in an awake patient as a bridge to lung transplantation

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TO THE EDITOR:

Lung transplantation (LTx) is an established treatment modality for advanced lung disease. Although the number of lung transplants is on the rise worldwide,[1] there is a risk of underlying disease progression in patients awaiting LTx, especially those with interstitial lung disease that progresses to respiratory failure requiring ventilatory support. Invasive mechanical ventilation (IMV) is the most common method of providing ventilatory support until LTx. However, IMV increases the risk of infections and can cause muscle failure as a result of patient immobilization and sedation drug use. Therefore, the use of an alternative method can increase the chances of successful LTx.

Although the use of extracorporeal membrane oxygenation (ECMO) as a bridge to LTx is common in transplant centers in North America and Europe, it remains limited in Brazil. ECMO is indicated for patients presenting with deterioration of respiratory function and hypoxemia or severe hypercapnia; in such cases, venovenous ECMO can maintain adequate gas exchange and acid-base balance. Although ECMO is mostly used in patients on IMV, the use of ECMO in patients who are awake and not receiving mechanical ventilation is an interesting and increasingly used alternative.[2]

Here, we report the case of a 41-year-old male patient diagnosed with systemic lupus erythematosus and pulmonary fibrosis secondary to connective tissue disease. The patient had been receiving continuous oxygen therapy for six months when he was referred for lung transplant evaluation. His FEV_1 was 2.01 L (56% of predicted), his FVC was 2.07 L (43% of predicted), and his DLCO was 31%. A few months after being added to the waiting list for LTx, the patient sought emergency room treatment, presenting with worsening dyspnea and hypoxemia. Initial management included supplemental oxygen via a nonrebreather mask and empirical antibiotic therapy. Test results showed disease progression, the patient being bedridden with severe hypoxemia. He was placed on noninvasive mechanical ventilation (NIMV) at high oxygen flow rates (an FiO_2 of 100%), and, given the imminent need for ventilatory support, the decision was made to start venovenous ECMO, the patient remaining awake. Inflow cannulation was performed in the right jugular vein, and outflow cannulation was performed in the right femoral vein, a coated circuit being used (Maquet, Rastatt, Germany). A request was made to the technical subcommittee to prioritize the patient on the waiting list for LTx. The ECMO settings were as follows: blood flow, 4 L/min; FiO_2, 100%; and gas flow, 4-5 L. Anticoagulation with heparin was used in order to maintain an activated clotting time of 180-220 s. The patient remained awake, was fed orally, and underwent physiotherapy. He was initially placed on intermittent NIMV, being subsequently switched to a nasal cannula (Figure 1). On postadmission day four, a compatible organ, from a 37-year-old donor (PaO_2, 240 mmHg), became available.

The patient underwent bilateral LTx, having remained on ECMO throughout the procedure, without reversal of anticoagulation. He was extubated on post-transplant day one and remained on ECMO until postoperative day three. The patient was discharged from the ICU on postoperative day ten and from the hospital on postoperative day 22, requiring no supplemental oxygen and ambulating. Pre- and post-transplant blood gas variables are shown in Table 1.

The management of patients awaiting LTx and presenting with respiratory dysfunction constitutes a

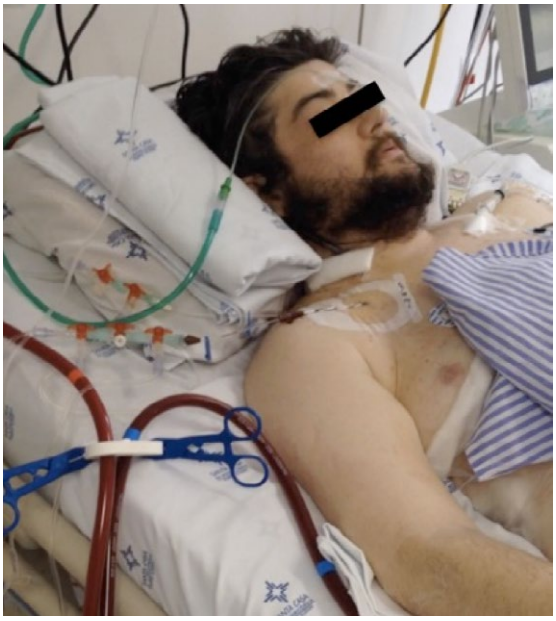

Figure 1. Patient awake and receiving extracorporeal membrane oxygenation.

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Table 1. Arterial blood gas variables and activated clotting time before and after extracorporeal membrane oxygenation and lung transplantation.

Variable	Pre-ECMO	Post-ECMO	IPOP	LTx + ECMO	LTx (Post-ECMO)
pH	7.41	7.41	7.48	7.47	7.42
$PaCO_2$, mmHg	60.5	42.9	41	30	44.8
PaO_2, mmHg	58.5	87.4	111	123	115
HCO_3, mmol/L	37.6	26.9	31	21.7	28.7
BE, mmol/L	10.3	2.5	0.5	-1.0	4.3
SaO_2, %	90	93	99	99	99
ACT		185	190	158	

ECMO: extracorporeal membrane oxygenation; IPOP: immediate postoperative period (with the use of ECMO and mechanical ventilation); LTx: lung transplantation; HCO_3: bicarbonate; BE: base excess; and ACT: activated clotting time.

challenge. Although IMV provides life support, its side effects reduce the chances of successful LTx and have a negative impact on patient outcomes. The use of ECMO in spontaneously breathing patients awaiting LTx constitutes a modern and efficient approach that allows patients to undergo active physiotherapy and feed normally while waiting for a compatible lung.

ECMO was first used as a bridge to LTx in 1975; however, up until the mid-2000s, ECMO had not yielded consistent results. The modernization of the ECMO membrane and circuit greatly improved the efficiency of the system, improving gas exchange and reducing the need for anticoagulation.

Toyoda et al.[3] reported their experience of pre-transplant ECMO at the University of Pittsburgh, comparing a group of patients in whom ECMO was used as a bridge to transplantation (the ECMO group; n = 24) with a group of patients who required no ECMO support before transplantation (the control group; n = 691). Primary graft dysfunction rates were higher and hospital stays were longer in the ECMO group than in the control group; however, one- and two-year survival rates were similar between the two groups (74% vs. 83% and 74% vs. 74%, respectively).

Fuehner et al.[4] studied 60 patients undergoing LTx between 2006 and 2011 and requiring a bridge to transplantation; of those 60 patients, 26 underwent ECMO and 34 underwent IMV. Six-month survival was 80% in the ECMO group and 50% in the IMV group, the postoperative hospital stay being shorter in the ECMO group. These differences might be due to ventilator-associated pneumonia and ventilator-induced diaphragmatic dysfunction. This hypothesis is supported by studies showing that IMV-induced diaphragmatic rest, even for brief periods, results in diaphragmatic dysfunction caused by varying degrees of muscle atrophy, delaying weaning from IMV.[5]

In the case reported here, the use of ECMO allowed our patient to undergo active physiotherapy and receive oral feeding while waiting for a compatible lung. ECMO allowed early extubation (on postoperative day one), being withdrawn on postoperative day three. This resulted in a short ICU stay, having a positive impact on the overall cost of transplantation. At this writing, it had been three years since the procedure was performed, and our patient had preserved lung function.

This was the first case in which our team used ECMO as a bridge to LTx, and the excellent result is consistent with the literature.

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Summary: An abstract in English, corresponding in content to the abstract in Portuguese, should be included.

Keywords: Three to six keywords in Portuguese defining the subject of the study should be included as well as the

corresponding keywords in English. Keywords in Portuguese must be based on the Descritores em Ciência da Saúde (DeCS, Health and Science Keywords), published by Bireme and available at: http://decs.bvs.br, whereas keywords in English should be based on the National Library of Medicine Medical Subject Headings (MeSH), available at: http://www.nlm.nih.gov/mesh/MBrowser.html.

Text:

Original articles: For original articles, the text (excluding the title page, abstracts, references, tables, figures and figure legends) should consist of 2000 to 3000 words. Tables and figures should be limited to a total of five. The number of references should not exceed 30. Original articles should be divided into the following sections: Introduction, Methods, Results, Discussion, Acknowledgments, and References. The Methods section should include a statement attesting to the fact the study has been approved by the ethics in human research committee or the ethics in animal research committee of the governing institution. There should also be a section describing the statistical analysis employed, with the respective references. In the Methods and Results sections, subheadings may be used, provided that they are limited to a reasonable number. Subheadings may not be used in the Introduction or Discussion.

Review and Update articles: Review and Update articles are written at the request of the Editorial Board, which may occasionally accept unsolicited manuscripts that are deemed to be of great interest. The text should not exceed 5000 words, excluding references and illustrations (figures or tables). The total number of illustrations should not exceed eight. The number of references should not exceed 60.

Pictorial essays: Pictorial essays are also submitted only at the request of the Editors or after the authors have consulted and been granted permission by the Editorial Board. The text accompanying such essays should not exceed 3000 words, excluding the references and tables. No more than 12 illustrations (figures and tables) may be used, and the number of references may not exceed 30.

Brief Communications: Brief communications should not exceed 1500 words, excluding references and tables. The total number of tables and figures should not exceed two, and the references should be limited to 20. The text should be unstructured.

Letters to the Editor: Letters to the Editor should be succinct original contributions, not exceeding 800 words and containing a maximum of 6 references. Comments and suggestions related to previously published materials or to any medical theme of interest will be considered for publication.

Correspondence: Authors may submit comments and suggestions related to material previously published in our journal. Such submissions should not exceed 500 words.

Imaging in Pulmonary Medicine: Submissions should not exceed 200 words, including the title, text, and references (no more than three). Authors may include up to three figures, bearing in mind that the entire content will be published on a single page.

Tables and Figures: All tables and figures should be in black and white, on separate pages, with legends and captions appearing at the foot of each. All tables and figures should be submitted as files in their original format. Tables should be submitted as Microsoft Word files, whereas figures should be submitted as Microsoft Excel, TIFF or JPG files. Photographs depicting surgical procedures, as well as those showing the results of exams or biopsies, in which staining and special techniques were used will be considered for publication in color, at no additional cost to the authors. Dimensions, units and symbols should be based on the corresponding guidelines set forth by the Associação Brasileira de Normas Técnicas (ABNT, Brazilian Association for the Establishment of Technical Norms), available at: http://www.abnt.org.br.

Legends: Legends should accompany the respective figures (graphs, photographs and illustrations) and tables. Each legend should be numbered with an Arabic numeral corresponding to its citation in the text. In addition, all abbreviations, acronyms, and symbols should be defined below each table or figure in which they appear.

References: References should be listed in order of their appearance in the text and should be numbered consecutively with Arabic numerals. The presentation should follow the Vancouver style, updated in October of 2004, according to the examples below. The titles of the journals listed should be abbreviated according to the style presented by the List of Journals Indexed in the Index Medicus of the National Library of Medicine, available at: http://www.ncbi.nlm.nih.gov/entrez/journals/loftext.noprov.html. A total of six authors may be listed. For works with more than six authors, list the first six, followed by 'et al.'

Examples: Journal Articles

1. Neder JA, Nery LE, Castelo A, Andreoni S, Lerario MC, Sachs AC et al. Prediction of metabolic and cardiopulmonary responses to maximum cycle ergometry: a randomized study. Eur Respir J. 1999;14(6):1204-13.

Abstracts

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

Chapter in a Book

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

Official Publications

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

Theses

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

Electronic publications

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

Homepages/URLs

7. Cancer-Pain.org [homepage on the Internet]. New York: Association of Cancer Online Resources, Inc.; c2000-01 [updated 2002 May 16; cited 2002 Jul 9]. Available from: http://www.cancer-pain.org/

Other situations:

In other situations not mentioned in these author instructions, authors should follow the recommendations given by the International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. Updated October 2004. Available at http://www.icmje.org/.

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