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Observational study of sleep, respiratory mechanics and quality of life in patients with non-cystic fibrosis bronchiectasis: a protocol study

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ABSTRACT

Introduction: Bronchiectasis is a chronic disorder characterised by permanent and irreversible abnormal dilation of the bronchi and bronchioles, primarily caused by repeated cycles of pulmonary infections and inflammation, which lead to reduced mucociliary clearance and to the excessive production of sputum. Patients with non-cystic fibrosis bronchiectasis may be predisposed to hypoxemia during sleep, or to symptoms that may lead to arousals and thereby reduce the quality of life, because of the irreversible dilation of the bronchi and the presence of secretions and airflow obstruction.

Methods and analysis: For this cross-sectional observational study, patients with a clinical diagnosis of non-cystic fibrosis bronchiectasis will be recruited from the Bronchiectasis Clinic of the Pneumology Department of the Santa Casa de Misericordia Hospital and the Federal University of São Paulo (São Paulo, Brazil). Patients of either sex will be included if high-resolution CT of the thorax and classic sweat test confirms they have non-cystic fibrosis bronchiectasis, are between 18 and 80 years old, use long-acting bronchodilators, are clinically stable for a least 1 month, agree to participate in the study and they sign a statement of informed consent. The first part of the study will involve a clinical evaluation, maximal respiratory pressures, spirometry and the Saint George's Respiratory Questionnaire. The Sleep Laboratory of the Master's and Doctoral Postgraduate Program in Rehabilitation Sciences of the Nove de Julho University (São Paulo, Brazil) will perform the polysomnographic studies, Berlin Questionnaire, Epworth Sleepiness Scale, waist and neck circumferences, modified Mallampati classification and tonsil index.

Ethics and dissemination: This protocol has been approved by the Human Research Ethics Committees of Santa Casa de Misericordia Hospital (process number 178/2012) and Human Research Ethics Committee of Nove de Julho University (process number 370474/2010). All participants will sign a statement of informed consent. The study findings will be published in peer-reviewed journals and presented at conferences.

Strengths and limitations of this study

- In the past four decades, scientific interest in sleep patterns has grown steadily. The results of epidemiological studies are applicable in clinical practice, and in the planning and implementation of public policies and programmes to control sleep disorders, and to assess their impact on individuals and societies.
- We hypothesise that patients with non-cystic fibrosis bronchiectasis due to irreversible dilation of the bronchi, and the presence of secretions and airway obstruction, may be predisposed to hypoxaemia during sleep or to symptoms that may lead to awakenings and thereby reduce the quality of life.
- There is scant research involving bronchiectasis and sleep. To our knowledge, only two studies exist. However, neither study used the gold standard—polysomnography—for evaluating sleep disorders.
- Such studies may contribute to a better understanding of the clinical course to explore potential therapeutic interventions for patients with bronchiectasis.
- The limitations of this study are related to the observational nature of its design, and due to the fact that all patients will be on medication for maintenance bronchodilator, which is relevant because the patients studied will need to undergo polysomnography with optimal medical therapy and clinical stability for at least 1 month, otherwise the results could vary substantially.

BACKGROUND

Bronchiectasis is a chronic disorder characterised by permanent and irreversible abnormal dilation of the bronchi and bronchioles, primarily caused by repeated cycles of pulmonary infections and inflammation, which lead to reduced mucociliary clearance and to the excessive production of sputum.[1–3] This condition is more frequent in females and generally occurs in the sixth decade of life. The most common clinical manifestations are chronic cough, fever, excessive purulent expectoration, sinusitis and muscle fatigue. Crackles are often present on auscultation and spirometry findings show airflow obstruction.[4–6]

The prevalence of bronchiectasis is not well defined and likely varies significantly in different populations.[7] It is estimated that at least 110 000 adult patients in the USA are diagnosed with bronchiectasis with prevalence rates of 4.2/100 000 individuals for patients aged 18–34 years and 272/100 000 individuals for patients 75 years or older.[8] Particular demographic groups (eg, individuals with little access to healthcare, those who live under deprived socioeconomic conditions and those who had high rates of lung infection in childhood) are at greater risk for bronchiectasis.[2 9] In a study of 42 500 hospitalisations at a Brazilian hospital specialising in lung diseases, 0.4% (170) patients hospitalised between 1978 and 2001 were diagnosed as having bronchiectasis.[10] Another recent study in Germany found an average annual rate of 9.4 bronchiectasis admissions per 100 000 population.[11]

High-resolution CT (HRCT) of the chest,[12–14] which is the gold standard used for diagnosing non-cystic fibrosis bronchiectasis, is increasing the diagnosis of this condition, despite the under-investigation of the general and functional characteristics of patients, especially in developing countries.[4 7] The aetiopathology of bronchiectasis is non-specific and is the final stage of diverse pathological processes. The most common condition is idiopathic, followed by postinfectious conditions or systemic diseases.[15] In a recent Brazilian study,[16] a major cause of bronchiectasis was infection, closely followed by pulmonary tuberculosis. On the basis of radiological examination, bronchiectasis can be classified as 'cylindrical', 'tubular', 'varicose', or 'vesicular'.[2] Because of irreversible dilation of the bronchi, and the presence of secretions and airflow obstruction, patients with non-cystic fibrosis bronchiectasis may be predisposed to hypoxaemia during sleep or to symptoms that may lead to arousals, thereby reducing the patient's quality of life (QoL).

To our knowledge, only two studies involving bronchiectasis and sleep exist. One study[17] was conducted in children with non-cystic fibrosis bronchiectasis, with the aim of assessing sleep quality through the administration of specific questionnaires. The authors of the study observed that these patients experienced sleep disorders in association with disease severity and that nocturnal symptoms increased the risk of poor sleep quality.[17]

The second study,[18] which involved adults, also used specific questionnaires to investigate the prevalence of sleep disturbances and determinants associated with sleep disturbances. Compared to healthy subjects, adults with steady-state bronchiectasis had a higher prevalence of sleep disturbances (based on the Pittsburgh Sleep Quality Index (PSQI) score >5), but not daytime sleepiness (based on the Epworth Sleepiness Scale (ESS) score ≥10). Compared to patients without sleep disturbances, patients with sleep disturbances had a more significantly impaired QoL that affected all domains. The author concluded that assessment and intervention of sleep disturbances are warranted and may improve the QoL.[18]

However, neither study used the gold standard—polysomnography (PSG)—for evaluating sleep disorders. Such studies may contribute to a better understanding of the clinical course to explore potential therapeutic interventions for patients with bronchiectasis.

We hypothesise that patients with non-cystic fibrosis bronchiectasis have a high prevalence of sleep disorders with oxyhaemoglobin desaturation and arousals during sleep, and consequent impairment in the QoL. The main objective of the present study is to describe sleep in patients with non-cystic fibrosis bronchiectasis through a complete nocturnal sleep study (ie, PSG). The secondary objectives are to stratify these patients by the risk of obstructive sleep apnoea (OSA) syndrome and excessive daytime sleepiness, and to assess the QoL.

METHODS/DESIGN
Study design and ethical considerations

A cross-sectional observational study will be performed at the Sleep Laboratory of the Master's and Doctoral Postgraduate Program in Rehabilitation Sciences of the Nove de Julho University (São Paulo, Brazil), and patients will be recruited from the Bronchiectasis Clinic of the Pneumology Department of the Santa Casa de Misericordia Hospital (São Paulo, Brazil) and the Pneumology Sector of the Federal University of São Paulo (São Paulo, Brazil) (figure 1).

The design, conduction and reporting of this study will follow the norms of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement,[19] and will agree to the ethical standards established in the 1961 Declaration of Helsinki (as revised in Hong Kong in 1989, and in Edinburgh, Scotland, in 2000) and the Regulatory Guidelines and Norms for Research Involving Human Subjects of the National Health Board of the Brazilian Health Ministry issued in October 1996.

This protocol has been approved by the Human Research Ethics Committees of Santa Casa de Misericordia Hospital (São Paulo, Brazil; process number 178/2012) and Human Research Ethics Committee of Nove de Julho University (São Paulo, Brazil; process number 370474/2010). All participants will sign a statement of informed consent. They will be allowed to
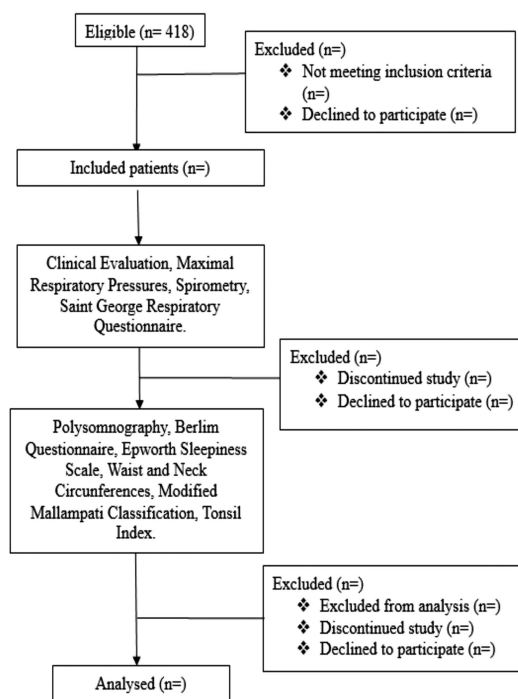
Figure 1 Design of the study.

abandon the study at any time, with no negative consequences. All procedures of the study will be confidential.

Eligibility criteria

The ethics committees approved the study. Patients must provide written, informed consent before any study procedures are performed. The bronchiectasis diagnosis will be based on chest HRCT, which is the gold standard for detecting the disease. The initial population includes 418 patients with bronchiectasis.

Inclusion criteria

Patients will be included after HRCT of the thorax and classic sweat test confirm non-cystic fibrosis bronchiectasis. Other inclusion criteria are an age of 18–80 years, either sex, clinical stability for a least 1 month, agreement to participate in the study and signing of the statement of informed consent.

Exclusion criteria

The exclusion criteria were patients with bronchiectasis stemming from cystic fibrosis (ie, chloride level in sweat >60 mmol/L), patients with other lung diseases and/or other comorbidities that may affect the diagnosis and/or a prognosis of disease outcome, patients with a smoking history, patients participating in another research protocol, or patients unable to understand any of the questionnaire.

Clinical evaluation

Physical examination will be performed to measure the systemic arterial pressure, heart rate, respiratory rate, pulmonary auscultation, anthropometric data, circumference

measurements (of the waist and neck), tonsils and Mallampati index.[20][21] Furthermore, specific questionnaires will be administered to determine the risk of OSA, excessive daytime sleepiness and QoL. After the physical examination, all participants will undergo pulmonary function tests (eg, spirometry and maximum respiratory pressure) and standard overnight PSG.

Anthropometric measurements

Body weight, height (model 200/5 anthropometric scale; Welmy Industria e Comercio Ltd, São Paulo, Brazil), neck circumference and waist circumference (WC) will be measured. The body mass index (BMI) will be calculated as follows: BMI=weight (kg)/height^2 (m^2). Circumferences will be measured using an inelastic tape with one-millimetre precision. The WC will be measured at the midpoint between the inferior costal margin and the upper iliac crest. The hip circumference will be obtained at the level of the femoral trochanters. The neck circumference will be measured below the cricoid cartilage and then at the level of the mid cervical spine.[22] This study will use the WHO cut-off points for WC (ie, >102 cm for men and >88 cm for women) and waist/hip ratio (ie, >1 for men and >0.85 for women).[23] The mobility and range of motion are provided by maximum inspiration and expiration.[22][24]

Sleep evaluation
Epworth sleepiness scale

The ESS is a simple and self-administered questionnaire with items addressing situations involving the occurrence of daytime and sleepiness activities of daily living in adults. The study participants will be instructed to classify their likelihood of feeling the desire to sleep or nap in eight situations on a scale of 0–3 (0, no chance of napping; 1, small chance of napping; 2, moderate chance of napping; and 3, strong chance of napping).[25–27]

Berlin questionnaire

The risk of OSA will be assessed using the Berlin Questionnaire.[28] The Berlin Questionnaire is self-applicable and can therefore be given to the patients so that they can respond without interference from the appraiser. This questionnaire has 10 items organised into three categories, as follows: (1) apnoea and snoring (5 items), (2) daytime sleepiness (4 items); and (3) systemic arterial hypertension and obesity (1 item). All marked responses will be considered positive. The patients will be divided into high risk or low risk of OSA, based on their responses from symptom questions grouped into three categories.

A patient is considered at high risk for OSA if two or more of the three following criteria are positive: (1) snoring with at least two of the following features: it has a higher loudness level than speech, it occurs at least 3–4 times a week, others complain about the patient's snoring, and others witness the patient having breathing pauses at least 3–4 times a week; (2) the patient has

fatigue early in the morning and during the day more than 3–4 times a week or falls asleep at the wheel while driving; and (3) the patient has hypertension or a BMI ≥30 kg/m^2.

Polysomnography

All patients will submit to standard level I PSG with monitoring using the following: EEG, electrooculography, submental electromyography, ECG, nasal cannula pressure transducer, thermistor, snoring sensor, thoracic and abdominal straps, body position sensor and pulse oximetry. The Somnologica Studio–Embla A10 V.3.1.2 sleep analysis system with 16 channels (Flaga; Hs Medical Devices, Reykjavik, Iceland) will be used for the PSG evaluation. All participants will be monitored by a PSG technician. All signals will be recorded continuously and the patients will be instructed to remain as relaxed as possible and sleep naturally, as if at home.[29][30]

The reading of the results will be based on the guidelines of the American Academy of Sleep Medicine (AASM)[31] and the criteria of the Brazilian Sleep Society. Apnoeas will be scored and classified by the recommended respiratory rules for adults suggested by the *AASM Manual for the Scoring of Sleep and Related Events*,[31] and hypopnoeas will be scored according to the alternative rules. Patients with an apnoea-hypopnoea index (AHI) of ≥5 events per hour total sleep time will be classified as having OSA. The AHI will be calculated as the number of apnoeas and hypopnoeas per hour of total sleep time. Hypopnoeas are defined as a discernible drop in air flow by ≥30% of the baseline for at least 10 s, followed by a peripheral oxyhaemoglobin desaturation fall of ≥4%. Apnoeas are defined as a lack of airflow or a reduction of ≥90% in the airflow signal for at least 10 s.[30][31] Readings will be performed manually by a specialised technician. A report of the results will be drafted by a sleep medicine specialist at the Nove de Julho University Sleep Laboratory (São Paulo, Brazil).

Pulmonary function test
Spirometry

All patients will be subjected to forced spirometry in accordance with the guidelines of the American Thoracic Society/European Respiratory Society[32] and the Brazilian Society of Pneumology. Forced vital capacity (FVC), forced expiratory volume in the first second (FEV$_1$) and FEV$_1$/FVC ratio, will be measured before and 15–20 min after the use of a short-acting bronchodilator (ie, albuterol, 400 µg).[33] All tests will be performed during clinical stability (ie, lack of increased dyspnoea, increased sputum and/or change in sputum purulence or change in medication use), and with the discontinuation of short-acting and long-acting β$_2$-agonists, at 6 and 12 h before the test, respectively.

The lung function tests will be performed using the KoKo PFT system, V.4.11 (nSpire Health, Inc, Longmont, Colorado, USA). The patients will perform the test in a comfortable position with the body erect and the upper limbs unsupported. To ensure accurate evaluation and reproducible results, all examinations will be performed by a competent technician trained in obtaining the necessary cooperation from the participants and appropriately operating the equipment. Before each examination, the spirometer will be calibrated using a 3-L syringe.[33]

Maximal respiratory pressures

The maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) are physiologically more suitable tests for determining respiratory muscle strength. The MIP is an indicator of respiratory failure and development of ventilatory capacity, and is indicated for evaluating the degree of abnormality and for monitoring the weakening of inspiratory muscles as the disease progresses in a patient.[34] The MIP and MEP will be determined by ventilatory efforts initiated from the functional residual capacity by requesting maximum inspiration and maximum expiration, respectively. Patients will be subjected to these tests on the same day they perform spirometry.

These tests will be performed in a peaceful environment, and patients will be instructed to breathe calmly and at rest, while sitting comfortably with their trunk at an angle of 90° to the thighs.[34] Patients will be encouraged by the evaluator during the manoeuver to achieve maximum efforts. The manoeuvers will be performed at least three times, separated by 1 min intervals, and with a support according to each; the largest absolute value will be considered for analysis.[35] The maximum ventilatory pressures will be evaluated by an analogue manometer (RECORD-GER-AR; Comércio de Produtos Médicos, Ltd, São Paulo, Brazil), with an operating range of±240 cm H$_2$O.

Quality of life
Saint George's respiratory questionnaire

The QoL will be assessed by the Saint George's Respiratory Questionnaire (SGRQ), which has been previously validated for use in bronchiectasis patients. The questionnaire contains 50 items that are divided into three domains: 'symptoms', 'activities' and 'impacts'. The total score and individual domain score range from 0 to 100. The higher the score, the worse the QoL. The minimal clinically important difference for the SGRQ will be 4 units.[36–38]

Quality control

The researchers in charge of data acquisition in this study will receive specific training to ensure data quality. Periodic external monitoring will be performed to verify the proper application of the methodology in collecting information and conducting the different tests.

Data analysis
Sample size

Because of the paucity of data in the literature regarding the evaluation of sleep disorders in adult patients with non-cystic fibrosis bronchiectasis, a pilot study was used

for the sample size calculation with a prevalence of 0.238 to the variable under study, in which we adopted a 90% confidence level and a 20% error (ie, ±10%). In this study, we determined a sample size of 49 patients.

Proposed statistical analyses

Kolmogorov–Smirnov normality test will first be performed to determine the presence or absence of a normal distribution sample. Descriptive analysis will be performed with the data expressed by the mean and SD, or by the median value and 95% CI, when appropriate. One-way analysis of variance will be used for comparisons between work shifts once the samples have a normal distribution. Lung function values will be linearly correlated with the PSG parameters for which either the Pearson or Spearman correlation test will be used, depending on the sample distribution. The non-paired Student t test or Mann–Whitney test will be used for comparisons between individuals with and without OSA. For the proposed statistical analyses, the level of statistical significance will be set at 5% ($p < 0.05$). Statistical tests will be performed with statistics software (SPSS V.14.0; SPSS, Chicago, Illinois, USA).

DISCUSSION

In the past four decades, scientific interest in sleep patterns has grown steadily. The results of epidemiological studies are applicable in clinical practice, and in the planning and implementation of public policies and programmes, to control sleep disorders and their impact on individuals and societies. The main objective of the present study is to describe sleep in patients with non-cystic fibrosis bronchiectasis through a complete nocturnal sleep study. We hypothesise that patients with non-cystic fibrosis bronchiectasis due to irreversible dilation of the bronchi, the presence of secretions and airway obstruction, may be predisposed to hypoxaemia during sleep or to symptoms that may lead to awakenings and reduced QoL.

Two studies have evaluated sleep in patients with non-cystic fibrosis bronchiectasis, but neither used the gold standard, PSG, to evaluate sleep disorders. To explore potential therapeutic interventions, new studies of patients with non-cystic fibrosis bronchiectasis, which is an orphan disease, may contribute to a better understanding of its clinical course.

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