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HIGHLIGHT

Investigation of chronic dyspnea

Protective mechanical ventilation and acute respiratory distress syndrome

Characterization of patients with asthma-COPD overlap

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Contents

EDITORIAL

Achievements of the last biennium, projections for the coming years, and the impact of COVID-19
Bruno Guedes Baldi, Irma de Godoy

Detailing the mechanisms of chronic dyspnea in patients during cardiopulmonary exercise testing
Zafeiris Louvaris, Daniel Langer, Rik Gosselink

Caring for patients at risk of ARDS: the role of driving pressure
Glauco Cabral Marinho Plens, Eduardo Leite Vieira Costa

Pulmonary rehabilitation after COVID-19
André Vinícius Santana, Andrea Daiane Fontana, Fabio Pitta

CONTINUING EDUCATION: IMAGING

Pericardial effusion
Edson Marchiori, Bruno Hochhegger, Gláucia Zanetti

CONTINUING EDUCATION: SCIENTIFIC METHODOLOGY

Reporting guidelines: essential tools for manuscript writing in medical research
Juliana Carvalho Ferreira, Cecilia M Patino

CONTINUING EDUCATION: RESPIRATORY PHYSIOLOGY

Quantification of oxygen exchange inefficiency in interstitial lung disease
José Alberto Neder, Danilo Cortozi Berton, Denis E O'Donnell

ORIGINAL ARTICLE

ASTHMA

Oral health-related quality of life in individuals with severe asthma
Rebeca Brasil-Oliveira, Álvaro Augusto Cruz, Adelmir Souza-Machado, Gabriela Pimentel Pinheiro, Debora dos Santos Inácio, Viviane Almeida Sarmento, Liliane Lins-Kusterer

THORACIC SURGERY AND RESPIRATORY ENDOSCOPY

Evolution of the surgical treatment of lung cancer at a tertiary referral center in Brazil, 2011-2018
Mariana Schettini Soares, Laura Maria Coltro, Pedro Henrique Cunha Leite, Priscila Berenice Costa, Letícia Leone Lauricella, Paulo Manuel Pêgo-Fernandes, Ricardo Mingarini Terra

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Clinical, laboratory, and functional characteristics of asthma-COPD overlap in patients with a primary diagnosis of COPD
Ana Paula Adriano Queiroz, Fernanda Rodrigues Fonseca, Alexânia de Rê, Rosemeri Maurici

LUNG DISEASES, INTERSTITIAL

Carbohydrate antigen 15-3 as a marker of disease severity in patients with chronic hypersensitivity pneumonitis
Paula Silva Gomes, Maria Raquel Soares, Maria Fernanda Munhoz Lages Marchenta, Gustavo de Souza Portes Meirelles, Rimarcs Gomes Ferreira, André Bezerra Botelho, Rafaela Boaventura Martins, Carlos Alberto de Castro Pereira

RESPIRATORY TRACT INFECTIONS

Charlson Comorbidity Index and other predictors of in-hospital mortality among adults with community-acquired pneumonia
Laura Fuchs Bahlis, Luciano Passamani Diogo, Sandra Costa Fuchs

ISSN 1806-3713

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Jornal Brasileiro de Pneumologia

Continuous and Bimonthly Publication, J Bras Pneumol. v. 47, n. 1, January/February 2021

Contents

SMOKING

Knowledge of and attitudes toward the WHO MPOWER policies to reduce tobacco use at the population level: a comparison between third-year and sixth-year medical students
Stella Regina Martins, André Salem Szklo, Marco Antônio Bussacos, Gustavo Faibischew Prado, Renato Batista Paceli, Frederico Leon Arrabal Fernandes, Elisa Maria Siqueira Lombardi, Rafaela Giunti Basso, Mário Terra-Filho, Ubiratan Paula Santos

CRITICAL CARE

Protective mechanical ventilation in patients with risk factors for ARDS: prospective cohort study
Cristiane Bastos-Netto, Maycon Moura Reboredo, Rodrigo Souza Vieira, Lídia Maria Carneiro da Fonseca, Erich Vidal Carvalho, Marcelo Alcantara Holanda, Bruno Valle Pinheiro

BRIEF COMMUNICATION

Vitamin D: association with eosinophil counts and IgE levels in children with asthma
Claudio Luiz Castro Gomes de Amorim, Joice Mara de Oliveira, Antenor Rodrigues, Karina Couto Furlanetto, Fabio Pitta

META-ANALYSIS

Efficiency of different protocols for oral hygiene combined with the use of chlorhexidine in the prevention of ventilator-associated pneumonia
Ana Carolina da Silva Pinto, Bruna Machado da Silva, Joel Ferreira Santiago-Junior, Sílvia Helena de Carvalho Sales-Peres

REVIEW ARTICLE

Environmental air pollution: respiratory effects
Ubiratan de Paula Santos, Marcos Abdo Arbex, Alfésio Luis Ferreira Braga, Rafael Futoshi Mizutani, José Eduardo Delfini Cançado, Mário Terra-Filho, José Miguel Chatkin

Pulmonology approach in the investigation of chronic unexplained dyspnea
Danilo Cortozi Berton, Nathalia Branco Schweitzer Mendes, Pedro Olivo-Neto, Igor Gorski Benedetto, Marcelo Basso Gazzana

LETTERS TO THE EDITOR

Agreement among four portable wireless pulse oximeters and in-office evaluation of peripheral oxygen saturation
Saulo Maia d'Avila Melo, Marília Ferraz de Oliveira Macedo, Juliana Silva Santana Pereira

Impact of extracorporeal membrane oxygenation in lung transplantation
Diego Corsetti Mondadori, William Lorenzi, Marlova Luzzi Caramori, Cristiano Feijó Andrade, Maurício Guidi Saueressig

Effect of very vigorous physical activity on cardiac autonomic modulation in smokers and nonsmokers: an epidemiological study
Diego G D Christofaro, William R Tebar, Bruna T C Saraiva, Gabriela C R Silva, Luiz Carlos M Vanderlei

Reference equations for plethysmographic lung volumes in White adults in Brazil as derived by linear regression
Thamine Lessa, Carlos Alberto de Castro Pereira, Maria Raquel Soares

Migratory pulmonary infiltrates in a patient with COVID-19 and lymphoma
Alfredo N C Santana, Felipe X Melo, Flavia D Xavier, Veronica M Amado

IMAGES IN PULMONARY MEDICINE

Calcified metastases of teratoma
Luciana Volpon Soares Souza, Arthur Soares Souza Jr, Edson Marchiori

ERRATUM

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Achievements of the last biennium, projections for the coming years, and the impact of COVID-19

Bruno Guedes Baldi[1,2], Irma de Godoy[3,4]

At the beginning of 2019, the perspectives for the following four years of management of the *Jornal Brasileiro de Pneumologia* (JBP) and the *Sociedade Brasileira de Pneumologia e Tisiologia* (SBPT, Brazilian Thoracic Association) were presented.(1) However, the COVID-19 pandemic resulted in the need to adapt the SBPT plans dramatically in 2020; its employees, directors, and members deserve to be commended for their invaluable contributions to that process

The COVID-19 pandemic also undoubtedly had a significant impact on the JBP. There was an increase in submissions, many related to COVID-19, which necessitated the active participation of editors and reviewers in order to determine what should be considered pertinent. The significant number of COVID-19-related submissions resulted in a similar challenge for the various journals in the field of respiratory medicine. The rapid evolution over a short period of time that science provided in the management of COVID-19 was noteworthy and unprecedented. The participation of several Brazilian researchers in national and international collaborations, resulting in the publication of robust studies that certainly contributed to increasing knowledge and improving the management of COVID-19, is also of note.(2-5) However, a colossal number of studies have been published on such subject, many of which have not employed the appropriate methodology or followed the principles of evidence-based medicine, producing results without sufficient novelty.

Six hundred articles were submitted to the JBP in 2020 (50% more than in 2019), of which 416 (69%) were related to studies conducted in Brazil. As a result, the rate of rejection increased and is currently 78%. In 2020, the journal received 90 COVID-19-related submissions, including editorials, letters to the editor, original articles, and review articles, only 20 (22%) of which were accepted for publication. One of the major challenges for editors and reviewers was to determine which COVID-19-related manuscripts would be relevant to JBP readers and were of adequate methodological quality. In addition, because of the urgency of the situation, we attempted to accelerate the evaluation, peer-review, and publication of articles regarding COVID-19. Once again, we must praise the work of the JBP editors and reviewers, not only because of the greater volume of articles to be evaluated but also (and primarily) because many of them work on the front lines in the fight against COVID-19.

In the last two years, a number of modifications have been implemented in the JBP, with the fundamental support of the SBPT: alignment with some SciELO proposals regarding the Open Science movement, such as the continuous publication of articles; a reduction in the time from submission to the response to authors, as well as in the time from approval to publication; discontinuation of the publication of the print version, which reduced the costs; dissemination of select articles via JBP social networks and on SBPT podcasts; creation of a continuing education series on respiratory physiology; expansion of the publication of consensus and guidelines on the main respiratory diseases, including the use of the Grading of Recommendations Assessment, Development and Evaluation methodology for the pharmacological approach(6); prioritization of articles with a greater clinical applicability; expansion of the number of editorials written by international authors; updating instructions to the authors and reviewers; and management of the Digital Object Identifiers directly by the JBP, thus streamlining their registration in the CrossRef database. During this period, the impact factor of the JBP has increased in the main international databases, reaching 1.87 in *Journal Citation Reports* and 1.80 in the *Scimago Journal & Country Rank* database.(7,8)

Some of the objectives and challenges for the next biennium include the following: to expand the role of the Vice-Editor in the JBP; to optimize the transition to the next board of directors; to establish rules for the SBPT guidelines, facilitating their uniformity and standardization with other international guidelines; to modernize the JBP website, increasing the speed of access; to further adapt to the measures recommended by the Open Science Collaboration, including allowing the submission of articles deposited on preprint servers(9); to limit the submission of manuscripts exclusively to those in English, while still publishing all articles in English and Portuguese; to continue producing relevant, up-to-date material regarding COVID-19; to expand the group of reviewers and to improve the peer-review process, thus increasing the quality of the articles submitted; and to garner greater interest from international researchers who are looking to submit good quality manuscripts.

Honoring its mission to offer quality continuing education to its members and to the population, the SBPT has reconfigured its performance, with the necessary urgency, without sacrificing scientific quality. The channels of

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communication have been expanded, and new products have been created by using online resources to provide the best existing evidence for the management and treatment of COVID-19 and other respiratory diseases. The SBPT has successfully organized innovative events such as the SBPT Virtual Conference. There were achievements related to professional practice, and the quality and security of the process of certifying new pulmonologists was guaranteed through the use of new formats. Member incorporation of and adherence to the new forms and products were quite gratifying to the SBPT Board of Directors.

As demonstrated above, the autonomy of the JBP revealed its efficiency. The 2021-22 administration, within the four-year plan initiated by the previous administration, will continue the projects initiated or scheduled, making the modifications necessary to adapt to the epidemiological context of the moment and to advances of scientific knowledge. Our proposals include the following: to meet the diversified demand in information technology to maintain and implement new activities that encourage the participation of members, which will be covered through the *Atualizar* ("Update") program; to continue to include new participants in SBPT events, guaranteeing the multiplicity and diversity of ideas regarding the scientific merit of each area (to that end, it is important to promote the activities of the New Leadership Commission); to strengthen relationships with medical institutions, such as the Brazilian Federal Medical Council, the Brazilian Medical Association, and state health care agencies, in order to coordinate measures related to the pandemic and to further the practice of respiratory medicine; and to promote activities to enable members to practice telemedicine activities and other new methods in pulmonology. In addition, partnerships with national and international medical societies will be prioritized, according to the interests of SBPT members, such as training courses, participation in events, lecturer exchange, and the development of guidelines. We will also attempt to create opportunities to demonstrate the importance of disseminating complementary knowledge, of promoting transversality in health care, and of encouraging a multidisciplinary approach. We will seek to ensure that the activities defined as *atos médicos* ("physician-performed procedures") are always respected. Our goals also include maintaining transparency in all aspects, including the financial activities of the SBPT. Other major goals include developing campaigns to stimulate communication, opening spaces for receiving feedback from our associates and from other sectors of society.

Local (state) societies are fundamental for coordinating the practice of respiratory medicine at the national level. Therefore, it is essential to maintain continuously a close partnership with such societies.

We thank everyone who participated in the activities of the SBPT and JBP in the last biennium, especially in 2020, to face the challenges imposed by COVID-19. We must also exalt the hard work of pulmonologists and other professionals working in the area of respiratory medicine in the fight against COVID-19 throughout Brazil. We count on the support of the SBPT members, authors, and reviewers to face the challenges of the next biennium, during which they will certainly continue to make valuable contributions to improve the SBPT and JBP. We hope that the pandemic will be definitively controlled as soon as possible so that face-to-face or hybrid meetings will again be possible.

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EDITORIAL

Detailing the mechanisms of chronic dyspnea in patients during cardiopulmonary exercise testing

Zafeiris Louvaris[1,2], Daniel Langer[1,2], Rik Gosselink[1,2]

Dyspnea is a distressing symptom that is defined as "the subjective experience of breathing discomfort".[1] The onset of dyspnea can be acute (during the transition from rest to physical activity) or chronic (persisting for more than one month).[1] Chronic dyspnea is one of the most common symptoms of many chronic diseases and conditions, such as cardiorespiratory diseases, cancer, and obesity, reducing exercise tolerance, physical activity levels, and health-related quality of life.[2] Epidemiological studies have estimated that 56-98% of patients with chronic respiratory diseases and 50-70% of patients with cancer complain of dyspnea, which can be the cause of up to 50% of admissions to ERs, with a peak incidence in patients between 55 and 69 years of age.[3]

Pathogenesis-directed therapy of underlying mechanisms is the cornerstone of the management of chronic dyspnea; however, dyspnea can persist despite optimal treatment of the underlying pathophysiology.[4] Identification of chronic dyspnea requires careful medical history taking, as well as physical examination and testing, typically including electrocardiography, chest X-ray, pulse oximetry, spirometry, and blood workup.[5] Nevertheless, even after the aforementioned clinical assessments, the origin of chronic dyspnea can remain unexplained in a large proportion of patients.[6] Therefore, it has been proposed that physiological stress-induced cardiopulmonary exercise testing (CPET) can help identify etiologies of dyspnea that are often missed in standard clinical examinations.[7]

In a review article published in the current issue of the JBP, Berton et al.[8] highlight the clinical utility of CPET in the evaluation of dyspnea. On the basis of clusters of findings in the literature, the authors describe a comprehensive approach to the predominant pathophysiological responses (Figure 1) that can lead to intolerable dyspnea during exercise, namely: a) oxygen delivery/utilization mismatch; b) mechanical ventilatory impairment; c) impaired gas exchange/altered ventilatory control; d) increased metabolic demands due to obesity; and e) dysfunctional breathing/hyperventilation disorders. In addition, the authors contrast those pathophysiological patterns with normal responses to CPET found in the literature, thus providing greater mechanistic insight into the genesis of dyspnea.

The review article by Berton et al.[8] makes a significant contribution to this field of study. The authors have provided pragmatic identification and interpretation of CPET responses that, if integrated into standard clinical examination and testing, can help health care professionals and clinicians identify potential sources of dyspnea. In 2020, Neder et al.[7] took another important step toward the identification of sources of dyspnea by establishing a frame of reference (established in healthy men and women between 20 and 85 years of age) for assessing the intensity of exertional dyspnea based on percentiles derived from the Borg scale score (0-10) at standardized work rates and minute ventilation during CPET.

Traditionally, CPET measures cardiovascular, respiratory, and metabolic responses. Berton et al.[8] highlighted the need for CPET to include additional assessments, such as pulmonary arterial pressure measurement and laryngoscopic assessment of vocal fold motion, to identify potential origins of dyspnea when central hemodynamic abnormalities or laryngeal obstruction are suspected. In this context, research increasingly acknowledges the utility of assessing inspiratory neural drive by diaphragmatic electromyography (EMGdi) with an esophageal catheter during CPET.[9] In fact, in a wide range of cardiorespiratory diseases, dyspnea is likely to be related to the load/capacity imbalance of the respiratory muscles.[10] The EMGdi recordings during exercise are closely related to dyspnea across levels of disease severity as well as in healthy individuals.[11,12] In addition, technological advances in the assessment of EMGdi have overcome the technical barriers of the past, such as the patient burden associated with esophageal catheter placement.[9] With regard to the complexity of analyses of EMG data, further advances have enabled a semi-automated method, leading to a more time-efficient analysis of EMGdi signals.[13] Therefore, the evaluation of inspiratory neural drive through its surrogate measure of EMGdi activity during CPET may offer an additional mechanistic insight into the origins of dyspnea across different pathologies.

Dyspnea is a multidimensional symptom resulting from multiple mechanisms (Figure 1). In patients with chronic lung diseases, recent evidence has shown that apart from ventilatory constraints, gas exchange abnormalities, and central hemodynamic impairment, insufficient adjustments in the perfusion of extradiaphragmatic respiratory muscles during exercise, assessed by near-infrared spectroscopy with indocyanine green (NIRS-ICG) for the determination of blood flow index (BFI), are associated with a greater perception of dyspnea.[14,15] One potential mechanism is that local reduction of respiratory muscle oxygenation during exercise increases respiratory muscle metabolic acidosis and sensory afferent traffic innervating respiratory muscles (type

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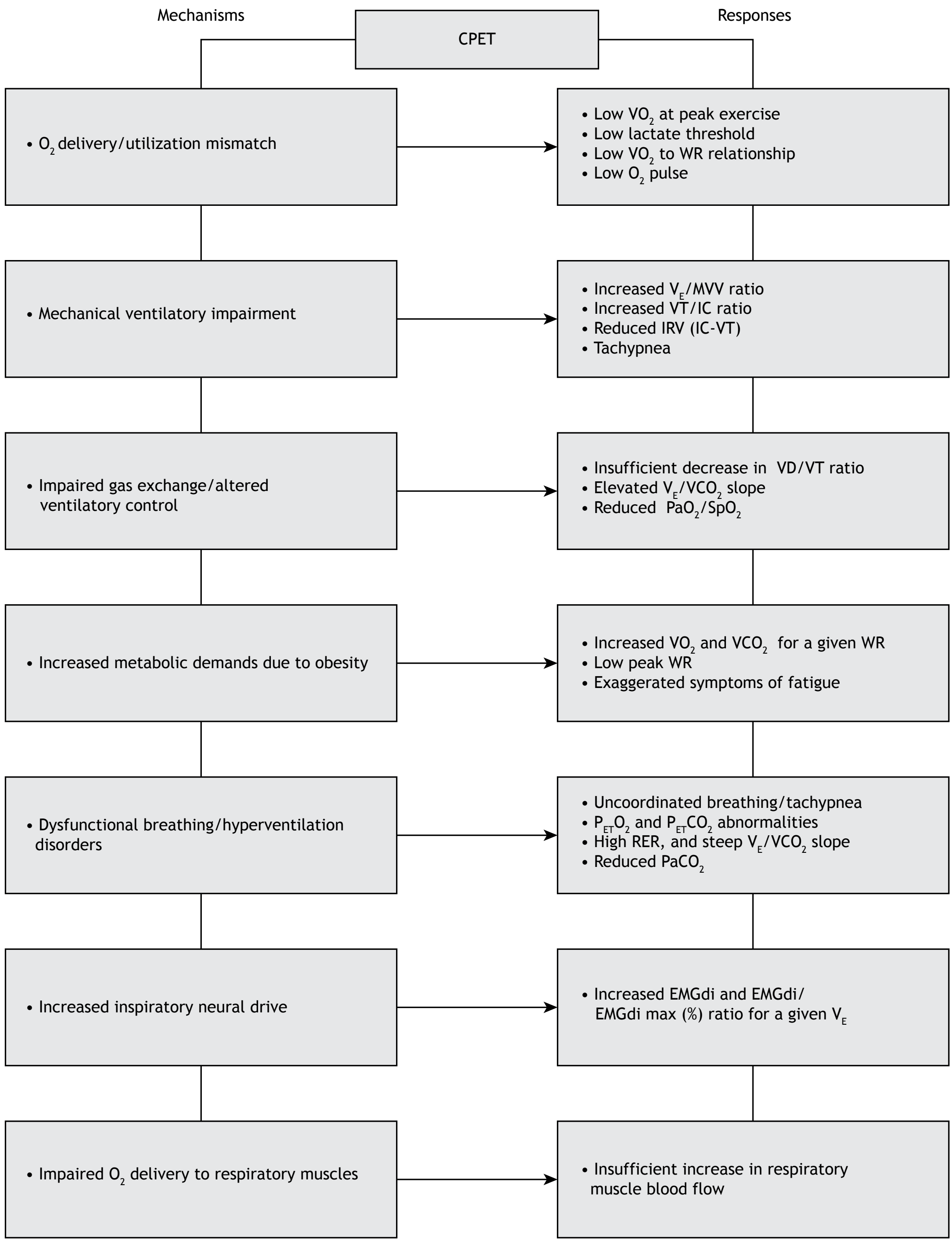

Figure 1. Summary of potential mechanisms and physiological responses during cardiopulmonary exercise testing for the diagnosis of unexplained chronic dyspnea reported in this editorial and by Berton et al.[8] CPET: cardiopulmonary exercise testing; VO_2: oxygen uptake; WR: work rate; V_E: minute ventilation; MVV: maximal voluntary ventilation; IC: inspiratory capacity; IRV: inspiratory residual volume; V_D: physiological dead space; VCO_2: carbon dioxide output; $P_{ET}O_2$: end-tidal oxygen pressure: $P_{ET}CO_2$: end-tidal carbon dioxide pressure; RER: respiratory exchange ratio; and EMGdi: diaphragmatic electromyography.

III–IV fibers) to the somatosensory cortex, thereby increasing the sensory intensity of unsatisfactory inspiration.[15] With the major advantage of avoiding arterial catheterization, NIRS-ICG for the determination of BFI provides a reliable, minimally invasive tool that can be integrated into the standardized CPET for collecting complementary information concerning respiratory muscle (and locomotor muscle) perfusion in order to detect or confirm the absence of this potential origin of dyspnea in various clinical populations.[16]

Identifying the etiologies of chronic unexplained dyspnea is undoubtedly a challenging process. The use of CPET and the translation of the advances described above to clinical settings is a logical step forward in facilitating the determination of the causes of chronic unexplained dyspnea, and the approach can be tailored to the unique physiology of each patient. More importantly, detailing the major physiological mechanisms may facilitate the choice of the appropriate therapeutic interventions.

AUTHOR CONTRIBUTIONS

ZL: conception. ZL, DL, and RG: drafting, revision, and approval of the final version of the manuscript.

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EDITORIAL

Caring for patients at risk of ARDS: the role of driving pressure

Glauco Cabral Marinho Plens[1], Eduardo Leite Vieira Costa[1,2]

Lung-protective strategies in patients with ARDS on mechanical ventilation (MV) are associated with reduced mortality.[1-3] Adherence to these strategies has improved progressively over the last two decades, because increasing numbers of physicians and respiratory therapists have come to recognize lung protection as the cornerstone of supportive therapy.[4] Lung-protective strategies represent a bundle of interventions to reduce lung injury aggravated by MV itself, known as ventilator-induced lung injury. These strategies usually aim to apply low tidal volumes (4-6 mL/kg of predicted body weight), low plateau pressures (< 30 cmH_2O), and enough PEEP to reach oxygenation goals. The rationale is to avoid lung overdistension and to minimize the mechanical stress imposed on the lungs, which are the primary pathophysiological mechanisms of ventilator-induced lung injury.[5] Recently, airway driving pressure (expressed as the difference between plateau pressure and PEEP) has been proposed as the primary variable that can be targeted in order to avoid lung injury. The idea is that limiting driving pressure can be safer in patients with injured lungs. In such patients, the size of the functional aerated lung can be considerably small, a baby lung, to borrow the term coined by Gattinoni et al.[6] The application of tidal volumes normalized to predicted body weight takes into account the size of the patient but not the size of the baby lung, which ends up being overdistended and overstressed.[7] Driving pressure is nothing more than tidal volume normalized to respiratory system compliance, which has been shown to follow closely the size of the functional lung.[8] A patient-level meta-analysis of trials involving patients with ARDS showed that lower driving pressures were associated with improved survival.[9] More importantly, the survival benefit of protective MV strategies was mediated by driving pressures, not by tidal volume or PEEP.[9]

The role of lung-protective strategies in patients without ARDS is less conclusive.[10] In this issue of the *Jornal Brasileiro de Pneumologia*, Bastos-Netto et al.[11] provide important data regarding the impact of lung-protective strategies in patients without ARDS at baseline who presented with risk factors for the disease. In a cohort of 116 patients on MV, the authors found that patients with maximum distending pressures < 15 cmH_2O had a lower 28-day mortality rate. Maximum distending pressure, a surrogate for driving pressure, was defined as the difference between maximum airway pressure and PEEP. In patients under strictly controlled MV, the difference between maximum distending pressure and driving pressure is simply the resistive pressure. As a result, this difference tends to be small, especially when airway resistance is low or when inspiratory and expiratory flows are both close to zero. In the presence of inspiratory or expiratory effort, maximum distending pressure can considerably underestimate driving pressure. In this scenario, end-inspiratory and end-expiratory airway occlusion maneuvers can be used in order to assess the degree of effort.[12] Interestingly, even when considering these limitations in the use of maximum distending pressures, lung protection was better defined when based on distending pressures than when based on tidal volumes: there was no survival benefit with tidal volumes < 8 mL/kg of predicted body weight. This finding is similar to what was found in patients with ARDS by Amato et al.[9] and suggests that, even in patients without ARDS, attention should be paid to distending pressures, especially in those with risk factors for ARDS.

Bastos-Netto et al.[11] have taken an important step toward a better understanding of the determinants of poor outcomes in patients under MV. As new evidence reveals the importance of driving pressure, we should be able to see more of its effects in unforeseen scenarios.

> *What a man sees depends both upon what he looks at and also upon what his previous visual-conception experience has taught him to see.*
>
> \- Thomas S. Kuhn

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EDITORIAL

Pulmonary rehabilitation after COVID-19

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The COVID-19 pandemic, caused by infection with the virus known as SARS-CoV-2, has created a complex scenario for global health, with various types of complications and levels of functional impairment in millions of individuals recovering from the disease. The severe form of the disease causes lung damage and may result in respiratory failure. Subsequently, the affected patients may develop pulmonary fibrosis, a consequence of the process of lung injury repair. Patients presenting with more severe forms of the disease often need respiratory support, which ranges from oxygen therapy to prolonged invasive mechanical ventilation. Prolonged hospitalization of patients requiring intensive care may have severe systemic consequences.[(1)] Although post-COVID-19 sequelae are more common in patients who developed the severe form of the disease, individuals who had moderate disease may also have some degree of functional impairment, as may those who did not require hospitalization.

Post-COVID-19 functional impairment can limit the ability of the individual to perform activities of daily living, reduce functionality, alter professional performance, and hinder social interaction. In addition, the affected individuals can become more sedentary, increasing the risk of comorbidities. Today, although it is still imperative to take action to reduce the risk of mortality, health care facilities need to readjust their strategies to target the physical and functional recovery, as well as the social reintegration, of those individuals through pulmonary rehabilitation.

PULMONARY REHABILITATION AFTER COVID-19

In addition to the disease itself, prolonged hospitalization (with or without the use of mechanical ventilation) can have deleterious effects, such as pulmonary, cardiovascular, muscle, and cognitive changes, as well as anxiety and depression.[(1)] It is not uncommon for a prolonged ICU stay to lead to the development of ICU-acquired muscle weakness, which hinders physical and functional recovery.[(2)] Patients who recover from COVID-19 after a prolonged ICU stay should undergo pulmonary rehabilitation, initially in an individualized, gradual manner during hospitalization, and continuing after hospital discharge in order to mitigate/reverse the consequences of the disease.[(3)] Ideally, the pulmonary rehabilitation of such patients should be conducted by a multidisciplinary team because of the multisystemic impairment caused by COVID-19.

Although early mobilization is essential to the recovery of critically ill patients with COVID-19, many such patients show a rapid drop in oxygen saturation in the beginning of the recovery phase,[(4)] which limits early rehabilitation to some extent. However, other objectives must be considered during hospitalization, such as improving respiratory symptoms and maintaining airway permeability. Therefore, an early bedside approach, special attention being given to any signs of clinical instability of the patient, is recommended.

In patients who have recovered from COVID-19, the physical and functional impairment can persist for weeks after hospital discharge, as can some symptoms (such as dyspnea, desaturation, cough, weakness, and fatigue). In addition to the damage caused by prolonged hospitalization and inactivity, the persistent high inflammatory burden and previous health conditions seem to have a negative influence on the recovery of such patients.[(3,5,6)] A PaO_2/FiO_2 ratio < 324 and BMI ≥ 33 kg/m^2 at hospital admission are independent predictors of persistent respiratory impairment and the need for follow-up.[(5)] To improve the evolution and, consequently, the prognosis of such patients, rehabilitation after discharge is also recommended, given that physical exercise is feasible and useful for survivors of critical illnesses.[(7)] Because there is as yet no large body of evidence on specific physical rehabilitation for COVID-19 survivors, it is recommended that low- to moderate-intensity exercises be prescribed, safety being a priority. The needs and the functional impairment of each individual must also be considered in the rehabilitation program.[(3)] Prior to hospital discharge, the need to use oxygen (at rest or during physical exertion) must also be evaluated.[(3)] Chart 1 describes some of the principles of rehabilitation for COVID-19 survivors.

HOME-BASED PULMONARY REHABILITATION

Given that SARS-CoV-2 continues to have a high rate of infection, physical distancing has still been strongly recommended. Physical distancing makes it practically impossible to carry out traditional outpatient rehabilitation in groups, and rehabilitation programs (including physical exercise programs) should therefore be adapted to be performed at home. The efficacy of home-based rehabilitation has been demonstrated in various studies, including some conducted in Brazil.[(8)] Patients who are more debilitated can also benefit from home-based rehabilitation because it allows them to avoid going to the outpatient clinic, which could hinder adherence to the program and increase the risk of reinfection. In addition,

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Chart 1. Pulmonary rehabilitation for COVID-19 survivors.[3,11,12]

General recommendations

Physical exercises must be adapted to individual needs and limitations of patients; symptoms during physical exercise (such as dyspnea, desaturation, and fatigue) should be taken into consideration; high-intensity exercises are not recommended; patients should receive instruction regarding the physical, psycho-emotional, and nutritional aspects of each stage of rehabilitation; and preventive measures, such as use of alcohol-based hand sanitizers, physical distancing, and personal protective equipment, are essential during the assessment and on-site monitoring of patients at risk of transmitting the virus or at risk of reinfection.

Assessment

- Need for oxygen at rest and on physical exertion; physical, cognitive, and emotional status; dyspnea; anxiety; depression; peripheral muscle strength; and respiratory function (spirometry or plethysmography) in individuals with persistent respiratory symptoms or considerable pulmonary involvement

During hospitalization

- Breathing exercises and bronchial hygiene, if necessary; expectoration into a closed recipient to avoid aerosolization
- Early mobilization in bed; body positioning management (sitting and standing); ambulation and light aerobic exercise (walking or cycling)
- Exercise characteristics
  - Intensity: Borg scale score ≤ 3 with a progressive increase to 4-6; frequency: 1-2 times a day; and duration: 10-45 min

After hospital discharge (6-8 weeks)

- Aerobic exercise: light intensity with gradual increase; 3-5 sessions per week; duration of 20-30 min; and intermittent training for patients with severe fatigue
- Strength training for the lower and upper limbs: progressive resistance training in 2-3 sessions per week, 8-12 repetitions
- Balance exercises, breathing exercises, and bronchial hygiene, if necessary
- Home-based rehabilitation is preferred; if possible, consider instructing family members to help with supervision; if performed at an outpatient clinic, individual sessions are preferable

Considerations for telerehabilitation

- Patient evaluation (via telemonitoring) with application of questionnaires over the telephone or even physical evaluation by videoconference
- Prescription of specific exercises for each patient, allowing them to be supervised (or not) by real-time videoconference
- Diary with information about limitations and occasional discomfort during exercises, to ensure safety
- Verification of the space and the safety of the place where the exercises will be performed
- Aerobic exercises for the lower limbs (e.g., walking)
- Strength training of the upper limbs (e.g., light weights, elastic bands, or other)
- Strength training of the lower limbs (e.g., squats)
- Frequency: at least twice a week to replace supervised training sessions at the outpatient clinic, in addition to an unsupervised home-based exercise program on at least two other days of the week (telemonitoring)
- Reassessment via telemonitoring

patients with severe post-COVID-19 sequelae often need help from family members, who can be trained by health professionals in their own home environment. Individualized rehabilitation of such patients and training of family members in the home environment allows the use of the resources available in each home, with the necessary adjustments, in an environment that is familiar to the patient. Finally, current technological tools (such as software and applications for tablets and cell phones) allow prescription, and remote monitoring of rehabilitation activities, providing greater safety for patients and family members.

TELEREHABILITATION

In an attempt to mitigate difficulties in the process of rehabilitating COVID-19 survivors and to reduce risks, greater attention has been given to telerehabilitation. Telerehabilitation uses telecommunication resources to offer rehabilitation remotely, in real time or not, the benefits of which are similar to those of face-to-face supervised rehabilitation,[9] thus minimizing barriers of distance, time, costs, and risks. The Brazilian Federal Council of Physiotherapy and Occupational Therapy, by means of Resolution no. 516 of March 20, 2020,[10] has authorized the teleconsultation, teleinterconsultation, and telemonitoring services that have already been endorsed by the World Health Organization. Chart 1 describes some principles of telerehabilitation in COVID-19 survivors.

FINAL CONSIDERATIONS

Pulmonary rehabilitation is recommended mainly to improve the physical and functional recovery of COVID-19 survivors before and after hospital discharge. Therefore, it is necessary to consider the needs of each patient carefully by performing a comprehensive assessment. Given the systemic manifestations of COVID-19, survivors should be monitored by a multidisciplinary team. There is as yet no robust body of evidence on the characteristics and effects of specific interventions for COVID-19 survivors. Therefore, current rehabilitation guidelines for that population are mainly based on preliminary results, expert opinions, and previous evidence on the rehabilitation of patients surviving critical illnesses.

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Pericardial effusion

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A 36-year-old woman presented with a two-month history of dry cough, retrosternal pain, episodes of low fever, and dyspnea on heavy exertion. An echocardiogram showed a moderate pericardial effusion (PE) and leaflet thickening. A chest CT scan revealed PE and small nodules in the left upper lobe, demonstrating the tree-in-bud pattern (Figure 1).

PE is an acute or chronic accumulation of fluid in the pericardial sac. In a healthy individual, the pericardial sac contains between 15 and 50 mL of serous fluid. The pericardium has limited elasticity and, in acute settings, only 150-200 mL of fluid is necessary to cause cardiac tamponade. In chronic settings, PE may become 1-2 L in size before it causes cardiac tamponade, as long as the accumulation is gradual and the parietal pericardium has adequate time to stretch and accommodate the increased volume.(1,2)

CT can be useful not only in identifying unsuspected PE but also in providing important information about mediastinal or pulmonary abnormalities that can be a guide to etiological diagnosis. Transthoracic echocardiography is the imaging test of choice for diagnosing PE, quantifying volume, and guiding pericardiocentesis.

PE can be classified by etiology as infectious, inflammatory, neoplastic, traumatic, cardiac, vascular, idiopathic, or other. Infectious PE can have a viral, bacterial, fungal, or parasitic etiology.(1)

PEs are asymptomatic per se unless they cause cardiac tamponade. Tuberculous PE usually develops insidiously, causing nonspecific systemic symptoms, such as fever, night sweats, fatigue, and weight loss. Chest pain, cough, and dyspnea are common.

The patient underwent pericardiocentesis. The pericardial fluid sample was negative for AFB, but the adenosine deaminase (ADA) level was 70 U/L. The patient was started on tuberculosis treatment on the basis of the clinical picture, the CT appearance of the lung lesion, and the high ADA level in the pericardial fluid. She responded well to tuberculosis treatment.

A definitive diagnosis of tuberculous pericarditis is based on demonstration of *Mycobacterium tuberculosis* (direct examination or culture) in pericardial fluid or in a biopsy specimen of the pericardium. A probable diagnosis is made if pericarditis is accompanied by evidence of tuberculosis elsewhere in the body, if pericardial fluid ADA levels are high, or if there is an appropriate response to antituberculosis chemotherapy.(1,2)

In patients suspected of tuberculous pericarditis, measurement of ADA levels should be mandatory, because waiting for pericardial fluid culture results, which not always are positive, can significantly delay the diagnosis. Early diagnosis and institution of appropriate therapy are essential to prevent mortality.

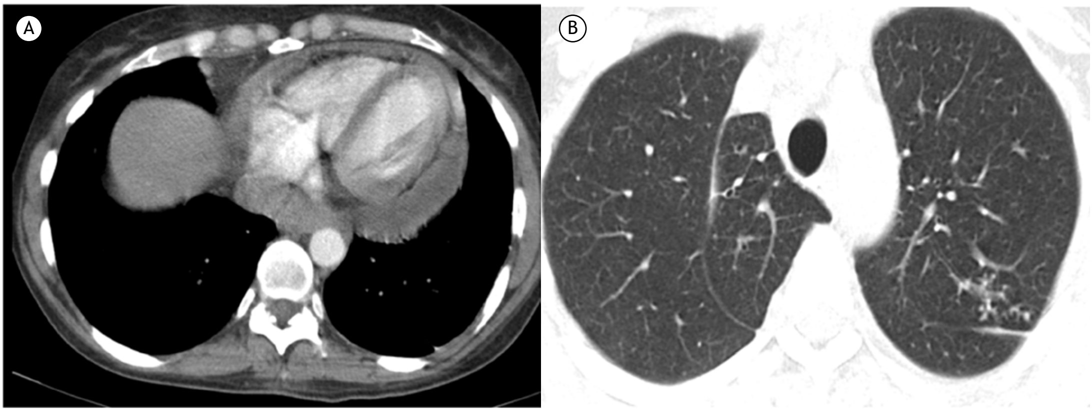

Figure 1. In A, an axial CT slice viewed at mediastinal window settings shows a fluid density collection involving the heart (pericardial effusion). In B, an axial CT slice viewed at parenchymal window settings shows nodular opacities in the upper lobe of the left lung, demonstrating the tree-in-bud pattern.

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Reporting guidelines: essential tools for manuscript writing in medical research

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PRACTICAL SCENARIO

Researchers conducted a prospective cohort study and evaluated mechanical ventilator waveforms to calculate the incidence of patient-ventilator asynchrony[(1)] among 103 patients admitted to the ICU of a university hospital in São Paulo, Brazil. They reported that a high incidence of asynchrony was associated with increased weaning failure, but not with mortality. The publication of the study results was written following the **ST**rengthening the **R**eporting of **OB**servational studies in **E**pidemiology (STROBE) reporting guidelines.[(2)]

WHAT ARE REPORTING GUIDELINES?

Reporting guidelines are tools that guide authors who are writing a scientific paper on specific study items to be reported to increase the research rigor, reproducibility, transparency, and acceptance of the study results and conclusions by the scientific community. Reporting guidelines typically describe the development process and provide researchers with a checklist of recommended items to be reported according to each study design. The checklist is very helpful because it provides authors with a framework that is easy to follow and useful when designing the whole research project: from study protocol development to study implementation, data analysis, and manuscript writing.

Reporting guidelines are specific to each study design (Table 1). The most commonly used reporting guidelines are those developed by the **E**nhancing the **QUA**lity and **T**ransparency **O**f health **R**esearch (EQUATOR) Network, a global initiative that seeks to improve the reporting quality of published health research globally.[(2)] The most widely known EQUATOR guidelines are **CON**solidated **S**tandards **O**f **R**eporting **T**rials (CONSORT) for randomized clinical trials (RCTs) and STROBE for observational studies. Several guidelines share particular items, including the study design in the manuscript title and the participant flow diagram, which informs how many individuals were screened for eligibility, how many were excluded, and why. Other recommended items are specific to each type of study design (e.g., the type of randomization procedure used in RCTs within the CONSORT guideline).

WHY ARE REPORTING GUIDELINES IMPORTANT?

Using reporting guidelines ensures that authors report all critical components of a research study, which helps the reader clearly understand all relevant aspects of the study. This is essential because when a manuscript conveys accurate and complete study information, procedures can be replicated by other researchers, and results can be included in systematic reviews or used by clinicians to inform clinical decision making. For example, when a manuscript reports the findings of an RCT and fails to report how many potential participants were excluded from the trial, the generalizability and the internal validity of the results could be compromised. Similarly, if the manuscript in our practical scenario[(1)] failed to report how many participants had been lost during follow-up, readers would be unable to evaluate the risk of bias in that cohort study. Therefore, the results would not be useful for clinical decision making.

The international research community increasingly recognizes that using reporting guidelines improves the quality of research and helps minimize the waste of resources in poorly reported research studies. As a result, most medical journals that have a high impact require that RCTs be written according to CONSORT guidelines, and most observational studies include STROBE flow diagrams.

Table 1. Reporting guidelines for most study designs.

Study design	Reporting guideline
Randomized trials	CONSORT[a]
Observational studies	STROBE[a]
Systematic reviews	PRISMA[a]
Study protocols	SPIRIT, PRISMA-P
Diagnostic/prognostic studies	STARD
Prognostic studies	TRIPOD
Case reports	CARE[a]
Clinical practice guidelines	AGREE, RIGHT
Qualitative research	SRQR, COREQ
Animal preclinical studies	ARRIVE
Quality improvement studies	SQUIRE
Economic evaluations	CHEERS

Adapted from Equator Network.[(2)] [a]These reporting guidelines have extensions (additional versions) that focus on variations of the study design or are specific for abstracts.

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Quantification of oxygen exchange inefficiency in interstitial lung disease

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BACKGROUND

Hypoxemia (low PaO_2) is a hallmark of moderate-to-severe interstitial lung disease (ILD). Ventilation/perfusion ($\dot{V}/\dot{Q}$) mismatch is a dominant mechanism, with a secondary role for diffusion limitation (at least at rest).(1) In some patients, intrapulmonary shunting and impaired alveolar exchange of oxygen (O_2) can occur ("physiological" shunt [$Shunt_{PHYS}$]),(2) leading to severe, irreversible or nearly irreversible hypoxemia. Because of the effect of gravity on pulmonary blood flow, any shunted fraction can increase in the upright position when extensive alveolar filling is present in dependent areas of the lung in the setting of relatively preserved capillary perfusion.

OVERVIEW

A 23-year-old woman reported progressive dyspnea and dry cough for a few months after an acute episode of fever and sore throat. On examination, she assumed the supine position (SpO_2 = 96% on room air), reporting dyspnea soon after sitting (platypnea); of note, her SpO_2 was consistently < 88% when she was in the upright position (orthodeoxia).(3) No environmental exposures were identified; however, she reported chronic use of nitrofurantoin for urinary tract infections. COVID-19 and HIV testing was negative, as was liver and connective tissue disease workup. Spirometry in the recumbent position (≈30°) revealed severe and proportional reductions in FEV_1 and FVC (Figure 1A). Arterial blood gas analysis after administration of 100% O_2 for 20 min revealed increased right-to-left shunt that almost doubled from the supine to the seated position (Figure 1B). Chest CT showed extensive ground-glass/reticular opacities, septal thickening, and traction bronchiectasis/bronchiolectasis, particularly in the anterior aspects of the lower lobes and in the right middle lobe/lingula (indeterminate usual interstitial pneumonia; Figure 1C). Transesophageal echocardiography

A	Pre-BD	% predicted	Post-BD	% predicted
FVC (L)	1.06	29	0.90	25
FEV_1 (L)	1.05	34	0.74	24
FEV_1/FVC	0.99		0.82	

B	Supine	Supine	Seated
Barometric pressure		760 mmHg (sea level)	
FiO_2	21	100	100
pH	7.43	7.42	7.39
$PaCO_2$ (mmHg)	41.5	47.2	44.6
HCO_3 (mmol/L)	27.7	30.0	26.7
PaO_2 (mmHg)	63.7	510.0	374.0
SaO_2 (%)	94.3	100	100
Estimated PAO_2 (mmHg)	NA	654.0	657.2
Estimated shunt (%)	NA	7.9	14.5

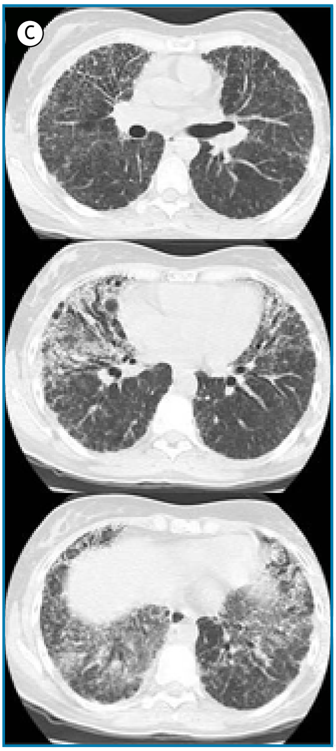

Figure 1. Spirometry (in A), arterial blood gas analysis (in B), and chest CT (in C) in a 23-year-old woman with complaints of progressive dyspnea following chronic nitrofurantoin use. In addition to severe restriction on spirometry and interstitial lung disease with craniocaudal distribution, right-to-left shunt measured during 100% O_2 breathing was increased in the supine position, further increasing in the upright position. BD: bronchodilator; HCO_3: bicarbonate; and PAO_2 = alveolar partial pressure of O_2.

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showed no structural cardiac abnormalities; however, microbubbles appeared in the left chambers every 3-8 beats after their identification in the right atrium (i.e., intrapulmonary shunt).[3] CT pulmonary angiography revealed no pulmonary embolism or arteriovenous malformations.

$Shunt_{PHYS}$ (venous admixture; normal ≤ 10%) can be subdivided into: a) anatomic shunt ($Shunt_{ANAT}$) via bronchial, pleural, and thebesian veins (normal ≤ 5%); b) capillary shunt ($Shunt_{CAP}$), representing pulmonary capillary blood in contact with completely unventilated alveoli; and c) shunt effect (i.e., perfusion in excess of ventilation).[2] Unlike the alveolar-arterial O_2 gradient,[4] $Shunt_{PHYS}$ is independent of the shape of the O_2 dissociation curve, but it requires sampling pulmonary arterial blood to obtain mixed venous oxygen content. Making the subject breathe pure O_2 for sufficient time to wash out nitrogen allows the measurement of the fraction of venous admixture caused by $Shunt_{ANAT}$ plus $Shunt_{CAP}$ (i.e., "absolute shunt") without the confounding influence of $V/\dot{Q}$ inequalities.[2] When intracardiac communication, pulmonary arteriovenous malformations, and hepatopulmonary syndrome are excluded as causes of orthodeoxia in ILD patients, other possible causes include increased $Shunt_{CAP}$ and undetected small arteriovenous channels (≤ 20 µm diameter).[5] The supine position increases venous return, which is more homogenously distributed to better ventilated areas (superior and posterior lung fields in the present case; Figure 1C), reducing the shunted fraction and improving oxygenation and dyspnea.[3]

CLINICAL MESSAGE

Platypnea-orthodeoxia is a potential cause of atypical/paroxysmal dyspnea and refractory hypoxemia in ILD patients in the upright position. Quantification of postural modifications in "absolute shunt" measured during 100% O_2 breathing provides a minimally invasive test of O_2 exchange efficiency that is dependent on changes in regional lung perfusion.

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ORIGINAL ARTICLE

Oral health-related quality of life in individuals with severe asthma

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ABSTRACT

Objective: To evaluate oral health-related quality of life (OHRQoL) among individuals with severe asthma, comparing it with that observed among individuals with mild-to-moderate asthma and individuals without asthma. **Methods:** We conducted a cross-sectional study of 125 individuals: 40 with severe asthma; 35 with mild-to-moderate asthma; and 50 without asthma. We calculated the decayed, missing, and filled teeth (DMFT) index, as well as the Periodontal Screening and Recording index, and determined the stimulated salivary flow rate. We applied three structured questionnaires: the 14-item Oral Health Impact Profile (OHIP-14); the Medical Outcomes Study 36-Item Short-Form Health Survey, version 2 (SF-36v2); and the Work Ability Index (WAI). **Results:** Periodontitis and reduced salivary flow were both more common in the severe asthma group than in the mild-to-moderate asthma and no-asthma groups. In addition, the WAI scores were lower in the severe asthma group than in the mild-to-moderate asthma and no-asthma groups, as were the scores for all SF-36v2 domains. The individuals with severe asthma also scored lower for the OHIP-14 domains than did those without asthma. Although the mean DMFT index did not differ significantly among the groups, the mean number of missing teeth was highest in the severe asthma group. Strong correlations between the SF-36v2 Component Summaries and poorer OHRQoL were only observed in the severe asthma group. **Conclusions:** Severe asthma appears to be associated with poorer oral health, poorer OHRQoL, a lower WAI, and lower scores for SF-36v2 domains.

Keywords: Oral health; Periodontal diseases; Asthma.

INTRODUCTION

Asthma is a variable, heterogeneous condition, characterized mainly by respiratory symptoms, including cough, wheezing, dyspnea, chest tightness, and (usually) reversible airflow limitation that is typically related to airway inflammation.(1) Chronic respiratory diseases affect more than one billion people worldwide, including three hundred million people with asthma.(2) In 2011, the Brazilian National Ministry of Health registered 175,000 hospitalizations for asthma in the country, where asthma accounts for more than 2,000 deaths per year.(3) Although approximately 23% of adults in Brazil presented with wheezing in 2017, only 12% received a physician diagnosis of asthma.(3) According to the World Health Organization (WHO),(4) asthma is underdiagnosed and its prevalence is therefore underestimated.

Because of the high prevalence of chronic respiratory diseases, the WHO recommends that the surveillance, prevention, and control of such diseases be expanded worldwide.(4) Many environmental and genetic factors influence their progression.(5) There is a strong association between respiratory diseases and periodontal disease, which has multiple determinants.(6)

The use of inhaled corticosteroids reduces the risk of severe asthma exacerbations and controls asthma symptoms in adults and adolescents.(1) However, corticosteroids can suppress the local immune system and increase individual susceptibility to infection with certain pathogens.(7) The cells of the immune system produce inflammatory cytokines when activated by pathogens. Those cytokines stimulate macrophages and osteoclasts to release hydrolases, collagenases, and matrix metalloproteinases. Metalloproteinases originating from periodontal disease-related inflammatory processes can affect the tissue structure of the respiratory system, exacerbating bronchial inflammation and worsening the manifestations of asthma.(8-11)

Asthma-related bone resorption is associated with the development of periodontal disease. Regular use of an inhaled corticosteroid can affect bone architecture by initiating a cascade of cellular and tissue events that predispose to bone loss.(12) Pro-inflammatory mediators of periodontal disease may also be associated with bronchial remodeling in individuals with severe asthma.(11) However, there is a gap in knowledge regarding the effect that severe asthma has on oral health-related quality

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of life (OHRQoL). We aimed to compare individuals with severe asthma, individuals with mild-to-moderate asthma, and individuals without asthma, in terms of their OHRQoL.

METHODS

Study design and population

We conducted a cross-sectional study from February of 2017 to November of 2019. The sample consisted of 125 patients, in three groups: a study group—comprising 40 patients enrolled in the *Programa para o Controle da Asma na Bahia* (ProAR, Bahia State Program for the Control of Asthma) with previously-untreated asthma that was categorized as severe in accordance with previous definitions of severity described elsewhere[13]—and two comparison groups—respectively comprising 35 patients with mild-to-moderate asthma, as defined in the Global Initiative for Asthma classification,[14] and 50 individuals without asthma. All of the patients with mild-to-moderate asthma were recruited from among those being followed at the ProAR Referral Outpatient Clinic and were using an inhaled corticosteroid. The individuals without asthma were recruited from among those being treated for other conditions at the ProAR Oral Health Clinic. The study was approved by the Research Ethics Committee of the Federal University of Bahia School of Medicine (Reference no. 2.663.115), in accordance with Brazilian National Health Council Resolution no. 466/2012 and with the 2013 World Medical Association Declaration of Helsinki. All participants gave written informed consent.

Information about demographic and socioeconomic characteristics, as well as about oral hygiene habits and associated comorbidities, were collected by a trained multidisciplinary team. During the anamnesis and clinical examination, the same dentist determined the decayed, missing, and filled teeth (DMFT) index, as well as the Periodontal Screening and Recording (PSR) index, for all participants. The dentist performed the PSR examination with a WHO-approved periodontal probe in the gingival sulcus, evaluating the probing depth (in millimeters) at six sites per tooth, excluding the third molars. The PSR examination can identify gingival bleeding, gingival recession, and calculi. For the identification of gingivitis or periodontitis, we applied the criteria established by the WHO[15] and the European Association of Dental Public Health.[16] Although there is no reference cutoff point for the frequency of tooth brushing, all patients are instructed to brush after meals. At 2 h after breakfast, we collected stimulated saliva samples by conducting salivary mechanical stimulation with sialogogues for 2 min, and asking participants to deposit the accumulated saliva into a graduated sterile tube. The quantity of saliva collected is expressed in mL/min. We defined reduced stimulated salivary flow as < 1 mL/min.[17]

We applied three structured questionnaires[18-20]: the 14-item Oral Health Impact Profile (OHIP-14) to assess OHRQoL; the Medical Outcomes Study 36-Item Short-Form Health Survey, version 2 (SF-36v2) to assess general health-related quality of life (HRQoL); and the Work Ability Index (WAI) to assess the perception that individuals have of their ability to work.

OHIP-14

The OHIP-14 is a comprehensive self-report measure of dysfunction, discomfort, and disability attributed to oral health status, being widely used for evaluating OHRQoL.[18] The OHIP-14 consists of 14 items stratified into seven domains: functional limitation; physical pain; psychological discomfort; physical disability; psychological disability; social disability; and handicap. The responses were classified with a Likert scale, ranging from "never" to "very often". Higher scores translate to a greater impact of oral health and poorer OHRQoL.

SF-36v2

The SF-36v2 consists of 36 items, covering eight domains: physical functioning; role-physical; bodily pain; general health; vitality; social functioning; role-emotional; and mental health. The grouping of these factors generates the Physical Component Summary (PCS) and Mental Component Summary (MCS).[19] We used the software PRO CoRE, version 1.3 (Optum, Inc., Johnston, RI, USA) to score the SF-36v2 survey and obtain the normalized scores.[19] The normalized SF-36v2 scores are adjusted to a mean of 50 with a standard deviation of 10, enabling comparisons between domains. OptumInsight Life Sciences Inc. (Johnston, RI, USA) granted permission to reproduce the output (License no. QM025905).

WAI

The WAI questionnaire[20] has seven components: current work ability in relation to lifetime best; work ability in relation to the demands of the job; current number of physician-diagnosed diseases; estimated work impairment due to disease; sick leave during the last 12 months; own prognosis of work ability 2 years from now; and mental resources. The cumulative WAI ranges from 7 points to 49 points, being categorized as follows[21]: poor (7-27 points); moderate (28-36 points); good (37-43 points); or excellent (44-49 points). The WAI has been translated to Portuguese,[22] as well as having been shown to have satisfactory construct validity for use in Brazil.[23]

Statistical analysis

We used the main outcome variable (OHIP-14 scores) to calculate the power of the test by using the MultNonParam package for RStudio, version 1.2.5019 (RStudio, Inc., Boston, MA, USA). We also used the nonparametric Kruskal-Wallis test, as previously described,[24] employing bootstrap (Monte Carlo) techniques to produce a power estimate based on the empirical cumulative distribution functions of the sample data. We performed a simulation with three groups: severe asthma (n = 40); mild-to-moderate asthma (n = 35); and no asthma (n = 50). The calculated power of the test was 99%, at a p-value of 0.01. Continuous variables are expressed as means and standard deviations, whereas categorical variables are expressed as absolute and relative frequencies. In 10% of the sample, the level of interobserver agreement was determined by calculating the kappa statistic.[25] The internal consistency and reliability of the scales were assessed by Cronbach's alpha, the values of which were considered satisfactory if 0.70-0.80 and ideal if 0.80-0.90.[26] The Kolmogorov-Smirnov test was used in order to evaluate the normality of the distribution. The Kruskal-Wallis test was used in order to determine the magnitude of differences among the three groups, and the Mann-Whitney U test was used in order to compare two independent samples. We evaluated the correlations among the OHIP-14 domains and the SF-36v2 Component Summary scores by using Pearson's correlation coefficient.[27] All statistical analyses were performed with the IBM SPSS Statistics software package, version 21.0 (IBM Corporation, Armonk, NY, USA).

RESULTS

The mean age in the severe asthma group (n = 40) was 51.8 ± 10.8 years, whereas it was 42.5 ± 14.2 years in the mild-to-moderate asthma group (n = 35) and 48.2 ± 12.4 years in the no-asthma group (n = 50).

Female and black/racially mixed individuals respectively accounted for 85.0% and 95.0% of those in the severe asthma group and 85.7% and 94.3% of those in the mild-to-moderate asthma group, compared with 48.0% and 76.0%, respectively, in the no-asthma group. There were no significant differences among the groups in terms of the level of education ($p > 0.05$) and tooth brushing frequency ($p > 0.05$). Most (90.0%) of the individuals in the no-asthma group were receiving a salary above the Brazilian national minimum wage, compared with 57.5% and 54.3% of those in the severe and mild-to-moderate asthma groups, respectively (Table 1).

The proportions of individuals with periodontitis and reduced salivary flow were 92.5% and 80.0%, respectively, in the severe asthma group, higher than the 54.3% and 74.3%, respectively, observed in the mild-to-moderate asthma group and the 14.0% and 26.0%, respectively, observed in the no-asthma group. Only 45.0% of the individuals in the severe asthma group had a sedentary lifestyle, compared with 97.1% of those in the mild-to-moderate asthma group and 60.0% of those in the no-asthma group. The proportion of individuals with a good or excellent WAI was highest (66.0%) in the no-asthma group, whereas that of those with a poor WAI was highest (47.5%) in the severe asthma group (Table 1). The interobserver agreement was substantial (kappa = 0.68).

Cronbach's alpha was ≥ 0.70 for the SF-36v2 domain scores and for the WAI. The WAI was consistently lower among the individuals in the severe asthma group than among those in the mild-to-moderate asthma and no asthma groups, as were the scores for the SF-36v2 HRQoL domains, as well as the PCS and MCS scores (Table 2). There were statistically significant differences among the groups for the SF-36v2 domains physical functioning, role-physical, bodily pain, general health, vitality, and role-emotional, as well as for the WAI ($p < 0.05$ for all). The DMFT index did not differ significantly among groups. However, the mean number of missing teeth was highest in the severe asthma group ($p < 0.05$) and the mean number of decayed teeth was highest (2.5 ± 2.0) in the no-asthma group ($p = 0.03$).

Cronbach's alpha was 0.80 for the OHIP-14 score. The mean scores for all OHIP-14 domains were significantly lower in the severe asthma group than in the no-asthma group (Table 3).

Strong negative correlations between the SF-36v2 Component Summary scores and the OHIP-14 scores (better OHRQoL in the presence of poorer HRQoL) were observed only in the severe asthma group (Table 4). The OHIP-14 domains functional limitation, psychological disability, and social disability correlated significantly with the PCS score, as did the total OHIP-14 score. The OHIP-14 psychological disability domain score and the total OHIP-14 score showed significant negative correlations with the MCS score.

DISCUSSION

In this cross-sectional study, we found that individuals with asthma showed poorer OHRQoL, higher numbers of missing teeth, and lower WAIs than did those without. We also found that individuals with severe asthma showed poorer OHRQoL, lower WAIs, and poorer HRQoL than did those with mild-to-moderate asthma and those without asthma. Negative correlations between the OHIP-14 scores and the SF-36v2 Component Summary scores were seen only in the severe asthma group, underscoring the need to use specific and general instruments in order to assess OHRQoL in individuals with asthma. It is noteworthy that all instruments presented good internal consistency, with Cronbach's alpha values ≥ 0.70. Although monthly incomes were highest in the no-asthma group, there were no significant differences among the groups in terms of the level of education, frequency of tooth brushing, or number of filled teeth. Individuals in the severe asthma group showed much higher numbers of missing teeth, as well as being much more likely to have periodontitis and reduced salivary flow. Access to dental treatment and oral health care was not found to minimize or avoid such alterations.

Table 1. Clinical and demographic characteristics of individuals with severe asthma, individuals with mild-to-moderate asthma, and individuals without asthma. Salvador, Brazil, 2017-2019.

Characteristic	Group			p*
	SA (n = 40)	MMA (n = 35)	NA (n = 50)	
Gender, n (%)				< 0.001
Female	34 (85.0)	30 (85.7)	24 (48.0)	
Male	6 (15.0)	5 (14.3)	26 (42.0)	
Skin color, n (%)				< 0.05
Black	17 (42.5)	16 (45.7)	14 (28.0)	
White	2 (5.0)	2 (5.7)	12 (24.0)	
Other	21 (52.5)	17 (48.6)	24 (48.0)	
Marital status, n (%)				< 0.001
Single	19 (47.5)	26 (74.3)	15 (30.0)	
Married/stable relationship	21 (52.1)	9 (25.7)	35 (70.0)	
Level of education, n (%)				NS
< 9 years of schooling	9 (22.5)	4 (11.4)	12 (24.0)	
9-12 years of schooling	28 (70.0)	27 (77.1)	31 (62.0)	
> 12 years of schooling	3 (7.5)	4 (11.4)	7 (14.0)	
Family income, n (%)				< 0.001
< the minimum wage†	17 (42.5)	16 (45.7)	5 (10.0)	
≥ the minimum wage†	23 (57.5)	19 (54.3)	45 (90.0)	
Smoking status, n (%)				NS
Current smoker	0 (0.0)	1 (2.9)	2 (4.0)	
Former smoker	15 (37.5)	6 (17.1)	19 (38.0)	
Alcohol consumption, n (%)				< 0.001
Current drinker	13 (32.5)	18 (51.4)	3 (6.0)	
Former drinker	7 (17.5)	6 (17.1)	31 (62.0)	
Physical activity, n (%)				< 0.05
Sedentary lifestyle	18 (45.0)	27 (77.1)	30 (60.0)	
Regular activity	22 (55.0)	8 (22.9)	20 (40.0)	
Work Ability Index, n (%)				< 0.001
Poor	19 (47.5)	8 (22.9)	5 (10.0)	
Moderate	18 (45.0)	26 (74.3)	12 (24.0)	
Good/Excellent	3 (7.5)	1 (2.9)	33 (66.0)	
Tooth brushing frequency, n (%)				NS
≤ 2 times a day	19 (47.5)	20 (57.1)	25 (50.0)	
> 2 times a day	21 (52.5)	15 (42.9)	25 (50.0)	
Dental flossing, n (%)	19 (47.5)	17 (48.6)	18 (36.0)	NS
Salivary flow, n (%)				< 0.001
Normal	8 (20.0)	9 (25.7)	37 (74.0)	
Reduced	32 (80.0)	26 (74.3)	13 (26.0)	
Periodontal disease, n (%)				< 0.001
Gingivitis	2 (5.0)	9 (25.7)	15 (30.0)	
Periodontitis	37 (92.5)	19 (54.3)	7 (14.0)	
Systemic arterial hypertension, n (%)	21 (52.5)	6 (17.1)	7 (14.0)	< 0.001
Diabetes, n (%)	3 (7.5)	1 (2.9)	2 (4.0)	NS

SA: severe asthma; MMA: mild-to-moderate asthma; NA: no asthma; NS, not significant.
*Pearson's chi-square test. †Brazilian national minimum wage = 241 USD/month.

Saliva has a number of functions in the oral cavity, including lubrication, mechanical cleaning, buffering capacity, antimicrobial activity, and tissue repair. Low salivary flow reduces the efficacy of these functions[28] and can therefore be considered a possible mediator of the worsened OHRQoL in individuals with asthma. In the present study, 80.0% and 74.3% of the individuals in the severe and mild-to-moderate asthma groups presented with reduced salivary flow, which may contribute to the development of periodontal disease and tooth loss. Monitoring salivary flow helps prevent oral health problems and preserve OHRQoL in patients with asthma. In a previous study, reduced salivary flow was associated with periodontal disease and poor HRQoL in

Table 2. Oral health, general health-related quality of life, and work ability in individuals with severe asthma, individuals with mild-to-moderate asthma, and individuals without asthma. Salvador, Brazil, 2017-2019.

Variable	Cronbach's alpha	Group SA (n = 40) Mean ± SD	Group MMA (n = 35) Mean ± SD	Group NA (n = 50) Mean ± SD	p Overall*	p SA vs. MMA†	p MMA vs. NA†	p SA vs. NA†
Decayed teeth	-	1.4 ± 2.0	1.3 ± 1.5	2.5 ± 2.0	0.003	0.755	0.006	< 0.05
Missing teeth	-	7.9 ± 7.2	5.0 ± 6.2	4.9 ± 2.6	0.031	0.017	0.134	NS
Filled teeth	-	4.2 ± 3.7	4.0 ± 4.0	4.7 ± 4.0	0.632	0.781	0.319	NS
DMFT index	-	13.5 ± 6.5	10.3 ± 6.9	12.0 ± 5.1	0.119	0.059	0.137	NS
OHIP-14 score	0.8	11.0 ± 10.5	6.2 ± 7.4	1.4 ± 2.6	0.001	0.013	0.003	< 0.001
SF-36v2 domain scores								
Physical functioning	0.9	41.5 ± 9.7	47.6 ± 8.6	51.5 ± 7.2	0.001	0.005	0.011	< 0.001
Role-physical	0.9	46.1 ± 10.5	52.3 ± 5.3	48.6 ± 9.1	0.020	0.012	0.016	NS
Bodily pain	0.8	42.6 ± 13.7	46.0 ± 12.0	53.3 ± 9.3	0.001	0.185	0.001	< 0.001
General health	0.7	42.8 ± 8.1	50.0 ± 8.3	50.6 ± 8.2	0.001	0.001	0.491	< 0.001
Vitality	0.7	47.0 ± 12.7	52.0 ± 10.1	55.3 ± 6.0	0.006	0.232	0.064	< 0.05
Social functioning	0.7	45.9 ± 13.0	50.5 ± 7.9	50.3 ± 7.9	0.101	0.229	0.024	NS
Role-emotional	0.9	42.8 ± 15.1	50.01 ± 9.4	45.2 ± 11.2	0.028	0.110	0.006	NS
Mental health	0.8	44.1 ± 14.4	48.6 ± 12.2	50.5± 6.2	0.180	0.181	0.661	NS
SF-36v2 summary scores								
PCS	-	43.5 ± 7.9	48.8 ± 7.0	52.3 ± 7.1	0.001	0.004	0.055	< 0.001
MCS	-	45.7 ± 13.8	50.6 ± 10.3	49.0 ± 5.4	0.224	0.265	0.061	NS
Work Ability Index	0.8	26.3 ± 8.1	30.9 ± 4.2	38.0 ± 37.5	0.001	0.022	0.016	< 0.001

SA: severe asthma; MMA: mild-to-moderate asthma; NA: no asthma; NS: not significant; DMFT: decayed, missing, and filled teeth; OHIP-14: 14-item Oral Health Impact Profile; SF-36v2: Medical Outcomes Study 36-Item Short-Form Health Survey, version 2; PCS: Physical Component Summary; and MCS: Mental Component Summary. *Kruskal-Wallis test. †Mann-Whitney U test.

patients with other systemic diseases.[29] We also found an association between poor OHRQoL and poor overall HRQoL in individuals with severe asthma. Nevertheless, further studies, analyzing the latent characteristics of the SF-36v2 and OHIP-14 constructs assessed,[30] are needed in order to confirm that correlation.

The association between periodontal infection and systemic conditions, such as respiratory tract diseases, has been investigated in recent decades. However, to our knowledge, there have been no studies investigating the impact that periodontal disease has on the OHRQoL of individuals with asthma. Some studies have suggested that there is a strong positive association between periodontitis and asthma severity.[11,31] However, there is as yet no evidence of a cause and effect relationship; it is not even known whether such an association would be bidirectional. In addition, those studies did not evaluate OHRQoL.

To our knowledge, this is the first study to evaluate OHRQoL, oral health profiles, and work ability in individuals with asthma. When HRQoL, oral health, and the WAI were considered, the individuals in the severe asthma group had lower normalized scores for all SF-36v2 domains, lower WAIs, and poorer OHRQoL than did those in the mild-to-moderate asthma and no-asthma groups. In a study of patients with chronic liver diseases,[29] poor oral health was also found to be associated with poor HRQoL and low work ability.

To understand and evaluate the effect that poor oral health has on the OHRQoL and functionality of individuals with asthma, we used various questionnaires. A psychometric analysis of the Portuguese-language version of the OHIP-14 suggested that the instrument is unidimensional and that the total score more precisely reflects the OHRQoL of individuals than do the individual domain scores.[32] However, we found that the OHIP-14 domain scores and total scores were both highest in the patients with severe asthma, regardless of whether the analysis is unidimensional or multidimensional.

Previous psychometric analyses of the SF-36 and OHIP-14 have shown significant correlations between the two.[30] However, our correlation analyses showed that the OHIP-14 scores correlated with the SF-36v2 Component Summary scores only in the severe asthma group. These findings underscore the need for dental care in patients with severe asthma.

Our study has some limitations. Because it was a cross-sectional study, it was not possible to identify associations between exposure and effect. In addition, it was not possible to recruit patients with asthma randomly from the ProAR cohort. It is noteworthy that all instruments we used presented good reliability. Furthermore, our study was performed at a referral center for asthma, and its population may therefore reflect the overall characteristics of patients with

Table 3. Oral health-related quality of life in individuals with severe asthma, individuals with mild-to-moderate asthma, and individuals without asthma. Salvador, Brazil, 2017-2019.

OHIP-14 scores	Group			p			
	SA (n = 40) Mean ± SD	MMA (n = 35) Mean ± SD	NA (n = 50) Mean ± SD	Overall	SA vs. MMA†	MMA vs. NA†	SA vs. NA†
Total score	11.0 ± 10.5	6.2 ± 7.4	1.4 ± 2.6	0.001	0.013	0.003	< 0.001
Domain scores							
Functional limitation	1.2 ± 2.0	0.3 ± 0.8	0.3 ± 0.6	0.027	0.021	0.529	< 0.05
Physical pain	3.0 ± 2.4	2.0 ± 2.5	1.0 ± 1.7	0.001	0.064	0.024	< 0.001
Psychological discomfort	1.8 ± 2.5	1.9 ± 2.7	0.1 ± 0.4	0.001	0.786	0.001	< 0.001
Physical disability	2.1 ± 2.3	0.8 ± 1.5	-	0.001	0.005	0.001	< 0.001
Psychological disability	2.6 ± 2.3	0.8 ± 1.6	-	0,001	0.020	0.001	< 0.001
Social disability	1.1 ± 0.8	1.0 ± 0.6	0.6 ± 0.5	0.037	0.215	0.008	NS
Handicap	0.6 ± 1.6	0.1 ± 0.2	-	0,001	0.020	0.247	< 0.001

SA: severe asthma; MMA: mild-to-moderate asthma; NA: no asthma; OHIP-14: 14-item Oral Health Impact Profile; and NS: not significant. *Kruskal-Wallis test. †Mann-Whitney U test.

Table 4. Pearson's correlation coefficients for the relationships between oral health-related quality of life scores and general health-related quality of life scores in individuals with severe asthma, individuals with mild-to-moderate asthma, and individuals without asthma. Salvador, Brazil, 2017-2019.

OHIP-14 scores	Group					
	SA (n = 40) SF-36v2 summary score		MMA (n = 35) SF-36v2 summary score		NA (n = 50) SF-36v2 summary score	
	PCS	MCS	PCS	MCS	PCS	MCS
Domain scores						
Functional limitation	−0.438*	−0.294	0.208	−0.243	−0.082	0.104
Physical pain	−0.183	−0.108	−0.193	−0.256	−0.250	0.010
Psychological discomfort	−0.298	−0.198	−0.022	−0.110	0.153	0.081
Physical disability	−0.265	0.013	0.083	−0.254	0.000	0.000
Psychological disability	−0.351†	−0.360†	−0.296	−0.123	0.000	0.000
Social disability	−0.331†	−0.169	−0.339	−0.152	0.003	−0.054
Handicap	−0.033	0.077	−0.082	0.129	0.000	0.000
Total score	−0.400*	−0.318†	−0.178	−0.219	−0.200	0.082

SA: severe asthma; MMA: mild-to-moderate asthma; NA: no asthma; SF-36v2: Medical Outcomes Study 36-Item Short-Form Health Survey, version 2 (general health-related quality of life measure); OHIP-14: 14-item Oral Health Impact Profile (oral health-related quality of life measure); PCS: Physical Component Summary; and MCS: Mental Component Summary. *Correlation significant at 0.01 (two-tailed). †Pearson's correlation coefficient significant at 0.05 (two-tailed).

asthma only in the state of Bahia. Moreover, the fact that we did not evaluate treatment data (total daily or cumulative dose of inhaled corticosteroids) or functional data (from tests such as spirometry) also limited our conclusions. However, to our knowledge, this was the first study to investigate the associations among OHRQoL, HRQoL, and WAI in individuals with severe asthma.

Severe asthma appears to be associated with poorer oral health, poorer OHRQoL, a lower WAI, and lower scores for the SF-36v2 HRQoL domains. Our findings underscore the need to provide periodontal care to patients with severe asthma.

AUTHOR CONTRIBUTIONS

RBO, VAS, and LLK: study conception and design; data analysis; drafting/revision of the manuscript; and final approval of the manuscript. AAC, ASM, and GPP: drafting/revision of the manuscript; and final approval of the manuscript. DSI: final approval of the manuscript.

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ORIGINAL ARTICLE

Evolution of the surgical treatment of lung cancer at a tertiary referral center in Brazil, 2011-2018

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Study carried out at the Instituto do Coração and the Instituto do Câncer do Estado de São Paulo, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.

ABSTRACT

Objective: To evaluate the evolution of clinical and epidemiological data, as well as data related to diagnosis, staging, treatment, and survival, among patients undergoing curative surgery for lung cancer at a tertiary referral center in the city of São Paulo, Brazil. **Methods:** This was a retrospective study of cases in the International Association for the Study of Lung Cancer database. We selected only cases of patients undergoing curative surgery between January of 2011 and April of 2018. We determined overall and disease-free survival at 36 months and compared the data between two periods (2011-2014 and 2015-2018). **Results:** Comparing the two periods (N = 437 cases), we observed trends toward increases in the number of female patients, as well as in the proportions of former smokers (44.09% vs. 53.59%), of patients diagnosed with adenocarcinoma (52.21% vs. 59.72%), and of patients diagnosed at an earlier pathological stage, together with a decrease in 30-day mortality (4.05% vs. 2.39%). There were significant increases in the proportions of cases diagnosed at an earlier clinical stage ($p = 0.002$) or incidentally ($p = 0.003$). Although lobectomy was the main surgical technique employed, there was a proportional increase in segmentectomies (2.67% vs. 7.11%; $p = 0.026$). Overall and disease-free survival rates were 79.4% (95% CI: 74.0-83.9%) and 75.1% (95% CI: 69.1-80.1%), respectively. The difference in overall survival between the periods lost statistical significance when adjusted for pathological stage, the only factor that affected survival (log-rank: $p = 0.038$ to $p = 0.079$). **Conclusions:** The clinical and epidemiological evolution presented in this study corroborates global trends. The decrease in 30-day mortality was probably due to better patient selection and improved surgical techniques.

Keywords: Lung neoplasms/surgery; Lung neoplasms/epidemiology; Lung neoplasms/therapy; Survival analysis; Thoracic surgery; Thoracic surgery, video-assisted.

INTRODUCTION

Lung cancer has evolved from being considered a rare neoplasm in the early 20th century[(1)] to being one of the leading malignancies in the world today, with an estimated more than 2 million new cases (11.6% of all cancer cases) in 2018. The high lethality of lung cancer underscores the importance of the disease, given that there were an estimated 1.8 million lung cancer deaths in that same year.[(2)]

In Brazil, according to the Brazilian National Cancer Institute, there were an estimated 31,270 new cases of lung cancer in 2018 (18,740 in men and 12,530 in women). In addition, lung cancer is the second leading cancer in men and the fourth leading cancer in women,[(3)] a similar scenario being seen in the city of São Paulo.[(4)] In a review article on lung cancer in Brazil, Araújo et al.[(5)] reported that the age-standardized 5-year survival rate in the country is 18%, which is in line with those reported worldwide, which range from 10% to 20%.[(6)]

Some aspects of the Brazilian reality make it difficult to apply findings from studies on lung cancer conducted in the United States and Europe. The inequalities between public and private medicine in Brazil, in terms of access to tests and treatment,[(5)] as well as the high incidence of granulomatous diseases,[(7)] influence our results. In the scientific literature of Brazil, there are estimates of the incidence of and mortality from lung cancer made by the Brazilian National Cancer Institute. However, other clinical data, as well as observed mortality and survival data, are scarce. Many of the studies conducted in Brazil were published long ago or were single-center studies with no focus on surgically treated lung cancer patients, proving data only related to histology, staging, type of treatment, and survival.[(8-13)]

The objective of the present study was to evaluate the evolution (from 2011 to 2018) of clinical and epidemiological data on lung cancer patients undergoing surgery with curative intent at a tertiary referral center

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in the state of São Paulo, Brazil. Data on treatment and postoperative survival were also evaluated.

METHODS

This was a single-center retrospective study based on data from an institutional database. At our center, the department of thoracic surgery not only has an internal database but also actively participates in databases of regional relevance—such as the São Paulo State Lung Cancer Registry—and of international relevance—such as the database of the Brazilian Society of Thoracic Surgery, which is linked to that of the European Society of Thoracic Surgeons, and the International Association for the Study of Lung Cancer (IASLC) database. The IASLC database, which is hosted on an international online platform, includes voluntary participation of various specialties, and gathers data on the clinical and epidemiological characteristics of lung cancer patients, as well as data on diagnosis, clinical/pathological staging, treatments, and survival. The information collected in various countries is used for assessing the prognostic value of factors currently used in the TNM classification and for assessing the use of new elements for potential inclusion in the staging system in the future. Ours is the only hospital in Brazil that is a contributor to the IASLC database,[14] and that collaboration allows greater representation of the Brazilian and Latin American populations in global studies that will result in periodic changes in lung cancer staging.

At our center, data entry is performed by physicians and nurses of the department of thoracic surgery, and entries are constantly audited by an experienced coordinator, who has authored studies in the area of data quality.[15,16] The data platform allows entry only of structured data and has security mechanisms that increase the accuracy and consistency of entries, ensuring that the data collected are of high quality.

In the present study, we used patient data from the IASLC database. We selected only cases of patients undergoing curative surgical resection of lung cancer between January of 2011 and April of 2018. Patients were followed until December of 2018. Patients without a pathology-confirmed diagnosis were excluded. Each entry in the database corresponds to a resected lung neoplasm, and more than one entry can exist for a given patient if they have had more than one lung neoplasm.

We initially analyzed data quality by using consolidated, indirect audit metrics, namely, completeness, accuracy, and consistency. The criteria for assessing consistency were age at diagnosis less than 10 years or greater than 100 years; date of diagnosis greater than the date of last contact (which directly affects the calculation of survival rates); and the presence of stages T3, T4, N1, N2, or N3 in patients classified as having clinical or pathological stage I disease. The staging criteria were adopted to assess the consistency of the data that depend directly on the health care professional performing the entries, given that only the basic data used to determine TNM staging are entered into the platform and staging is calculated manually. We used a minimum proportion of 80% as the standard of quality, as did the European Society of Thoracic Surgeons[17] when auditing its database.

We assessed demographic variables—gender, age at surgery, smoking, comorbidities, and ECOG performance status—tumor detection mode, histological type, clinical/pathological stage according to the eighth edition Lung Cancer Stage Classification,[18] type of surgical resection, 30-day mortality, and treatment with chemotherapy, radiotherapy, or both. To determine which variables affected survival, we performed Cox regression analysis of histological type, date of surgery (see below), and pathological stage. By using information gathered at the last contact, we determined overall survival and disease-free survival at 36 months. The analysis included only patients undergoing surgery prior to the end of December of 2015. We stratified the cases of resected lung cancer by period (on the basis of date of surgery): 2011-2014 and 2015-2018. We compared the two periods on the basis of the same data cited above, in order to determine whether there were differences over time in the variables of interest. We also compared the two periods in terms of unadjusted overall survival and overall survival adjusted for pathological stage.

Categorical variables were compared by using Pearson's chi-square test. For the continuous numeric variable (age), sample normality was tested with the Shapiro-Wilk test, and, subsequently, comparative analysis was performed by using the Mann-Whitney test because the sample was not normally distributed. Values of $p < 0.05$ were considered significant. From the postoperative follow-up data, we calculated overall survival and disease-free survival at 36 months for the entire study period, as well as for the 2011-2014 and 2015-2018 periods, using the Kaplan-Meier method and the log-rank test for comparisons. We used the STATA statistical software package, version 13 (Stata Corp, College Station, TX, USA).

The present study was evaluated and approved by the Research Ethics Committee of the University of São Paulo School of Medicine (Protocol no. 88741718.3.0000.0065). The requirement for written informed consent was waived because this was a retrospective study using medical record information from a database.

RESULTS

Between January of 2011 and April of 2018, there were a total of 442 cases of patients undergoing lung cancer, and those cases were subsequently entered into the IASLC database. We excluded 5 of those cases because of missing pathology results. After exclusions, the sample comprised 437 cases of lung cancer in 431 patients.

We initially assessed the quality of the data entered into the IASLC database, in order to determine whether it was feasible to analyze them in the present study (Table 1). No variables were excluded because of poor quality, given that all of the variables studied showed a completeness above 90%, an accuracy of 100%, and a consistency of 100%.

Analysis of the variables revealed higher proportions of female patients (52.67%) and of patients with a history of smoking (73.66%, of whom 48.72% were former smokers). The mean age at surgery was 63.96 ± 11.60 years. The most common comorbidities were cardiovascular disease (49.07%) and respiratory disease (31.40%). The 30-day mortality rate was 3.25%. The clinical and epidemiological data are detailed in Table 2.

Most cases were diagnosed incidentally (60.14%), and the most common histological type was adenocarcinoma (55.84%). The distribution of clinical and pathological stages is described in Table 3, as are the other cancer-related data. Most patients underwent PET/CT for cancer staging (85.13%; Table 3). Of the surgical patients evaluated, 82.61% underwent lobectomy, 81.65% did not undergo chemotherapy, and 96.09% did not undergo radiotherapy (Table 4).

For the analysis of overall and disease-free survival at 36 months, we evaluated 285 and 263 patients, respectively, and the probability of survival at the end of the observation period was 79.4% (95% CI: 74.0-83.9%) and 75.1% (95% CI: 69.1-80.1%), respectively (Figure 1). Cox regression analysis revealed that only pathological stage was an independent factor associated with survival (Table 5).

After stratifying the cases by period, we found that 226 resections were performed in 222 patients (4 patients with two lesions) in the 2011-2014 period and that 211 resections were performed in 209 patients (2 patients with two lesions) in the 2015-2018 period.

Comparing the 2011-2014 and 2015-2018 periods, we observed an upward, although not statistically significant, trend in the number of female patients and a similar mean age (63.78 years vs. 64.15 years; p = 0.778). The proportion of former smokers increased (from 44.09% to 53.59%; p = 0.137). Although the proportion of patients with comorbidities was higher in the 2015-2018 period, mortality was lower, but not statistically significantly so (p = 0.331; Table 2).

Table 1. Data quality control

Type	Missing or inconsistent data, n	Quality parameter, %
Completeness		
Gender	0	100.00
Age	0	100.00
Smoking	2	99.54
ECOG performance status	2	99.54
Mode of diagnosis	3	99.31
Differentiation	41	90.62
Histological type	0	100.00
Clinical staging	2	99.54
Pathological staging	2	99.54
Endobronchial ultrasound	1	99.77
Type of resection	0	100.00
Systemic treatment	1	99.77
Chemotherapy in advanced-stage disease	3	99.31
Syntactic accuracy		
Gender	0	100.00
Age	0	100.00
Smoking	0	100.00
ECOG performance status	0	100.00
Mode of diagnosis	0	100.00
Differentiation	0	100.00
Histological type	0	100.00
Clinical staging	0	100.00
Pathological staging	0	100.00
Endobronchial ultrasound	0	100.00
Type of resection	0	100.00
Systemic treatment	0	100.00
Chemotherapy in advanced-stage disease	0	100.00
Consistency		
Age at diagnosis < 10 or > 110 years	0	100.00
T3/T4 and clinical stage	0	100.00
T3/T4 and pathological stage	0	100.00
N1-N3 and clinical stage	0	100.00
N1-N3 and pathological stage	0	100.00
Date of diagnosis > date of last contact	0	100.00

Table 2. Patient characteristics.[a]

Characteristic	Total	2011-2014 period	2015-2018 period	p
Gender				
Male	204 (47.33)	108 (48.65)	96 (45.93)	0.573
Female	227 (52.67)	114 (51.35)	113 (54.07)	
Total	431 (100.00)	222 (100.00)	208 (100.00)	
Age at surgery, years	63.96 ± 11.60	63.78 ± 12.46	64.15 ± 10.64	0.778
Smoking				
Nonsmoker	113 (26.34)	62 (28.18)	51 (24.40)	0.137
Former smoker	209 (48.72)	97 (44.09)	112 (53.59)	
Smoker	107 (24.94)	61 (27.73)	46 (22.01)	
Total	429 (100.00)	220 (100.00)	209 (100.00)	
ECOG performance status				
0	284 (66.20)	171 (77.73)	113 (54.07)	< 0.001
1	134 (31.24)	44 (20.00)	90 (43.06)	
2	10 (2.33)	4 (1.82)	6 (2.87)	
3	1 (0.23)	1 (0.45)	-	
Total	429 (100.00)	220 (100.00)	209 (100.00)	
Diabetes mellitus	77 (17.91)	37 (16.74)	40 (19.14)	0.517
Total	430 (100.00)	221 (100.00)	209 (100.00)	
Renal disease	14 (3.26)	3 (1.36)	11 (5.26)	0.023
Total	430 (100.00)	221 (100.00)	209 (100.00)	
Respiratory disease	135 (31.40)	65 (29.41)	70 (33.49)	0.362
Total	430 (100.00)	221 (100.00)	209 (100.00)	
Cardiovascular disease	211 (49.07)	95 (42.99)	116 (55.50)	0.009
Total	430 (100.00)	221 (100.00)	209 (100.00)	
30-day mortality	14 (3.25)	9 (4.05)	5 (2.39)	0.331
Total	431 (100.00)	222 (100.00)	209 (100.00)	

[a]Values expressed as n (%) or as mean ± SD.

In the 2011-2014 and 2015-2018 periods, most of the cases of lung cancer (52.47% and 68.25%, respectively) were diagnosed incidentally (p = 0.003). In both periods, adenocarcinoma was the most common histological type, followed by squamous cell carcinoma. However, the proportion of cases of adenocarcinoma increased from 52.21% to 59.72%, whereas the proportion of cases of squamous cell carcinoma decreased from 23.89% to 19.91% (p = 0.406 for both). In the 2015-2018 period, we observed an upward trend in the proportions of cases diagnosed at an earlier clinical stage (p = 0.002) and of cases diagnosed at an earlier pathological stage (p = 0.084; Table 3).

We observed that the proportion of surgical patients who underwent invasive staging by endobronchial ultrasound decreased from the 2011-2014 period to the 2015-2018 period (from 64.44% to 28.91%; p < 0.001), as did the proportion of those who underwent invasive staging by video-assisted mediastinoscopy (from 29.20% to 21.33%; p = 0.059). Data on the staging tests performed are presented in Table 3.

Although lobectomy was the most common type of surgical resection in both periods, we observed a significant increase in the proportion of segmentectomies (from 2.67% to 7.11%; p = 0.026). In addition, there was a trend toward an increase in the proportion of patients undergoing chemotherapy, especially adjuvant chemotherapy (from 13.78% to 19.91%; p = 0.145). After separating patients undergoing chemotherapy for pathological stage I disease from those undergoing chemotherapy for pathological stage II-IV disease (Table 4), we found that the increase was more marked among those diagnosed at a more advanced stage and that the number of patients undergoing adjuvant therapy nearly doubled in the 2015-2018 period. Treatment-related data are presented in Table 4.

The difference in overall survival between the periods lost statistical significance when adjusted for pathological stage (log-rank: p = 0.038 to p = 0.079; Figure 1).

DISCUSSION

After an indirect audit, which confirmed the quality of the patient data, we found that the clinical and demographic characteristics were similar to those reported in recent studies conducted in Brazil,[5,10,11] except for the data related to overall and disease-free survival at 36 months, which were both above 75% in the present study. That difference is probably due to the characteristics of our study, in which we evaluated surgically curable patients (i.e., patients with earlier-stage disease). The similarity between overall and disease-free survival rates demonstrates the direct relationship between relapse/progression and mortality.

When comparing patients operated on before 2015 with those operated on after 2015, we found trends already seen worldwide, such as an increased incidence

Table 3. Lung cancer characteristics and staging tests/procedures.[a]

Characteristic	Total	2011-2014 period	2015-2018 period	p
Mode of diagnosis				
Incidental	261 (60.14)	117 (52.47)	144 (68.25)	
Symptoms	169 (38.94)	104 (46.64)	65 (30.81)	0.003
Screening	4 (0.92)	2 (0.90)	2 (0.95)	
Total	434 (100.00)	223 (100.00)	211 (100.00)	
Differentiation				
Good	87 (21.97)	52 (27.66)	35 (16.83)	
Moderate	195 (49.24)	95 (50.53)	100 (48.08)	0.003
Poor	114 (28.79)	41 (21.81)	73 (35.10)	
Total	396 (100.00)	188 (100.00)	208 (100.00)	
Histological type				
Adenocarcinoma	244 (55.84)	118 (52.21)	126 (59.72)	
Squamous cell carcinoma	96 (21.97)	54 (23.89)	42 (19.91)	0.406
Carcinoid tumor	62 (14.19)	33 (14.60)	29 (13.74)	
Other	35 (8.01)	21 (9.29)	14 (6.63)	
Total	437 (100.00)	226 (100.00)	211 (100.00)	
Clinical stage				
IA1	20 (4.60)	6 (2.68)	14 (6.64)	
IA2	107 (24.60)	41 (18.30)	66 (31.28)	
IA3	67 (15.40)	37 (16.52)	30 (14.22)	
IB	70 (16.09)	40 (17.86)	30 (14.22)	
IIA	36 (8.28)	14 (6.25)	22 (10.43)	
IIB	64 (14.71)	38 (16.96)	26 (12.32)	0.002
IIIA	53 (12.18)	35 (15.63)	18 (8.53)	
IIIB	7 (1.61)	6 (2.68)	1 (0.47)	
IIIC	3 (0.69)	3 (1.34)	0 (0.0)	
IVA	5 (1.15)	2 (0.89)	3 (1.42)	
IVB	3 (0.69)	2 (0.89)	1 (0.47)	
Total	435 (100.00)	224 (100.00)	211 (100.00)	
Pathological stage				
0	3 (0.69)	1 (0.45)	2 (0.95)	
IA1	29 (6.67)	11 (4.91)	18 (8.53)	
IA2	80 (18.39)	33 (14.73)	47 (22.27)	
IA3	57 (13.10)	34 (15.18)	23 (10.90)	
IB	68 (15.63)	38 (16.96)	30 (14.22)	
IIA	28 (6.44)	15 (6.70)	13 (6.16)	0.084
IIB	66 (15.17)	33 (14.73)	33 (15.64)	
IIIA	79 (18.16)	48 (21.43)	31 (14.69)	
IIIB	17 (3.91)	7 (3.13)	10 (4.74)	
IIIC	0 (0.0)	0 (0.0)	0 (0.0)	
IVA	5 (1.15)	2 (0.89)	3 (1.42)	
IVB	3 (0.69)	2 (0.89)	1 (0.47)	
Total	435 (100.00)	224 (100.00)	211 (100.00)	
PET/CT	372 (85.13)	187 (82.74)	185 (87.68)	0.147
Total	437 (100.00)	226 (100.00)	211 (100.00)	
Endobronchial ultrasound	206 (47.25)	145 (64.44)	61 (28.91)	< 0.001
Total	436 (100.00)	225 (100.00)	211 (100.00)	
Video-assisted mediastinoscopy	111 (25.40)	66 (29.20)	45 (21.33)	0.059
Total	437 (100.00)	226 (100.00)	211 (100.00)	

[a]Values expressed as n (%).

of lung cancer in women.[19,20] Brazil has been the country with the highest upward trend in the number of new lung cancer cases in women in the past 10 years.[21] An increased incidence of adenocarcinoma, together with a reduced incidence of squamous cell carcinoma,[22] was also observed in our patients. These trends are in agreement with those reported in other recent studies on the clinical and epidemiological profile of lung cancer in Brazil.[23,24] A progressive decrease in smoking rates in the country[25] was also found in the 2015-2018 period, during which there was a higher proportion of former smokers.

There is as yet no lung cancer screening program in Brazil, although there have been studies demonstrating the benefit of such a program, including the National Lung Screening Trial[26] and the Dutch-Belgian Lung Cancer Screening Trial,[27] as well as a study conducted in Brazil.[28] In the present study, less than 1% of patients were diagnosed by screening. In most cases, the diagnosis was made either incidentally,

Table 4. Treatment.[a]

Treatment	Total	2011-2014 period	2015-2018 period	p
Surgery				
Type of resection				
Lobectomy	361 (82.61)	187 (82.74)	174 (82.46)	
Bilobectomy	16 (3.66)	12 (5.31)	4 (1.90)	
Pneumonectomy	31 (7.09)	14 (6.19)	17 (8.06)	0.026
Segmentectomy	21 (4.81)	6 (2.67)	15 (7.11)	
Wedge resection	6 (1.37)	5 (2.21)	1 (0.47)	
Airway resection	2 (0.46)	2 (0.88)	-	
Total	437 (100.00)	226 (100.00)	211 (100.00)	
Systemic treatment				
Did not undergo	356 (81.65)	189 (84.00)	167 (79.15)	
Stages II/III/IV	122 (61.93)	74 (69.81)	48 (52.75)	
Postoperative	73 (16.74)	31 (13.78)	42 (19.91)	
Stages II/III/IV	70 (35.53)	29 (27.36)	41 (45.05)	0.145
Preoperative	7 (1.61)	5 (2.22)	2 (0.95)	
Stages II/III/IV	5 (2.54)	3 (2.83)	2 (2.20)	
Total	436 (100.00)	225 (100.00)	211 (100.00)	
Total	197 (100.00)	106 (100.00)	91 (100.00)	
Radiotherapy				
Did not undergo	418 (96.09)	217 (96.88)	201 (95.26)	
Postoperative	12 (2.76)	3 (1.34)	9 (4.27)	0.081
Preoperative	5 (1.15)	4 (1.79)	1 (0.47)	
Total	435 (100.00)	224 (100.00)	211 (100.00)	

[a]Values expressed as n (%).

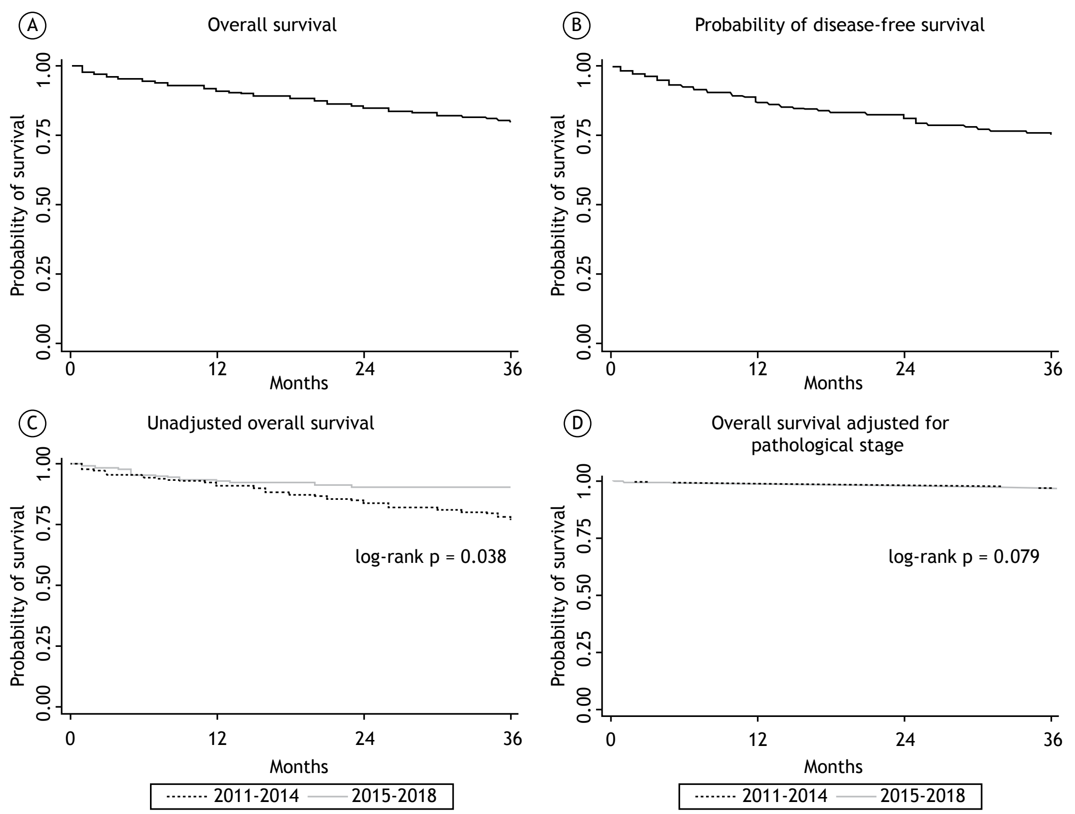

Figure 1. Kaplan-Meier curves. Overall survival (in A) and disease-free survival (in B) at 36 months for all patients operated on until 2015. Unadjusted overall survival (in C) and overall survival adjusted for pathological stage (in D) for the 2011-2014 and 2015-2018 periods.

especially in patients operated on more recently, or on the basis of symptoms, forms of diagnosis that reduce the chances of early diagnosis and potentially curative surgical treatment. The increase in the number of incidental diagnoses may have occurred for one of two reasons: either patients underwent

Table 5. Cox regression model for variables that affected overall survival (n = 405).

Variable	Hazard ratio (95% CI)
Histological type	
Squamous cell carcinoma	1.06 (0.59-1.92)
Carcinoid tumor	0.15 (0.20-1.08)
Other	1.33 (0.63-2.82)
Pathological stage	
II	3.83 (1.78-8.26)
III	7.50 (3.74-15.07)
Period	
2015-2018	0.63 (0.35-1.13)

imaging studies more frequently and malignancy was a finding; or, more likely, the symptom-based diagnoses corresponded to more advanced disease for which surgical treatment is not indicated, which excluded the patients from the present analysis.

Earlier clinical and pathological stages were found to predominate among patients undergoing surgical resection between 2015 and 2018. Patients diagnosed at a more advanced stage, who thereby lost the benefit of surgical treatment, were probably referred for systemic therapy and therefore were not included in our analysis. Cox regression analysis revealed that only pathological stage had a significant impact on overall survival in our study, which, in a way, validated staging in our population. That variable was also a determinant of the difference in overall survival between the two periods analyzed, because, when the curves were adjusted for pathological stage, that difference lost statistical significance. Therefore, efficient patient selection was found to be the main factor associated with the increased survival observed in the 2015-2018 period. That factor is probably also related to the decrease in 30-day mortality in the 2015-2018 period, even among patients who were more severely ill, which is to be expected.[29]

Another factor that may have contributed to the decrease in mortality in the 2015-2018 period was improved surgical technique, given the increasing proportion of minimally invasive procedures, especially those performed by video-assisted thoracoscopy, as well as those performed by robotic surgery, which started being used in 2015.[30,31] Lobectomy was the most commonly performed surgical procedure, corresponding to more than 80% of the cases in the 2011-2014 and 2015-2018 periods. However, we observed a significant increase in segmentectomies in the 2015-2018 period, which is in line with a trend in the current surgical literature that underscores the benefits of sublobar resection as an alternative to lobectomy in patients with limited lung function, multifocal disease,[32] or early-stage disease.[33,34] Ongoing prospective studies are seeking to prove that overall survival is similar between anatomic sublobar resection and lobectomy,[35,36] and the similarity of postoperative morbidity and mortality between the two techniques has been proven.[36,37] We also observed a reduction in the number of wedge resections, which have limited oncological value.[38,39]

There were decreases in the use of invasive mediastinal staging by video-assisted mediastinoscopy and, especially, by endobronchial ultrasound, the decrease in the latter being statistically significant. These decreases are attributable to an increased rate of staging-based diagnosis of mediastinal lymph node involvement, with such patients being referred to the oncology department for systemic treatment alone after a diagnosis of locally advanced disease. Another factor that may explain these decreases is the increased incidence of earlier-stage cases that do not require invasive mediastinal staging.[40]

One advantage of the present study is the high reliability of the data analyzed. The fact that, at our center, data entry is performed by health care professionals committed to providing care and to maintaining the database, together with the fact that entries are constantly audited, certainly has a positive impact on the quality of the data analyzed, making the findings of the present study more reliable. Another advantage is the use of observed data rather than estimated data, thus providing an update on the lung cancer situation in Brazil and adding to the existing body of knowledge in terms of clinical and epidemiological data, as well as in terms of information on staging and treatment.

Because this was a study of surgically treated lung cancer patients, the evaluation of patients diagnosed at an advanced stage, who are still the majority among lung cancer patients in Brazil and were not included in the present study, could represent a limitation, potentially reducing the generalizability of the findings. The small number of patients is also a limitation because this was a single-center study. Another potential bias to be considered is the fact that, when comparing survival between the two periods, we found that the duration of follow-up was shorter in the 2015-2018 period.

We conclude that the clinical and epidemiological profile of lung cancer patients in Brazil has followed worldwide trends. We also found that advances in patient selection (priority being given to early-stage tumors), in surgical technique, and in perioperative care, as well as an increase in the number of segmentectomies, have led to lower surgical mortality rates. That decrease occurred despite the fact that patients who are more severely ill have undergone surgery with curative intent in recent years, underscoring the benefits of the changes implemented.

AUTHOR CONTRIBUTIONS

RMT and PMPF: substantial contribution to the study design; data analysis and interpretation; drafting and revision of the manuscript; and approval of the final version to be published. MSS, PHCL, PBC, LMC, and LLL: data entry into the IASLC database; data collection and analysis and drafting and revision of the manuscript.

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ORIGINAL ARTICLE

Clinical, laboratory, and functional characteristics of asthma-COPD overlap in patients with a primary diagnosis of COPD

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ABSTRACT

Objective: To evaluate the frequency of asthma-COPD overlap (ACO) in patients with COPD and to compare, from a clinical, laboratory, and functional point of view, patients with and without ACO, according to different diagnostic criteria. **Methods:** The participants underwent evaluation by a pulmonologist, together with spirometry and blood tests. All of the patients were instructed to record their PEF twice a day. The diagnosis of ACO was based on the *Proyecto Latinoamericano de Investigación en Obstrucción Pulmonar* (PLATINO, Latin American Project for the Investigation of Obstructive Lung Disease) criteria, the American Thoracic Society (ATS) Roundtable criteria, and the Spanish criteria. We investigated patient histories of exacerbations and hospitalizations, after which we applied the COPD Assessment Test and the modified Medical Research Council scale, to classify risk and symptoms in accordance with the GOLD criteria. **Results:** Of the 51 COPD patients, 14 (27.5%), 8 (12.2%), and 18 (40.0) were diagnosed with ACO on the basis of the PLATINO, ATS Roundtable, and Spanish criteria, respectively. The values for pre-bronchodilator FVC, post-bronchodilator FVC, and pre-bronchodilator FEV_1 were significantly lower among the patients with ACO than among those with COPD only (1.9 ± 0.4 L vs. 2.4 ± 0.7 L, 2.1 ± 0.5 L vs. 2.5 ± 0.8 L, and 1.0 ± 0.3 L vs. 1.3 ± 0.5 L, respectively). When the Spanish criteria were applied, IgE levels were significantly higher among the patients with ACO than among those with COPD only (363.7 ± 525.9 kU/L vs. 58.2 ± 81.6 kU/L). A history of asthma was more common among the patients with ACO ($p < 0.001$ for all criteria). **Conclusions:** In our sample, patients with ACO were more likely to report previous episodes of asthma and had worse lung function than did those with COPD only. The ATS Roundtable criteria appear to be the most judicious, although concordance was greatest between the PLATINO and the Spanish criteria.

Keywords: Asthma/diagnosis; Pulmonary disease, chronic obstructive/diagnosis; Asthma-chronic obstructive pulmonary disease overlap syndrome/diagnosis.

INTRODUCTION

Asthma and COPD are diseases that are well understood scientifically and have particular features, determining their distinction. However, it can be difficult to reach an accurate diagnosis in patients with clinical findings consistent with both diseases. Therefore, GINA and GOLD have proposed the term asthma-COPD overlap (ACO).[1,2] In brief, ACO may be used to describe patients with asthma who have features of COPD (specifically, incompletely reversible airflow obstruction) or to describe patients with COPD who have features of asthma (such as bronchodilator responsiveness and bronchial hyperresponsiveness).[3]

It is estimated that from 0.9% to 11.1% of the general population can be classified as having ACO.[4] However, ACO is not a primary diagnosis, and patients with this condition are usually found among patients with asthma or COPD.[5] Having that in mind, the prevalence of ACO among patients with a primary diagnosis of COPD is estimated to range from 4.2% to 68.7%. This variation is due to the availability of various sets of criteria for the classification of patients with ACO.[4,5]

Of the 35 studies reviewed by Uchida et al.,[4] most defined ACO as a combination of asthma and COPD, on the basis of factors such as a history of asthma, symptoms of cough and wheezing, airflow limitation, bronchial hyperresponsiveness, and bronchodilator responsiveness. Those studies, however, differ greatly in terms of the characteristics used in the diagnosis and the way they are used.

Many of the studies that sought to evaluate the characteristics of patients with ACO found that these individuals have more severe symptoms, a greater number of exacerbations and hospitalizations, poorer quality of life, and poorer prognosis than do those without ACO.[6-8] These characteristics translate to high health costs for these subjects.[9]

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The aforementioned findings may be due to a lack of concrete data to inform the appropriate therapeutic choice for each patient profile. Once the clinical features of patients have been identified, treatment can be personalized, optimizing outcomes in terms of both functional performance and quality of life. Therefore, the present study aimed to evaluate the frequency of ACO in a sample of patients with a primary diagnosis of COPD and to compare, from a clinical, laboratory, and functional standpoint, patients with ACO and those with COPD only.

METHODS

This cross-sectional observational study was conducted to evaluate the frequency of ACO in a sample of patients with a primary diagnosis of COPD and to compare those with and without ACO from a clinical, laboratory, and functional standpoint. This study is nested within the Follow-COPD Cohort Study, which is ongoing at the Center for Research on Asthma and Airway Inflammation of the Professor Polydoro Ernani de São Thiago University Hospital, located in the city of Florianópolis, Brazil, and was approved by the Human Research Ethics Committee of the Federal University of Santa Catarina (CAAE no. 85662718.5.0000.0121), located in that same city.

Our sample, which comprised participants from the Follow-COPD Cohort Study, was selected in an intentional and non-probabilistic manner. The inclusion criteria adopted in that study were as follows: having been diagnosed with COPD; being a former or current smoker; having been clinically stable for at least one month; having been on appropriate medical treatment for at least one month; and having agreed to participate in the study by giving written informed consent. The exclusion criteria adopted in that study was having a clinically significant oncological, cardiovascular, neurological, musculoskeletal, rheumatological, or cognitive comorbidity that limited one's understanding of and adherence to the proposed evaluation methods.

Patients had an appointment with a pulmonologist, in which sociodemographic and clinical data were collected. Blood tests for peripheral eosinophil count and IgE were also requested. The request for blood tests was sent to primary health care clinics so that the tests could be performed at third-party laboratories affiliated with the Brazilian Unified Health Care System.

The diagnosis of COPD was based on the GOLD criteria,[2] which include the presence of symptoms (dyspnea, chronic cough, and production of secretion), exposure to risk factors, and a post-bronchodilator FEV_1/FVC ratio < 0.70 on spirometry, which was performed with the Koko Sx 1000 spirometer (PDS Instrumentation Inc., Louisville, CO, USA). In addition, patients completed the COPD Assessment Test and the modified Medical Research Council dyspnea scale, the scores of which, together with the history of exacerbations and hospitalizations, were used in order to classify risk and symptoms.[2]

For the diagnosis of ACO, three different sets of criteria were used. The first, established by the *Proyecto Latinoamericano de Investigación en Obstrucción Pulmonar* (PLATINO, Latin American Project for the Investigation of Obstructive Lung Disease),[6] defines COPD as a post-bronchodilator FEV_1/FVC ratio < 0.70 and defines asthma as wheezing in the previous 12 months and bronchodilator responsiveness in FEV_1 or FVC (≥ 200 mL and ≥ 12%), although a report of previous asthma diagnosis can also be used. ACO is defined as combined features of both COPD and asthma. The second set of criteria, established at the American Thoracic Society conference (ATS Roundtable),[10] includes three major and three minor characteristics—all three major characteristics and at least one minor characteristic are required for the diagnosis of ACO. The major characteristics include non-reversible airflow limitation (a post-bronchodilator FEV_1/FVC < 0.70) in individuals over 40 years of age, a smoking history ≥ 10 pack-years, and either a history of asthma before age 40 or bronchodilator responsiveness in FEV_1 (> 400 mL). The minor characteristics include a history of atopy or allergic rhinitis, bronchodilator responsiveness in FEV_1 (≥ 200 mL and ≥ 12%) at two distinct time points, and a peripheral blood eosinophil count ≥ 300 cells/mm^3. The third set of criteria, established by Cosio et al.[11] and designated the Spanish criteria, is based on a previous diagnosis of COPD (age > 40 years, a post-bronchodilator FEV_1/FVC < 0.7, and exposure to tobacco smoke) and comprises two major and three minor characteristics—at least one major characteristic or two minor characteristics are required for the diagnosis of ACO. The major characteristics include a history of asthma and bronchodilator responsiveness in FEV_1 (≥ 400 mL and ≥ 15%), whereas the minor characteristics include an IgE level > 100 kU/L, a history of atopy, bronchodilator responsiveness in FEV_1 (≥ 200 mL and ≥ 12%) at two time points, and a blood eosinophil count > 5%.

Patients were instructed to measure their PEF in the morning and in the evening for 30 days, with a portable PEF meter (Medicate; Dorja, Itu, Brazil), and to record their PEF values in a diary. The highest morning and evening PEF values for 7 consecutive days during which the diary was appropriately completed were used. Daily variation in PEF (ΔPEF) is the difference between the highest morning PEF value and the highest evening PEF value, whereas percent change in PEF is calculated as ΔPEF divided by the highest daily PEF value and multiplied by 100.

Statistical analysis

Continuous variables were expressed as means and standard deviations, and categorical variables were expressed as absolute and relative frequencies. The chi-square test was used to determine associations between nominal variables, and the Student's t-test was used to compare means between groups. The kappa statistic was used to assess concordance between the different diagnostic criteria for ACO. Values of $p < 0.05$

were considered significant. The data were analyzed with the IBM SPSS Statistics software package, version 22.0 (IBM Corporation, Armonk, NY, USA).

RESULTS

All 51 patients who participated in the Follow-COPD Cohort Study between January of 2018 and July of 2019 were evaluated. Of those, 27 (52.9%) were men, 27 (52.9%) had had at least one COPD exacerbation in the previous year, and 6 (11.8%) had been hospitalized in the previous year. Other characteristics of the sample are described in Table 1.

Airflow limitation was classified as mild (grade 1), in 3 patients (5.9%); moderate (grade 2), in 18 (35.3%); severe (grade 3), in 19 (37.3%); and very severe (grade 4), in 11 (21.6%). With regard to risk and symptoms, 13 patients (25.0%) were classified as group A, 17 (33.3%) were classified as group B, and 21 (41.2%) were classified as group D, with no patients being classified as group C.

All 51 participants were evaluated using the PLATINO criteria, 49 were evaluated using the ATS Roundtable criteria, and only 45 were evaluated using the Spanish criteria, because 2 and 4 patients had no eosinophil count and no IgE level results, respectively. In this sample of COPD patients, the frequency of ACO was 27.5% (n = 14), 12.2% (n = 6), and 40.0% (n = 18) according to the PLATINO, ATS Roundtable, and Spanish criteria, respectively.

Patients with ACO, regardless of the diagnostic criteria used, were more likely to report previous episodes of asthma than were those with COPD only (Table 2). In addition, patients with ACO were more likely to have bronchodilator responsiveness at two distinct time points than were those with COPD only. Patients with ACO according to the Spanish criteria were more likely to have an elevation in IgE than were those with COPD only, as well as having higher IgE values (Table 3).

There were no differences in spirometry results between patients with and without ACO when the Spanish criteria were applied; however, differences were found when the PLATINO and the ATS Roundtable criteria were applied. When the PLATINO criteria were used, there were differences between the two groups in pre- and post-bronchodilator FVC (in L) and in pre-bronchodilator FEV_1 (in L). When the ATS Roundtable criteria were used, differences also were found between the two groups in pre-bronchodilator FVC (in L) and in pre-bronchodilator FEV_1 (in L). Table 4 shows the spirometry results for patients with and without ACO, by diagnostic criteria.

An analysis of concordance between the three different sets of criteria for the diagnosis of ACO used in the present study showed moderate concordance between the PLATINO and the ATS Roundtable criteria and between the Spanish and the ATS Roundtable criteria, but strong concordance between the PLATINO and the Spanish criteria. Table 5 shows the assessment of concordance between the different diagnostic criteria.

Table 1. Characteristics of the sample (N = 51).[a]

Characteristic	Result
Age, years	64.1 ± 8.4
BMI, kg/m²	25.5 ± 5.5
Smoking history, pack-years	47.3 ± 30.4
Eosinophils, cells/mm³	286.2 ± 431.7
Eosinophils, %	3.2 ± 2.1
CAT score	18 (9-29)
mMRC dyspnea scale score	2 (1-4)
Pulmonary function	
Pre-BD FVC, L	2.2 ± 0.7
Pre-BD FVC, % pred	64.3 ± 18.2
Pre-BD FEV_1, L	1.2 ± 0.5
Pre-BD FEV_1, % pred	44.5 ± 17.6
Pre-BD FEV_1/FVC	0.5 ± 0.1
Post-BD FVC, L	2.4 ± 0.7
Post-BD FVC, % pred	67.7 ± 19.2
Post-BD FEV_1, L	1.3 ± 0.5
Post-BD FEV_1, % pred	47.5 ± 18.3
Post-BD FEV_1/FVC	0.5 ± 0.1
BD responsiveness: FVC, mL	118.6 ±148.6
BD responsiveness: FEV_1, mL	83.7 ± 94.0

CAT: COPD Assessment Test; mMRC: modified Medical Research Council; BD: bronchodilator; and pred: predicted value. [a]Values expressed as mean ± SD or as median (IQR).

DISCUSSION

In the present study, when the PLATINO criteria were applied to a cohort of patients with COPD, the frequency of ACO was 27.5%. Patients with ACO had worse pre- and post-bronchodilator FVC and worse pre-bronchodilator FEV_1 than did patients with COPD only. In addition, a history of asthma was more common among those with ACO than among those with COPD only.

When applying the PLATINO criteria to patients with a primary diagnosis of COPD, Jo et al.[(5)] reported the presence of ACO in 48.3% of the participants, whereas in the studies by Mendy et al.[(12)] and Menezes et al.,[(6)] the frequency of ACO was 12.6% and 12.4%, respectively. The discrepancy between the studies can be partly explained by methodological characteristics. By including subjects with and without respiratory problems, population-based studies[(6,12)] may find a reduced frequency of ACO in comparison with studies that exclusively include patients with COPD. In contrast, studies that include only patients with COPD[(5)] are subject to the fact that COPD is an underdiagnosed disease and they therefore tend to include patients with more symptoms and greater airflow limitation,[(13,14)] among whom are patients with ACO.

Patients classified as having ACO on the basis of the PLATINO and the ATS Roundtable criteria have worse lung function than do those with COPD only. This profile has been described in various studies that used different diagnostic criteria: patients with ACO

Table 2. Frequency of patients with asthma-COPD overlap or COPD only, by diagnostic criteria.[a]

Characteristic	Criteria					
	PLATINO		ATS Roundtable		Spanish	
	ACO (n = 14)	COPD (n = 37)	ACO (n = 6)	COPD (n = 43)	ACO (n = 18)	COPD (n = 27)
Male gender	6 (42.9)	21 (56.8)	1 (16.7)	24 (55.8)	10 (55.6)	14 (51.9)
History of asthma	12 (85.7)	0 (0.0)**	6 (100.0)	4 (9.3)**	12 (66.7)	0 (0.0)**
History of atopy	8 (57.1)	17 (45.9)	5 (83.3)	20 (46.5)	11 (61.1)	11 (40.7)
Eosinophils ≥ 300 cells/mm³	2 (20.0)	8 (25.0)	1 (16.7)	9 (20.9)	5 (27.8)	5 (18.5)
IgE > 100 kU/L	5 (41.7)	7 (22.6)	3 (50.0)	9 (20.9)	10 (55.6)	2 (7.4)**
CAT score ≥ 10	10 (71.4)	27 (73.0)	6 (100.0)	30 (69.8)	13 (72.2)	19 (70.4)
mMRC dyspnea scale score ≥ 2	8 (57.1)	20 (54.1)	5 (83.3)	23 (53.5)	9 (50.0)	14 (51.9)
BD responsiveness: FVC > 350 mL	1 (7.1)	1 (2.7)	0 (0.0)	2 (4.7)	1 (5.6)	1 (3.7)
BD responsiveness: FEV_1 > 200 mL and 12%	2 (14.3)	2 (5.4)	0 (0.0)	4 (9.3)	1 (5.6)	3 (11.1)
BD responsiveness: FEV_1 > 200 mL and 12% at two time points	2 (20.0)	2 (6.7)	2 (33.3)	2 (4.7)*	2 (11.1)	1 (3.7)
Airflow limitation						
Mild	0 (0.0)	3 (8.1)	0 (0.0)	3 (7.0)	0 (0.0)	2 (7.4)
Moderate	3 (21.4)	15 (40.5)	1 (16.7)	17 (39.5)	6 (33.3)	10 (37.0)
Severe	6 (42.9)	13 (35.1)	4 (66.7)	15 (34.9)	7 (38.9)	10 (37.0)
Very severe	5 (35.7)	6 (16.2)	1 (16.7)	8 (18.6)	5 (27.8)	5 (18.5)
Risk and symptom classification						
A	4 (28.6)	9 (24.3)	0 (0.0)	12 (27.9)	5 (27.8)	7 (25.9)
B	4 (28.6)	13 (35.1)	2 (33.3)	14 (32.6)	5 (27.8)	11 (40.7)
D	6 (42.9)	15 (40.5)	4 (66.7)	17 (39.5)	8 (44.4)	9 (33.3)

PLATINO: *Proyecto Latinoamericano de Investigación en Obstrucción Pulmonar* (Latin American Project for the Investigation of Obstructive Lung Disease); ATS: American Thoracic Society; ACO: asthma-COPD overlap; CAT: COPD Assessment Test; mMRC: modified Medical Research Council; and BD: bronchodilator. [a]Values expressed as n (%). *p < 0.05. **p < 0.01.

Table 3. Comparison of clinical characteristics between patients with asthma-COPD overlap and those with COPD only, by diagnostic criteria.[a]

Characteristic	Criteria					
	PLATINO		ATS Roundtable		Spanish	
	ACO (n = 14)	COPD (n = 37)	ACO (n = 6)	COPD (n = 14)	ACO (n = 37)	COPD (n = 6)
Age, years	62.1 ± 9.2	64.9 ± 8.0	60 ± 10.8	64.2 ± 7.8	62.1 ± 9.6	65.9 ± 6.3
BMI, kg/m²	25 ± 4.5	25.7 ± 5.8	25.1 ± 5.9	25.8 ± 5.5	26.7 ± 6.3	24.8 ± 5.2
Smoking history, pack-years	39.5 ± 27.2	50.2 ± 31.4	46.9 ± 35.8	48.0 ± 30.5	47.6 ± 33.3	44.1 ± 26.3
Exacerbation in the previous year	1.5 ± 1.5	1.2 ± 1.5	2.3 ± 1.6	1.2 ± 1.5	1.4 ± 1.4	1.0 ± 1.4
Hospitalization in the previous year	0.14 ± 0.4	0.14 ± 0.4	0.0 ± 0.0	0.2 ± 0.4*	0.2 ± 0.4	0.1 ± 0.5
Eosinophils, cells/mm³	200.1 ± 129.1	315.7 ± 493.5	187.6 ± 101.3	299.1 ± 457.1	281.5 ± 174.5	293.6 ± 532.8
Eosinophils, %	2.9 ± 2.0	3.3 ± 2.1	2.6 ± 1.3	3.3 ± 2.2	3.8 ± 2.2	3.0 ± 2.1
IgE, kU/L	305.05 ± 601.6	122.3 ± 182.6	482.3 ± 916.3	134.8 ± 195.2	363.7 ± 525.9	58.2 ± 81.6*
Daily variation in PEF, L/min	21.7 ± 12.2	21.6 ± 13.8	13.9 ± 8.6	22.7 ± 13.6	25.1 ± 12.7	19.6 ± 13.7
Daily variation in PEF, %	10.4 ± 7	9.5 ± 5.0	8.9 ± 7.7	9.9 ± 5.4	9.8 ± 4.9	9.4 ± 5.9

PLATINO: *Proyecto Latinoamericano de Investigación en Obstrucción Pulmonar* (Latin American Project for the Investigation of Obstructive Lung Disease); ATS: American Thoracic Society; and ACO: asthma-COPD overlap. [a]Values expressed as mean ± SD. *p < 0.05.

had reduced FEV_1 (absolute and relative values), FVC (absolute and relative values), and FEV_1/FVC ratio when compared with those with COPD only,[6,12,15-17] as well as when compared with those with asthma only.[12,18] In contrast, two studies that used different diagnostic criteria reported better lung function in patients with ACO. Kauppi et al.[7] reported that pre- and post-bronchodilator FVC (as percent of predicted) and post-bronchodilator FEV_1 (as percent of predicted) were higher in the ACO group than in the COPD-only group, but they were lower in the ACO group than in the asthma-only group. In the study by Cosentino et al.,[19] the FEV_1/FVC ratio was also higher in the ACO group.

Table 4. Comparison of pulmonary function between patients with asthma-COPD overlap and those with COPD only, by diagnostic criteria.[a]

Characteristic	Criteria					
	PLATINO		ATS Roundtable		Spanish	
	ACO (n = 14)	COPD (n = 37)	ACO (n = 6)	COPD (n = 14)	ACO (n = 37)	COPD (n = 6)
Pre-BD FVC, L	1.9 ± 0.4	2.4 ± 0.7*	1.9 ± 0.4	2.3 ± 0.7*	2.3 ± 0.7	2.2 ± 0.6
Pre-BD FVC, % pred	58.2 ± 13.5	66.6 ± 19.4	59.9 ± 17.8	65.2 ± 18.7	63.2 ± 15.8	63.0 ± 18.9
Pre-BD FEV_1, L	1.0 ± 0.3	1.3 ± 0.5*	1.0 ± 0.2	1.2 ± 0.5*	1.2 ± 0.5	1.2 ± 0.4
Pre-BD FEV_1, % pred	38.3 ± 12.7	46.8 ± 18.8	40.3 ± 13.8	45.6 ± 18.3	42.7 ± 14.5	43.9 ± 18.0
Pre-BD FEV_1/FVC	0.5 ± 0.1	0.5 ± 0.1	0.5 ± 0.1	0.5 ± 0.1	0.5 ± 0.1	0.5 ± 0.1
Post-BD FVC, L	2.1 ± 0.5	2.5 ± 0.8*	2.0 ± 0.4	2.4 ± 0.7	2.4 ± 0.8	2.3 ± 0.6
Post-BD FVC, % pred	62.1 ± 16.4	69.9 ± 20.0	63.8 ± 19.1	68.6 ± 19.7	66.3 ± 17.6	66.7 ± 19.6
Post-BD FEV_1, L	1.1 ± 0.4	1.3 ± 0.5	1.1 ± 0.2	1.3 ± 0.5	1.3 ± 0.5	1.2 ± 0.4
Post-BD FEV_1, % pred	42.0 ± 15.7	49.6 ± 18.9	43.9 ± 14.6	48.9 ± 18.8	45.6 ± 16.2	47.3 ± 18.5
Post-BD FEV_1/FVC	0.5 ± 0.1	0.5 ± 0.1	0.5 ± 0.1	0.5 ± 0.1	0.5 ± 0.1	0.5 ± 0.1
BD responsiveness: FVC, mL	132.9 ± 158.9	113.2 ± 146.4	136.7 ± 108.2	119.1 ± 153.8	113.3 ± 140.8	123.3 ± 159.4
BD responsiveness: FEV_1, mL	108.6 ± 108.3	74.3 ± 87.8	113.3 ± 49.3	85.6 ± 95.8	90.0 ± 99.9	87.0 ± 91.5

PLATINO: *Proyecto Latinoamericano de Investigación en Obstrucción Pulmonar* (Latin American Project for the Investigation of Obstructive Lung Disease); ATS: American Thoracic Society; ACO: asthma-COPD overlap; BD: bronchodilator; and pred: predicted value. [a]Values expressed as mean ± SD. *p < 0.05.

Table 5. Assessment of concordance between the diagnostic criteria used.

Criteria	PLATINO			Spanish		
	With ACO	Without ACO	Kappa	With ACO	Without ACO	Kappa
ATS Roundtable						
With ACO	6 (100%)	0 (0%)	0.60	6 (100%)	0 (0%)	0.43
Without ACO	37 (86%)	6 (14%)		10 (27%)	27 (73%)	
Spanish						
With ACO	13 (72.2)	5 (27.8%)	0.71			
Without ACO	1 (3.7%)	26 (96.3%)				

PLATINO: *Proyecto Latinoamericano de Investigación en Obstrucción Pulmonar* (Latin American Project for the Investigation of Obstructive Lung Disease); and ;ACO: asthma-COPD overlap.

Bronchodilator responsiveness, despite being a consensus among different diagnostic criteria,[6,10,11] remains a source of debate and divergence among researchers.[20-22] This divergence stems from the fact that positive bronchodilator responsiveness is common in patients with COPD[23] and that this is an inconstant finding, which may vary from one spirometry test to another.[24] Those results corroborate findings of the present study, in which only when the ATS Roundtable criteria were used did we find differences between the ACO and the COPD-only groups in terms of bronchodilator responsiveness on two or more spirometry tests. Therefore, bronchodilator responsiveness should not be used in isolation for the diagnosis of ACO, but rather in combination with other characteristics.[25] In addition to bronchodilator responsiveness, a history of asthma and blood levels of eosinophils and IgE are characteristics that are usually part of diagnostic criteria for ACO.[6,10,11]

Patients with ACO are more likely to report previous episodes of asthma than are those with COPD only, regardless of the criteria used. This is easily explained by the fact that all criteria include this characteristic as a key factor in diagnosing ACO. A study by Barrecheguren et al.[26] demonstrated that COPD patients who were diagnosed with ACO solely on the basis of a history of asthma had characteristics similar to those of COPD patients diagnosed with ACO on the basis of the Spanish criteria. A similar finding was reported in a study in which the addition of characteristics other than a history of asthma made no difference in the diagnosis of ACO.[27] Therefore, besides a diagnosis of COPD (FEV_1/FVC < 0.7), a history of asthma has been described as an important characteristic in identifying patients with ACO.

A common feature of asthma is ΔPEF, determined by using a peak flow meter, an important instrument in the management of asthma.[1] However, this instrument has also proven to be an ally to COPD patients in monitoring and preventing exacerbations.[28] Therefore, some studies have used ΔPEF as a feature of asthma that contributes to identifying ACO,[4,25] and one population-based study even demonstrated that patients with ACO have lower PEF than do patients with either asthma or COPD only.[12] However, there were no differences in PEF between the groups in the present study.

In our study, no differences were found in peripheral blood eosinophil counts between patients with ACO and those with COPD only. However, recent studies have highlighted the relationship between high blood eosinophil levels and asthma-related features, such as increased bronchodilator responsiveness and increased responsiveness to treatment with inhaled corticosteroids.[21] Therefore, blood eosinophil counts in patients with COPD have been suggested as indicative of ACO[22] and as a predictor of treatment responsiveness.[29]

Although total IgE levels do not provide information related to atopic etiology as do specific IgE levels, they appear to be related to atopy in asthma[30] and are therefore included in some criteria for the diagnosis of ACO.[4] In the present study, only when the Spanish criteria were used did we find differences in IgE levels between patients with ACO and patients with COPD only, as in the study by Jo et al.[5] However, the Spanish criteria are the only criteria that use IgE as a required characteristic for the diagnosis of ACO, which can generate debate about the veracity of this finding and about the role of IgE levels in the diagnosis of ACO.

As expected, different criteria resulted in different frequencies of ACO. This finding has been addressed in other studies,[5,31] in which, when the ATS Roundtable criteria were applied, 1.9-11.9% of the participants were diagnosed with ACO, whereas, when the Spanish criteria were applied, 31.3-47.7% received this diagnosis. This confirms the findings of the present study: the ATS Roundtable criteria proved to be more rigorous than did the Spanish and the PLATINO criteria in discriminating between COPD and ACO.

Of the three sets of criteria analyzed in the present study, the PLATINO criteria appear to be the simplest and therefore the most appropriate for application in epidemiological studies and clinical practice, given that only two characteristics are required for the diagnosis of ACO. The need for testing bronchodilator responsiveness at least at two different time points and performing biochemical tests makes the application of the Spanish and the ATS Roundtable criteria more complex. However, spirometry and measurement of blood levels of eosinophils and total IgE are standardized and accessible, as well as being recommended by GOLD (respectively, for monitoring lung function and for estimating treatment efficacy and predicting exacerbations),[2] which enables the application of the Spanish and the ATS Roundtable criteria in clinical practice. In addition, although the Spanish criteria are similar in format to the ATS Roundtable criteria, they showed greater concordance with the PLATINO criteria, which leads one to question whether the ATS Roundtable criteria impose too strict conditions for the diagnosis of ACO. In contrast, an analysis of the conditions imposed by the PLATINO and the Spanish criteria shows that the characteristics of the former are included in the latter, that is, a diagnosis of COPD as defined by GOLD[2] and a history of asthma, which results in strong concordance between these two sets of criteria.

The present study has some limitations. The fact that this was a small convenience sample consisting of patients followed at a public hospital outpatient clinic who had a primary diagnosis of COPD compromises the generalizability of the findings, as well as being able to affect those findings and even the frequency of ACO. Therefore, further studies are required for external validation of these findings. A self-reported history of asthma, despite being a variable that is widely accepted and valid in studies, is subject to patient subjectivity. With regard to laboratory findings, data on eosinophil and IgE levels were missing for some patients, which may have affected not only the application of the diagnostic criteria but also the comparisons between the groups. The measurement of PEF, despite instructions, was subject to errors in diary completion and patient subjectivity.

We therefore conclude that the frequency of ACO in this cohort of patients with COPD was 27.5%. Patients with ACO were more likely to report previous episodes of asthma and had worse lung function than did those with COPD only. Of the diagnostic criteria used in this study, the ATS Roundtable criteria appear to be the most judicious, although concordance was greatest between the PLATINO and the Spanish criteria.

Further studies are needed to determine the importance, as well as the specificity and sensitivity, of the different characteristics that comprise the diagnostic criteria for ACO. In addition, longitudinal studies should be considered to follow patients with ACO from a clinical, laboratory, and functional standpoint, as well as in terms of important outcomes, such as hospitalizations and mortality.

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ORIGINAL ARTICLE

Carbohydrate antigen 15-3 as a marker of disease severity in patients with chronic hypersensitivity pneumonitis

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ABSTRACT

Objective: Biomarkers associated with mucin 1, such as Krebs von den Lungen-6 and carbohydrate antigen (CA) 15-3, are increased in various interstitial lung diseases. Our aim was to determine whether CA 15-3 could be considered a biomarker of disease severity in patients with chronic hypersensitivity pneumonitis (cHP). **Methods:** This was a prospective observational study involving adult patients with cHP. Serum levels of CA 15-3 were measured and were correlated with variables related to disease severity and extension. HRCT scans were quantitatively analyzed using a computational platform and an image analysis tool (Computer Aided Lung Informatics for Pathology Evaluation and Rating). CA 15-3 levels were normalized by logarithmic transformation. **Results:** The sample comprised 41 patients. The mean age of the patients was 60.1 ± 11.6 years. The mean FVC in % of predicted was 70.3% ± 17.3%, and the median of the serum level of CA 15-3 was 48.1 U/mL. CA 15-3 levels inversely correlated with FVC in % of predicted ($r = -0{,}30$; $p = 0{,}05$), DLCO in % of predicted ($r = -0{,}54$; $p < 0{,}01$), and SpO_2 at the end of a 4-min step test ($r = -0{,}59$; $p < 0{,}01$), but they directly correlated with total quantitative HRCT scores ($r = 0{,}47$; $p = 0{,}004$), especially regarding ground-glass opacities ($r = 0.58$; $p < 0{,}001$). **Conclusions:** CA 15-3 is likely to be a biomarker of disease severity of patients with cHP, particularly regarding gas exchange abnormalities.

Keywords: Antigens, tumor-associated, carbohydrate; Alveolitis, extrinsic allergic; Biomarkers; Lung diseases, interstitial.

INTRODUCTION

Hypersensitivity pneumonitis (HP) is an interstitial lung disease (ILD) caused by inhaled, mostly organic, antigens. The current classification differentiates HP between fibrotic and nonfibrotic HP.[1,2] The diagnosis of chronic HP (cHP) has prognostic and therapeutic implications.[2,3]

A biomarker able to detect disease activity and severity can be useful in cHP. Krebs von den Lungen-6 (KL-6) is a mucin 1 (MUC1) epitope. KL-6 is a membrane glycoprotein encoded by the *MUC1* gene and expressed on the surface of lung epithelial cells.[4] KL-6 is an important biomarker of various ILDs; however, KL-6 quantification assays are unavailable in most countries.[5] Carbohydrate antigen (CA) 15-3 is also a MUC1 epitope but, unlike KL-6, CA 15-3 quantification assays are widely available. CA 15-3 levels are correlated with KL-6 in ILDs, including a subset group of patients with HP.[6-8] In addition, CA 15-3 levels are correlated with disease extent on HRCT in patients with ILD associated with systemic sclerosis.[9]

The objective of the present study was to determine the role of CA 15-3 as a biomarker of disease severity in patients with cHP. We evaluated whether CA 15-3 levels would correlate with disease extent on the basis of perception of dyspnea, lung function, SpO_2 after exercising, and HRCT.

METHODS

This was a prospective observational study involving consecutive patients with cHP who sought medical attention at a university hospital located in the city of São Paulo, Brazil, between December of 2015 and October of 2017.

All patients underwent spirometry and DLCO measurement, and the results were compared with reference values.[10,11] SpO_2 was measured at rest and at the end of a 4-min step test (SpO_2-Ex).[12] Transthoracic echocardiography and HRCT results, as well as serum levels of CA 15-3 (Elecsys CA 15-3; Roche Diagnostics, Rotkreuz, Switzerland) and perception of dyspnea, measured by the modified Medical Research Council (mMRC) scale and the Mahler scale, were recorded.[13,14] The reference range of serum CA 15-3 using Elecsys CA 15-3 assay is < 26.4 U/mL.[15]

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The inclusion criteria were as follows: being ≥ 18 years of age and being diagnosed with cHP in accordance with the criteria proposed by Salisbury et al.[2] for probable HP. Axial disease distribution on HRCT was added as a suggestive HRCT finding.[16] HP was classified as chronic in the presence of symptoms or radiological evidence of disease for at least 3 months. HP was classified as fibrotic or nonfibrotic according to the presence of findings indicative of fibrosis on HRCT.[1] Bronchoscopy, bronchoalveolar lavage, transbronchial lung biopsy (TBB), and/or surgical lung biopsy (SLB) were performed, taking contraindications into account, if definitive diagnosis was not reached by the abovementioned methods.[17]

The exclusion criteria were as follows: being a current smoker; having other potential causes for ILDs; having SpO_2 at rest < 89%; being unable to perform spirometry and DLCO measurement; having breast cancer, colon cancer, pancreatic disease, hepatitis, liver cirrhosis, or symptoms of gastroesophageal reflux disease; and having a change in diagnosis during follow-up.

We classified HP as active or inactive. HP was considered active if there was worsening of dyspnea or a significant decrease in FVC (≥ 10% in relation to baseline values) or in DLCO (≥ 15% in relation to baseline values) within the last 6-12 months prior to inclusion in the study. Improvement or stability in the perception of dyspnea and in lung function parameters indicated inactive HP.

All HRCT scans were acquired with 1-mm collimation, the findings being defined in accordance with the Fleischner Society recommendations.[18] Quantitative analysis of HRCT scans was performed using a computational platform (Lung Texture Analysis [LTA]; Imbio, Minneapolis, MN, USA) and an image analysis tool (Computer Aided Lung Informatics for Pathology Evaluation and Rating [CALIPER]; Imbio). LTA provides detailed quantification of textures by lung region and is able to identify accurately ILDs and other fibrotic conditions (such as honeycombing, reticular opacities, and ground-glass opacities) as well as hyperlucent areas, and normal lung parenchyma. A total score can be calculated.[19]

The present study was approved by the Research Ethics Committee of the *Universidade Federal de São Paulo* (Protocol no. 2.391.623). All patients gave written informed consent.

Statistical analysis

Continuous variables were expressed as means and standard deviations or medians and interquartile ranges. Categorical variables were described in absolute and relative frequencies.

Because CA 15-3 levels had a nonparametric distribution, the values were transformed into natural logarithms that adjusted to normal distribution (Shapiro-Wilk test). Then, the Pearson's correlation test was used to correlate serum levels of CA 15-3 with pulmonary function variables, and Spearman's correlation coefficients were used to correlate serum levels of CA 15-3 with Mahler scale scores and with HRCT scores derived from CALIPER. We used ANOVA followed by Tukey's test to compare serum levels of CA 15-3 with mMRC scale scores. All statistical analyses were performed with the IBM SPSS Statistics software package, version 21.0 (IBM Corporation, Armonk, NY, USA).

RESULTS

The initial sample comprised 52 patients diagnosed with cHP: 9 and 2 were excluded prior to the beginning of the study and during the study period, respectively. Of those 2 patients, 1 presented with rapid progression of the disease, and the anatomopathological findings obtained from SLB revealed usual interstitial pneumonia, final diagnosis being idiopathic pulmonary fibrosis (IPF); and 1 was diagnosed with connective tissue disease during follow-up (Figure 1). Therefore, 41 patients were included in final analysis. The baseline characteristics of the final sample are shown in Table 1. At the time of initial evaluation, 29 patients (70.7%) had received no treatment.

All of the patients were exposed to inhaled antigens, mold and birds being the most frequent types of antigens, and presented with respiratory symptoms. Thirteen patients (31.7%) were exposed to both molds and birds. Of the 41 patients, in regard to their admission to the study, 22 (51.2%) and 19 (46.3%) had had a recent and a previous exposure to antigens, respectively.

In the sample as a whole, 13 (31.7%) and 28 (68.3%) of the patients, respectively, presented with one and with two or more tomographic findings suggestive of cHP. Features indicative of fibrosis on HRCT were present in 28 (68.3%) of the patients.

Of the 41 patients, 4 (9.8%) had a definitive diagnosis of cHP and needed to undergo no other diagnostic methods; 23 (56.1%) and 14 (34.1%) underwent TBB and SLB, respectively. Among those who underwent TBB, increased lymphocytes in bronchoalveolar lavage fluid (> 20%) were found in 15 patients.

Biopsies revealed findings that were diagnostic of or consistent with HP in 19 of the 37 patients (51%): classic HP, in 6 (2 by TBB and 4 by SLB); findings indicative of bronchiolar injury (bronchiolitis obliterans, peribronchiolar metaplasia, or air trapping), in 10 (3 by TBB and 7 by SLB); and airway-centered Interstitial fibrosis, in 3 (by SLB). Only 1 patient presented with a usual interstitial pneumonia pattern, but this pattern was associated with other typical HP findings.

Median serum levels of CA 15-3 were 48.1 U/mL, ranging from 13.2 U/mL to 228.7 U/mL. In the sample as a whole, 22 and 19 patients had inactive and active cHP, respectively, the mean natural logarithms of the serum levels of CA 15-3 being 3.65 ± 0.64 and. 4.20 ± 0.77 ($t = 2.48$, $p = 0.02$). Using the ROC curve and anti-normal logarithm transformation, the best cutoff point was 51.3 U/mL.

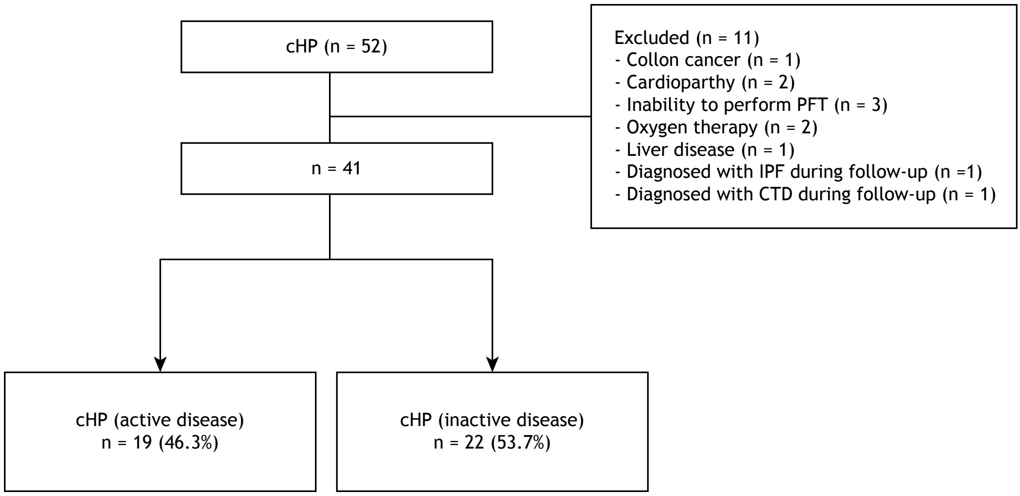

Figure 1. Flow chart of the study selection process. cHP: chronic hypersensitivity pneumonitis; PFT: pulmonary function test; IPF: idiopathic pulmonary fibrosis; and CTD: connective tissue disease.

Table 1. Baseline characteristics of the patients studied.[a]

Characteristic	(N = 41)
Age, years	60.1 ± 11.6
Female	30 (73.2)
Smoking status	
Nonsmoker	26 (63.4)
Former smoker	15 (36.6)
Lymphocytes in BALF, %	24 [4-76]
Lymphocytes in BALF > 20%[b]	13 (59)
FVC, % of predicted	70.3 ± 17.3
DLCO, % of predicted	54.5 ± 19.0
mMRC score	2 [1-3]
Mahler score	7 [5-8]
SpO_2 at rest	96 [93.5–97.0]
SpO_2-Ex	88 [83.5–92.5]
Serum CA 15-3, U/mL	48.1 [26.9-83.6]
HRCT findings	
Indicative of fibrosis	28 (68.3)
Ground-glass opacities	36 (87.8)
Centrilobular nodules	10 (24.4)
Honeycombing	11 (26.8)
Emphysema	13 (31.7)
Traction bronchiectasis	25 (60.9)
Bronchiolectasis	21 (51.2)
Air trapping	27 (65.8)
Axial distribution	24 (58.5)
Predominant disease in upper lobes	2 (4.9)
Pharmacological treatment at inclusion	
None	29 (71)
Prednisone	9 (22)
Immunosuppressant[c]	3 (7)

BALF: bronchoalveolar lavage fluid; mMRC: modified Medical Research Council; SpO_2-Ex: SpO_2 measured at the end of a 4-min step test; and CA: carbohydrate antigen. [a]Values expressed as n (%), mean ± SD, or median [IQR]. [b]n = 22. [c]Associated with prednisone in 2 patients.

Environmental exposure preceded the symptoms in all cases. No significant differences in CA 15-3 levels were found between the groups that had recent and previous environmental exposure (data not shown). Twenty-seven patients were able to avoid environmental exposure, which resulted in clinical improvement in 21 patients (but not in 6), 12 continued to be exposed, and that information was considered uncertain in 2. When we compared the patients who continued to be exposed to antigens plus those who avoided it but showed no clinical improvement (n = 18) with those who avoided environmental exposure and showed clinical improvement (n = 21), the CA 15-3 levels were lower in the latter group (4.241 ± 0.780 U/mL vs. 3.602 ± 0.634 U/mL; $t = 2.82$; $p < 0.01$). The ROC curve showed that the best cutoff point between the two groups was 55.3 U/mL.

No differences in CA 15-3 levels were found between nonsmokers and former smokers (data not shown). In addition, CA 15-3 levels were similar between patients who had had no treatment up to the time of initial evaluation (n = 29) and those who had been treated (n = 12): [3.97 ± 0.78 U/mL vs. 3.76 ± 0.68 U/mL; $p = 0.40$).

There was a statistically significant difference between CA 15-3 levels and mMRC scale scores ($Z = 5.45$; $p < 0.01$). Tukey's test showed that there was also a statistically significant difference between patients with an mMRC score = 3 and those with an mMRC score = 1-2 ($p < 0.05$, data not shown). There was a significant but poor inverse correlation between the perception of dyspnea measured by the Mahler scale and CA 15-3 levels ($r_s = −0.31$; $p = 0.04$). No differences were found regarding FVC in % of predicted (FVC%), DLCO in % of predicted (DLCO%), or SpO_2-Ex between nonsmokers and former smokers (data not shown).

There was a significant negative correlation between the serum levels of CA 15-3 and FVC% ($r = −0.30$; p

= 0.05), DLCO% (r= −0.54; p < 0.01), and SpO_2-Ex (r = −0.59; p < 0.01; Figure 2).

There were no significant differences in CA 15-3 levels between patients with (n = 28) and without (n = 13) findings indicative of fibrosis on HRCT (4.015 ± 0.711 U/mL vs. 3.681 ± 0.808 U/mL; p = 0.19).

By CALIPER analysis, there was a statistically significant correlation between CA 15-3 levels and the following HRCT scores: total ground-glass opacities, total honeycombing, total fibrosis score (i.e., total reticular opacities plus honeycombing), and total score (Table 2 and Figure 3). The correlation between serum levels of CA 15-3 and CALIPER quantification of total ground-glass opacities is shown in Figure 3.

DISCUSSION

The present study showed that, in patients with cHP, there is an inverse correlation of serum levels of CA 15-3 with FVC%, DLCO%, and SpO_2-Ex, as well as there is a direct correlation of those CA 15-3 levels with the extent of disease on HRCT, especially that related to the quantification of ground-glass opacities. There are various histopathological findings related to HP.[20-22] In the present study, we used the criteria proposed by Salisbury et al.[2] for the diagnosis of HP.

A biomarker is defined as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention."[23] Several biomarkers have been studied in ILDs, especially in IPF, and can provide information about the course of the disease.[24,25] KL-6 is now classified as a human MUC1 protein. Regenerating type II pneumocytes are the primary cellular source of KL-6/MUC1 in the affected lungs of patients with ILD.[5] Extensive investigations performed primarily in Japan revealed that serum levels of KL-6/MUC1 are elevated in 70-100% of patients with various ILDs, including HP.[5] Sequential changes of serum levels of KL-6 can predict the progression of ILD.[26]

CA 15-3 is a tumor marker for many types of cancer, most notably breast cancer. Similarly to KL-6, it is also derived from MUC1, but CA 15-3 measurement is widely available, is fully automated, and has low costs. Previous studies showed that CA 15-3 levels have a high correlation with KL-6 levels in patients with ILDs, especially in those with fibrotic ILDs.[6-8] In one study, CA 15-3 levels were shown to be elevated in 26 patients with HP, and the correlation between KL-6 and CA 15-3 levels was very strong.[8] In another study involving patients with cHP, KL-6 levels were measured during different seasons and were shown to be increased during summer as a result of the greater humidity in the households at that time of the year.[27]

In our study, there was a statistically significant direct correlation between dyspnea scores and serum levels of CA 15-3. In addition, there was an inverse correlation between serum levels of CA 15-3 and lung function indicators of disease severity: FVC%, DLCO%, and SpO_2-Ex.

A prospective study evaluated 85 patients and found higher serum levels of CA 15-3 in patients with FVC% < 50%.[26] In the present study, there was a strong correlation of serum levels of CA 15-3 with gas exchange variables, DLCO%, and SpO_2-Ex, suggesting that CA 15-3 was an indicator of the extent of alveolar damage.

One study measured CA 15-3 levels in 84 patients with systemic sclerosis and ILD and found that such levels strongly correlated with semiquantitative HRCT scores.[9] Jacob et al.[19] studied patients with HP and found that CALIPER quantitative analysis was more accurate than visual HRCT scores and that there was a better correlation with functional and morphological variables. In the present study, the quantitative analysis of HRCT findings was carried out using LTA and CALIPER. There was a direct correlation between serum levels of CA 15-3 and the following HRCT findings: total ground-glass opacities, total honeycombing, and total fibrosis score (i.e., total reticular opacities plus honeycombing). One study evaluated patients with

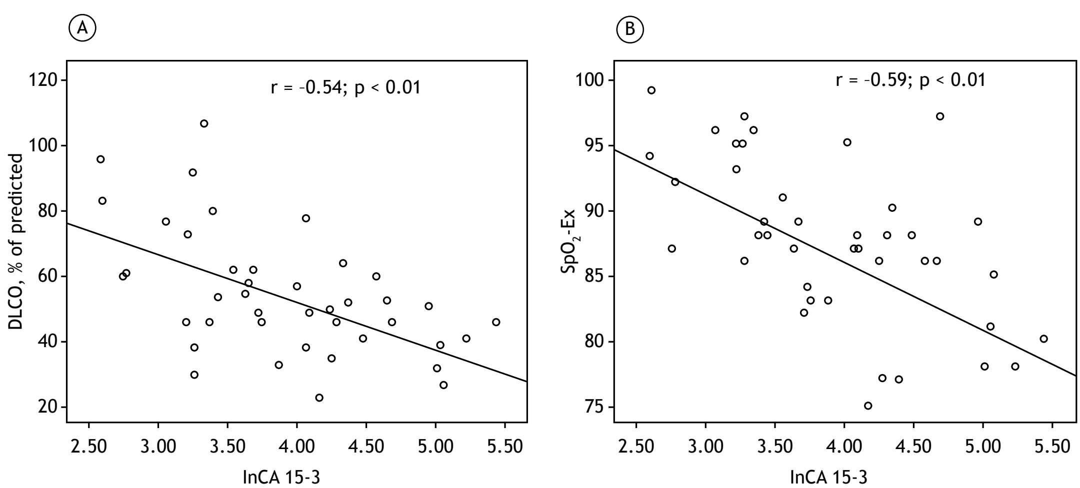

Figure 2. Correlation of natural logarithm (ln) of serum levels of carbohydrate antigen (CA) 15-3 with DLCO in % of predicted (in A) and SpO_2 at the end of a 4-min step test (SpO_2-Ex).

Table 2. Correlation between carbohydrate antigen (CA) 15-3 levels and tomographic findings.[a]

HRCT finding	Spearman's correlation coefficient	p
Total ground-glass opacities	0.54	0.001
Total hyperlucent areas	0.35	0.03
Total honeycombing	0.36	0.03
Total fibrosis score	0.34	0.04
Total findings	0.47	0.004

[a]CALIPER quantitative analysis.

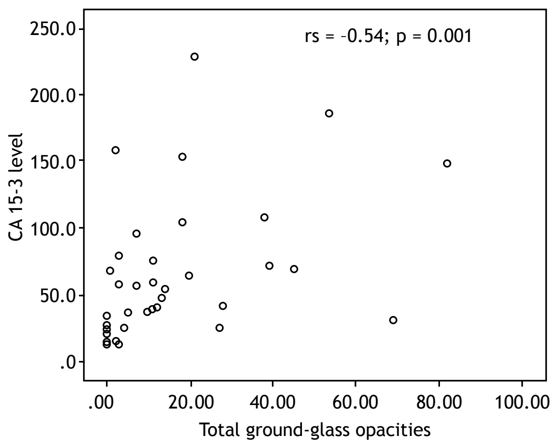

Figure 3. Correlation between serum levels of carbohydrate antigen (CA) 15-3 and computerized quantitative analysis of total ground-glass opacities.

IPF who underwent lung transplantation and showed that CA 15-3 levels decreased after the procedure.[28] This result corroborates the relationship between CA 15-3 levels and the extension of ILDs.

There are limitations in the present study. In 8 cases, HRCT was not performed in our hospital, and this resulted in the use of different tomographic techniques. However, those images were considered adequate for CALIPER analysis. Former smokers were not excluded, and that might have affected some functional and tomographic findings. However, serum levels of CA 15-3 were similar between nonsmokers and former smokers. In addition, KL-6 quantitative assays were unavailable, and, therefore, no comparisons between KL-6 and CA 15-3 levels were made.

When a candidate biomarker is identified, it should be easily measurable and mechanistically plausible. It should be validated in another study and undergo biological testing to establish its role in the pathogenesis of a disease.[22]

In conclusion, CA 15-3 is likely to be a biomarker of disease severity in patients with cHP, particularly regarding gas exchange abnormalities.

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AUTHOR CONTRIBUTIONS

RGF: histological analysis of the study and approval of the final version. MRS, ABB, and RBM: study design, manuscript drafting, and approval of the final version. MFMLM and GSPM: analysis of HRCT images and approval of the final version. CACP: coordination, statistical analysis, manuscript drafting, and approval of the final version. PSG: study design, data collection, manuscript drafting, and approval of the final version.

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ORIGINAL ARTICLE

Charlson Comorbidity Index and other predictors of in-hospital mortality among adults with community-acquired pneumonia

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ABSTRACT

Objective: To compare the performance of Charlson Comorbidity Index (CCI) with those of the mental **C**onfusion, **U**rea, **R**espiratory rate, **B**lood pressure, and age = **65** years (CURB-65) score and the Pneumonia Severity Index (PSI) as predictors of all-cause in-hospital mortality in patients with community-acquired pneumonia (CAP). **Methods:** This was a cohort study involving hospitalized patients with CAP between April of 2014 and March of 2015. Clinical, laboratory, and radiological data were obtained in the ER, and the scores of CCI, CURB-65, and PSI were calculated. The performance of the models was compared using ROC curves and AUCs (95% CI). **Results:** Of the 459 patients evaluated, 304 met the eligibility criteria. The all-cause in-hospital mortality rate was 15.5%, and 89 (29.3%) of the patients were admitted to the ICU. The AUC for the CCI was significantly greater than those for CURB-65 and PSI (0.83 vs. 0.73 and 0.75, respectively). **Conclusions:** In this sample of hospitalized patients with CAP, CCI was a better predictor of all-cause in-hospital mortality than were the PSI and CURB-65.

Keywords: Pneumonia, ROC curve; Predictive value of tests; Severity of illness index.

INTRODUCTION

Community-acquired pneumonia (CAP) remains to be the leading cause of death from infectious diseases in the world,[1] with an annual incidence of 5-11 cases per 1,000 population, causing major impacts on health care systems.[2] In the USA, more than 60,000 CAP-related deaths were reported among individuals aged ≥ 15 years in 2005, and the annual economic burden was still high in 2010 (17 billion dollars).[3]

Early identification of patients at risk of death is a tenet of CAP management, the definition of CAP severity being the most important aspect guiding the decision to hospital admission.[4,5] However, clinical assessment might not accurately capture the severity of the disease and the potential for complications or death.[5,6] As a result, the use of severity scores[7-9] has been recommended to evaluate patients with CAP and to establish the need for intensive care.

Among the best known CAP risk prediction models, the mental **C**onfusion, **U**rea, **R**espiratory rate, **B**lood pressure, and age = **65** years (CURB-65) score[10] and the Pneumonia Severity Index (PSI),[11] whose predictive capacity for mortality is 0.79 and 0.82, respectively, have been validated for use in a variety of clinical scenarios.[12] However, both of these models rely on pneumonia-specific criteria and, therefore, do not account for risks associated with comorbidities. Nevertheless, previous studies[13,14] have shown that information regarding the number of comorbidities and degree of health status involvement is helpful to establish prognosis. In that situation, a general score such as the Charlson Comorbidity Index (CCI)[15] can be useful. The CCI, which was developed to standardize the assessment of comorbid conditions[13] and 1- and 10-year all-cause mortality,[15] is a well-established predictor of in-hospital mortality in nonsurgical patients[16] and in those with specific diseases.[17] However, the use of the CCI to predict in-hospital mortality in CAP patients, especially as an alternative to pneumonia-specific severity scores, has yet to be investigated. Thus, the objective of the present study was to compare the performance of CCI with those of CURB-65 and PSI as predictors of all cause in-hospital mortality in patients with CAP.

METHODS

Study population

This study was carried out in a 130-bed general community hospital located in the city of Montenegro, state of Rio Grande do Sul, Brazil. The hospital provides public health care through the Brazilian Unified Health Care System to a population of about 160,000 from 19 cities. CAP was the main reason for admission to the hospital, with a mortality rate of approximately 15.5%.[18] At the time the present study was conducted, the hospital was beginning to implement the use of severity indices to assess the need for admission in patients seeking the ER. The health care professionals in charge of collecting standardized data to calculate the indices were trained by the research team. During the training stage, 100% of the assessments were performed in duplicate, which produced an overall inter-rater agreement of 96.3%.

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Study design

In the present cohort study, we evaluated patients ≥ 14 years of age presenting to our ER with respiratory complaints between April of 2014 and March of 2015. Patients with a clinical and radiographic diagnosis of CAP requiring hospitalization were included in the study. We excluded patients with hospital-acquired pneumonia (characterized by admission to urgent-care facilities for at least 2 days); patients originating from retirement homes, shelters, or other health care institutions; patients on intravenous antibiotic treatment or chemotherapy; patients treated for pressure ulcers in the previous 30 days; and patients undergoing renal replacement therapy.

The results of severity assessment using the risk prediction models were recorded in the medical charts of the patients and taken as baseline data for the cohort. The clinical progress of patients was assessed during hospitalization. Hospital discharge was defined as the clinical outcome measure.

CAP was diagnosed on the basis of at least one of the following chest X-ray findings: new or progressive infiltrate, consolidation, or cavitation; and at least one of the following signs or symptoms: fever > 38°C with no other known cause, leukopenia (< 4,000 leukocytes/mm^3), or leukocytosis (≥ 12,000 leukocytes/mm^3). In addition, in patients aged ≥ 70 years, changes in mental state with no other evident cause and at least two of the following were considered for the diagnosis of CAP: recent cough with purulent sputum, changes in expectoration, increase in respiratory secretions, increase in the frequency of aspiration, onset or worsening of cough, dyspnea or tachypnea, wheezing, or worsening of gas exchange (for example, oxygen desaturation [PaO_2/FiO_2 ≤ 240], increased need for oxygen, or need for mechanical ventilation).

The study was approved by the institutional review board (Protocol no. 150168).

Study variables

Clinical, laboratory, and radiological data recorded in the medical chart were obtained in the first 24 h after the ER consultation, including age, sex, origin, RR, blood pressure, temperature, HR, presence of mental confusion, SpO_2, comorbidities (added to the medical record by an attending physician), history of hospital admissions, chest X-ray findings (reported by a radiologist), and results of laboratory tests requested during the ER visit. Laboratory tests included arterial blood gas analysis, urea, serum creatinine, glucose, sodium, and blood workup. Information regarding antibiotic treatment duration, length of hospital stay, length of ICU stay, and need for mechanical ventilation was also collected. The major outcome measure was all-cause in-hospital mortality recorded in the medical chart and confirmed through review of the discharge summary or of the death certificate accordingly. This information was available for all CAP patients treated at the hospital during the study period. The discharge summary was prepared by an attending physician after discharge in all cases.

For the analysis, patients were grouped into two categories—low risk or intermediate/high risk—according to the cutoff point of each model: the CCI[15] covers 19 variables related to comorbidities, with scores ranging from 1 to 6, patients with a CCI of 0-2 being classified as at a low risk of death/admission; CURB-65[10] is based on the assessment of five clinical characteristics, with scores ranging from 0 to 5, patients with a CURB-65 of 0 or 1 being classified as at a low risk of death/admission; the PSI[11] relies on 20 clinical variables to generate a score with five classes representing progressive increase in the risk of death, patients with a PSI score of 1 or 2 being classified as at a low risk of death.

Data analysis and sample size calculation

In order to determine the capacity of CCI, CURB-65, and PSI to predict the risk of death, ROC curves and the C statistic (corresponding to the AUC) were used. The measure of calibration used was the Hosmer-Lemeshow test. An AUC of 0.5 indicates no discriminating power, an AUC of 0.7-0.8 indicates clinical usefulness, and values above 0.8 indicate excellent predictive capacity.[19] AUCs were compared using DeLong's method for CCI vs. CURB-65 and PSI. The comparison among the proportions of patients classified as being at a low risk by the three indices was performed using McNemar's test. A two-tailed $p < 0.05$ was considered statistically significant. A bivariate analysis of clinical characteristics vs. mortality was performed using the Student's t test for means and standard deviations or Pearson's chi-square test for proportions.

All analyses were performed with the SPSS Statistics software package, version 17 (SPSS Inc., Chicago, IL, USA) and Epidat, version 3.0 (Dirección Xeral de Saúde Pública de la Consellería de Sanidade, Xunta de Galicia, Santiago de Compostela, Spain).

The sample size was calculated using a simulation approach, considering differences between the scores in terms of sensitivity (ranging from 75% to 95%), specificity (from 50% to 70%), a survival:death ratio of 6:1, a statistical power of at least 80%, and a 95% CI. The resulting sample size was 304 patients.

RESULTS

Between April of 2014 and March of 2015, 459 patients with respiratory infections were evaluated. Of those, 155 did not meet the diagnostic criteria for CAP, and 304 were enrolled in the study (Figure 1). The mean age of the participants was 67.1 ± 17.3 years, 210 (69.0%) lived in urban areas, 171 (56.3%) were male, and 149 (49.0%) had asthma or COPD as a pre-existing lung disease. During the follow-up period, 47 patients (15.5%) died, 89 (29.3%) were admitted to the ICU, and 98 (32.2%) required mechanical ventilation (Table 1).

Clinical examination revealed that approximately one-third of the participants had airway secretions, and sputum was collected. Specimens for culture (sputum or blood) were collected from 203 patients (66.8%), and infectious agents were isolated in 52. The most common infectious agent was *Streptococcus pneumoniae*, in 19 patients (36.5%). Treatment was based on amoxicillin-clavulanate (72.2%) and/or azithromycin (65.6%). Mean duration of hospital stay was 7.2 ± 7.4 days (median, 5.0 days).

Table 2 shows that the scores of the three risk prediction models increased linearly with the increase in the mortality rate. The number of patients considered to be at a low risk according to the CCI, CURB-65, and PSI were 74 (24.3%), 89 (29.3%), and 80 (26.3%), respectively. The death rate of patients classified as being at a low risk by the CCI, CURB-65, and PSI was low (1.4%, 4.5%, and 3.7%, respectively).

Table 3 shows that the AUCs ranged from 0.73 to 0.84. The CCI had the greatest AUC, which was significantly different from the AUCs calculated for PSI ($p = 0.04$) and CURB-65 ($p = 0.02$). A CCI ≥ 3 and a PSI ≥ 3 were capable of detecting 93.6% of patients at risk of death at admission, whereas a CURB-65 score ≥ 2 detected 72.3% of patients in that category. Conversely, the PSI had the lowest specificity, and CURB-65 had the highest specificity to detect patients at risk of death at admission. Even though all models had low positive predictive values, negative predictive values were high: the likelihood of death was 7.0% using a CURB-65 score of < 2, 3.8% using a PSI of < 3, and 2.2% using a CCI of < 3.

Figure 2 shows that CCI was an excellent predictor of all-cause in-hospital mortality, with a greater AUC (0.83) than those for curb-65 (0.73; $p = 0.02$) and PSI (0.75; $p = 0.04$). There was no statistical difference between the AUCs of CURB-65 and PSI ($p = 0.7$). After Hosmer-Lemeshow calibration, p values for CCI, PSI, and CURB-65 were 0.9988, 0.9769, and 0.9906, respectively.

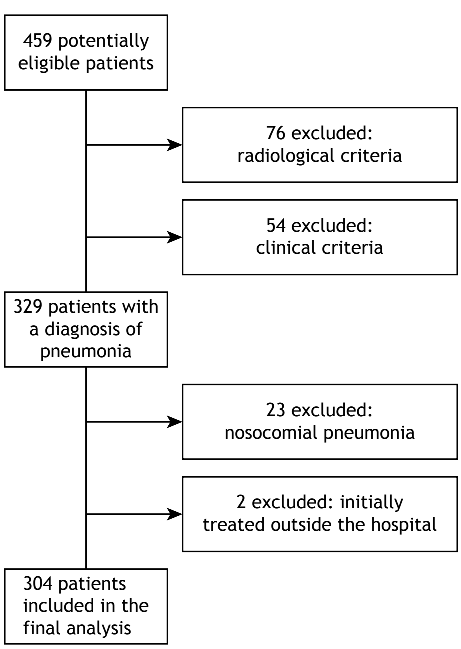

Figure 1. Flow chart of patient inclusion in the study.

An analysis of sensitivity comparing patients with and without previous lung disease did not reveal differences among the models to predict in-hospital mortality. The CCI for patients without previous lung disease (0.86; 95% CI: 0.78-0.93) was similar to that for those with previous lung disease (0.82; 95% CI: 0.73-0.91).

In our study, we decided not to exclude patients with a do-not-resuscitate order (n = 29), and 24 of those patients died. When we excluded those patients, there were no important changes in the AUCs (CCI = 0.83; CURB-65 = 0.75; and PSI = 0.74).

DISCUSSION

The present study using the C statistic showed that the CCI performed better than did CURB-65 and PSI to predict all-cause in-hospital mortality in patients admitted for CAP. To the best of our knowledge, this was the first study assessing the CCI as a predictor of all-cause in-hospital mortality in patients with CAP spontaneously seeking emergency care at a community hospital over a period of 1 year.

A previous study comparing the CCI with CURB-65 and PSI enrolled only elderly hospitalized individuals with pneumonia. The study did not detect a statistical difference between mortality prediction scores over 1 year.[(20)] The AUCs observed in the present study are similar to those previously described for CURB-65 (0.73 to 0.76) and PSI (0.70 to 0.80).[(11,21-24)] It is important to note that the scores do not measure the same construct. The CCI is a comorbidity score, with several variables. Unlike the CCI, CURB-65 and CRB-65 (no measurement of urea) scores are viewed as markers of disease severity at admission that are similar to PSI. Our findings support the notion that, despite being a general score, the CCI has an excellent predictive performance in patients with CAP.

The number of variables covered by a score can be associated with its overall performance; nevertheless, despite including a similar number of variables, the CCI and PSI differ regarding comorbidities, which are covered by the CCI, whereas PSI only accounts for pneumonia-specific characteristics. We confirmed the high sensitivity of CCI and found a low proportion of CAP patients who received a low-risk CCI and died (1.4%). These findings suggest that the CCI has more potential for clinical use than does the PSI or CURB-65.

The use of risk prediction models is warranted by guidelines for CAP management.[(7-9)] However, the detection of CAP severity is usually determined by clinical assessment,[(21)] which is frequently performed without the support from an objective, structured

Table 1. Characteristics of the hospitalized patients with community-acquired pneumonia (N = 304).[a]

Variable	Total	In-hospital death Yes (n = 47)	In-hospital death No (n = 257)	p
Age, years	67.1 ± 17.3	77.5 ± 12.7	65.21 ± 17.3	0.02
Sex				
Male	171 (56.2)	28 (16.4)	143 (83.6)	0.6
Female	133 (43.8)	19 (14.3)	114 (85.7)	
Skin color				
White	290 (95.4)	46 (15.9)	244 (84.1)	0.7
Non-White	14 (4.6)	1 (7.1)	13 (92.9)	
Smoking				
Yes	155 (51.0)	23 (14.8)	132 (85.2)	0.9
No	149 (49.0)	24 (16.1)	125 (83.9)	
Diabetes mellitus				
Yes	46 (15.1)	8 (17.4)	38 (82.6)	0.7
No	258 (84.9)	39 (15.1)	219 (84.9)	
Neoplasia				
Yes	39 (12.8)	15 (38.5)	24 (61.5)	< 0.001
No	265 (87.2)	32 (12.1)	233 (87.9)	
Heart failure				
Yes	71 (23.4)	15 (21.1)	56 (78.9)	0.14
No	233 (76.6)	32 (13.7)	201 (86.3)	
Chronic lung disease				
Yes	150 (49.3)	23 (15.3)	127 (84.7)	1.0
No	154 (50.7)	24 (15.6)	130 (84.4)	
Dementia				
Yes	65 (21.4)	23 (35.4)	42 (64.6)	< 0.001
No	239 (78.6)	24 (10.0)	215 (90.0)	
Myocardial infarction				
Yes	27 (8.9)	8 (29.6)	19 (70.4)	0.047
No	277 (91.1)	39 (14.1)	238 (85.9)	
Stroke				
Yes	76 (25)	26 (34.2)	50 (65.8)	< 0.001
No	228 (75)	21 (9.2)	207 (90.8)	
Chronic kidney disease				< 0.001
Yes	34 (11.2)	13 (38.2)	21 (61.8)	
No	270(88.8)	34 (12.6)	236 (87.4)	
ICU admission				
Yes	89 (29.3)	31 (34.8)	58 (65.2)	< 0.001
No	215 (70.7)	16 (7.4)	199 (92.6)	
Mechanical ventilation				< 0.001
Yes	98 (32.2)	35 (35.7)	63 (64.3)	
No	206 (67.8)	12 (5.8)	194 (94.2)	

[a]Values expressed as mean ± SD or n (%).

tool.[22] In this sense, the CCI has the advantage of being part of the usual assessment of severity in emergency services and, consequently, does not need to be introduced in the routine of patient care for the assessment of individuals with pneumonia. In addition, since the CCI does not require laboratory tests, it is appropriate for use in emergency settings. Finally, the CCI has been validated in a variety of clinical scenarios, and the results obtained so far consistently show that the CCI is a good predictor of mortality.[16,23,24] In the present study, the sensitivity analysis showed that the CCI had a prognostic performance that was similar in patients with and without previous lung disease.

The results of the present study must be interpreted in light of some potential limitations. All study participants were enrolled in one single center in a mid-sized city, which could limit the generalizability

Table 2. All-cause in-hospital mortality and need for mechanical ventilation as a function of the scores of the risk prediction models studied.[a]

Risk prediction model score	Total (N = 304)	In-hospital mortality (n = 47)	Mechanical ventilation (n = 98)
CCI			
0-2	74 (24.3)	1 (1.4)	12 (16.2)
3-5	101 (33.2)	7 (6.9)	23 (22.8)
6-8	98 (32.2)	21 (21.4)	47 (48.0)
8-17	31 (10.2)	18 (58.1)	16 (51.6)
CURB-65			
0	17 (5.5)	0 (0.0)	1 (5.9)
I	72 (23.7)	4 (5.6)	16 (22.2)
II	97 (31.9)	9 (9.3)	23 (23.7)
III	82 (26.9)	21 (25.6)	35 (42.7)
IV	33 (10.8)	11 (33.3)	21 (63.6)
V	3 (1.0)	2 (66.7)	2 (66.7)
PSI			
I	37 (12.2)	0 (0.0)	8 (21.6)
II	13 (4.3)	1 (7.7)	2 (15.4)
III	30 (9.9)	2 (6.7)	6 (20.0)
IV	126 (41.4)	11 (8.7)	24 (19.0)
V	98 (32.2)	33 (33.7)	58 (59.2)

CCI: Charlson Comorbidity Index; CURB-65: mental **C**onfusion, **U**rea, **R**espiratory rate, **B**lood pressure, and age = **65** years; and PSI: Pneumonia Severity Index. [a]Values expressed as n (%).

Table 3. Prognostic value of the risk prediction models studied for all-cause in-hospital mortality.

Score	AUC (95% CI)	Cutoff	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
CCI	0.84 (0.78-0.90)	≥ 3	93.6 (85.6-100.0)	51.8 (45.5-58.0)	26.2 (19.3-33.1)	97.8 (94.9-100)
CURB-65*	0.73 (0.66-0.81)	≥ 2	72.3 (58.5-86.2)	67.3 (61.4-73.2)	28.8 (20.2-37.4)	93.0 (89.0-97.0)
PSI**	0.75 (0.68-0.82)	≥ 3	93.6 (85.6-100.0)	29.9 (24.2-35.7)	19.6 (14.2-35.7)	96.2 (91.4-100)

PPV: positive predictive value; NVP: negative predictive value; CCI: Charlson Comorbidity Index; CURB-65: mental **C**onfusion, **U**rea, **R**espiratory rate, **B**lood pressure, and age = **65** years; and PSI: Pneumonia Severity Index. *p = 0.02 for CCI vs. CURB-65. **p = 0.04 for CCI vs. PSI.

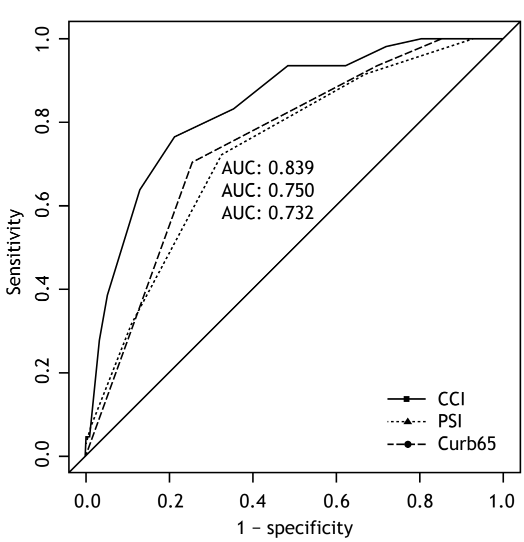

Figure 2. Area under the ROC curve of the risk prediction models studied for all-cause in-hospital mortality. CCI: Charlson Comorbidity Index; PSI: Pneumonia Severity Index; and CURB-65: mental **C**onfusion, **U**rea, **R**espiratory rate, **B**lood pressure, and age = **65** years.

of the findings to a certain extent. Conversely, it is likely that all eligible patients were included, since the community hospital is the only institution where patients with CAP can be hospitalized in that geographic area. Another positive aspect is that, during the study, the CCI was being assessed as an institutional strategy for decision-making regarding hospital admission. This translated into institutional engagement, standardization of clinical assessment, and design of clinical forms for data collection to be adopted by the ER. As a result, there were no losses to follow-up and the information collected had high quality, both of which are strengths of this study. Finally, similarly to all studies with a retrospective design, there are possible limitations, such as confounding and information biases. However, we do not believe that this affected the validity of our findings. The data in use were mainly assessed and documented during the hospital stay of the patients.

Another point that should be emphasized is that our results could not be generalized to the outpatient population. Patients admitted with CAP have their own characteristics, older age being one of the most important ones. The mean age of the patients in our study was 67 years, and only 24 patients were younger than 40 years of age. Data in the literature suggest that PSI has poor performance in younger patients,[25,26] and it is possible that the same occurs with the CCI. Due to the small number of deaths in younger patients (only 1), it was not possible to make this kind of assessment in the present study.

In conclusion, the present study showed that the CCI, when compared with PSI and CURB-65, is a better predictor of all-cause in-hospital mortality in patients with CAP. Using the CCI in ERs might contribute to reducing the mortality of patients with CAP.

AUTHOR CONTRIBUTIONS

LFB: study conception and design, interpretation of data, drafting and revision of the manuscript, and approval of the final version; LPD and SCF: study conception and design, drafting and revision of the manuscript, and approval of the final version.

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ORIGINAL ARTICLE

Knowledge of and attitudes toward the WHO MPOWER policies to reduce tobacco use at the population level: a comparison between third-year and sixth-year medical students

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ABSTRACT

Objective: To evaluate third- and sixth-year medical students in Brazil in terms of their knowledge of and attitudes toward the WHO MPOWER policies to reduce tobacco use. **Methods:** The WHO Global Health Professions Student Survey was applied in five cohorts of medical students evaluated in their third and sixth years of medical school, between 2008 and 2015. Comparisons were drawn between the two years of medical school in terms of the proportions of students who experimented with or used tobacco products in the last 30 days prior to the survey; knowledge of and compliance with smoke-free policies on the university campus; formal training on smoking cessation strategies; and self-recognition as role models for patients/society. **Results:** Of the 943 students who completed the survey, approximately 6% had smoked cigarettes in the last 30 days prior to the survey. Comparing the third and sixth years of medical school, we observed a significant increase in the proportion of students who were knowledgeable about smoking cessation strategies (22.74% vs. 95.84%; $p < 0.001$) and in that of those who recognized their role as models for patients/society (84.5% vs. 89.7%; $p = 0.023$). Student knowledge of the smoking policies on the university campus was associated with an increase in self-recognition as role models (adjusted absolute difference = 6.7%; adjusted $p = 0.050$). **Conclusions:** Knowledge of smoking cessation strategies and self-recognition as role models for patients/society increase over the course of medical school and are associated with the implementation of smoke-free policies.

Keywords: World Health Organization; Education, public health professional; Students, medical; Tobacco; Capacity building; Health behavior.

INTRODUCTION

Every year, tobacco use kills more than 8 million people worldwide.(1) In 2008, the WHO Framework Convention on Tobacco Control drafted six key policies to reduce demand for tobacco products. These measures are known as MPOWER, an acronym for the following recommendations: **M**onitor tobacco use and prevention policies; **P**rotect people from tobacco smoke; **O**ffer help to quit; **W**arn about the dangers of tobacco; **E**nforce bans on tobacco advertising, promotion, and sponsorship; and **R**aise taxes on tobacco.(2)

The seventh WHO Report on the Global Tobacco Epidemic,(3) launched in Brazil in July of 2019, was a milestone for tobacco control policies in the country. On that occasion, Brazil was recognized as the second country in the world to implement, at the highest level, all of the measures contained in the MPOWER package.

Most smokers want to quit, and the chance of cessation increases with health professionals offering help to quit tobacco use (behavioral and/or pharmacological approach). Offering help to quit smoking is a cost-effective population-based intervention.(3,4) The WHO report emphasized the need to expand the **O**ffer policy, by making more smoking cessation facilities available as an essential component of any tobacco control strategy.(3) Moreover, the WHO report highlighted that when offering help to quit smoking comes together with other tobacco control strategies, such as tax raises and smoking bans, that policy has a greater impact.(3)

In order to continue expanding the smoking treatment network, apart from increasing the availability of pharmacological therapy, ongoing attention to the formal training of future health professionals on smoking cessation approaches is necessary.(5-7) In this sense,

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we assume that if medical students are aware of the benefits of smoking cessation, they will be more likely to avoid smoking themselves and will act as role models for their patients.[8]

The present study aimed to evaluate medical students in Brazil in terms of their knowledge of and attitudes toward the WHO MPOWER policies to reduce tobacco use in the population, over the course of medical school. Therefore, third- and sixth-year medical students completed the WHO Global Health Professions Student Survey (GHPSS).[9]

METHODS

This was a prospective cohort study conducted among undergraduate third- and sixth-year medical students at the University of São Paulo School of Medicine, located in the city of São Paulo, Brazil. Information about the objectives of the current study was provided in the classroom by the authors responsible for the study. Students signed an informed consent form and then completed the WHO GHPSS.[9] The survey has been translated into Portuguese and validated for use in Brazil.[10,11]

Third-year medical students completed the survey in June of 2008-2012. Those third-year medical students, when they were in their sixth year of medical school (i.e., between 2011 and 2015), were invited to complete the same survey again, which created five student cohorts to be followed. In addition, we collected the answers of the sixth-year students who were not in the classroom in their third year of medical school when the survey had been applied in the previous years. It is important to mention that, of a total of 175 third-year students enrolled in the medical school annually between 2008 and 2012 (N = 875), 556 (63.5%) completed the survey. Of the sixth-year medical students, 110, 61, 82, 66, and 68 completed the survey in 2011, 2012, 2013, 2014, and 2015, respectively, totaling 387 (44.2%) of the total number of enrolled students (N = 875). Moreover, 203 (36.5%) of the third-year students were successfully followed up over the study period.

For descriptive statistical analysis, we selected the following variables related to the current and future implementation of the MPOWER policies at the university—**M**onitor: prevalence of cigarette use, proportion of experimentation with other forms of tobacco (chewing tobacco, snuff, bidis, cigars, or pipes), and proportion of experimentation with water pipes[12]; **P**rotect: protecting people from tobacco smoke was analyzed by the dichotomous variable related to the perception of the enforcement of smoking ban in the university ("Does your school have an official smoking ban policy in school buildings and clinics?" and "Is your school's official smoking ban in school buildings and clinics enforced?"); **O**ffer: students who reported having received formal training on smoking cessation strategies ("Have you received any formal training to address the issue of smoking cessation with patients at the medical school?"); and self-recognition as role models for patients/society ("Do you recognize yourself as a role model for your patients and the population?").[13,14]

For all descriptive statistical analyses, the chi-square test was used in order to compare the corresponding proportions between medical school years among all third- and sixth-year medical students who completed the survey. We also considered a secondary analytical sample for descriptive analyses that consisted of students who were successfully followed up over time (36.5% of the third-year students) in order to control for unmeasured characteristics that might otherwise confound the results. Moreover, among the students who were not lost to follow-up, in order to assess a possible mechanism to explain the relationship between school year and student perception of their role as models for patients/society (Figure 1), the differences in the proportion between third- and six-year medical students who answered "yes" to the question "Do you recognize yourself as a role model for your patients and the population?" were simultaneously adjusted for demographic and socioenvironmental variables. Because the response variable was dichotomous (i.e., yes or no), and given the public health implications of our study, crude absolute differences in the proportions were obtained from a generalized linear model using the binomial family and Gaussian link function.[15,16] Overall differences by medical school year in the proportions of the "role model" variable were simultaneously adjusted for age, smoking status, and the "smoking ban" variable (model A); then, we also added to the model the selected question about the curriculum "Have you received any formal training on how to approach smokers?" (model B); and, finally, we also considered a sensitivity analysis that included the entire baseline sample (third-year students), that is, students who were and were not lost to follow-up.

All analyses were performed with the Stata statistical software package, version 15.0 (StataCorp LP, College Station, TX, USA), and the study was approved by the research ethics committee of the institution (CAPPesq no. 0277/08).

RESULTS

Table 1 shows that there was a higher proportion of males who completed the survey among third-year medical students than among sixth-year students, although that difference was not statistically significant. The mean age of third- and sixth-year medical students was 22.2 years and 24.6 years, respectively. A low proportion of cigarette consumption and a high proportion of experimentation with water pipes were found in both groups.

We found a statistically significant increase in the proportion of medical students who reported having received formal training on smoking cessation approaches (22.7% in the third-year group vs. 95.8%

in the sixth-year group), as well as in the perception of compliance with the environmental tobacco smoke control policy inside university buildings/hospitals (59.3% vs. 69.0%). Detailed information on the proportion of students who stated that the smoking ban in school buildings and clinics is enforced can be found in the supplementary material.

The proportion of affirmative answers to the question regarding self-recognition as role models for patients/society was high in both groups, being higher in the sixth-year-student group (89.7% vs. 84.5%). Additional descriptive analyses, such as the prevalence of use of and experimentation with other forms of tobacco (stratified by sex), as well as the attitudes toward, beliefs about, and knowledge of such products, can be found in the supplementary material.

Table 2 shows that the proportion of males, the proportion of experimentation with water pipes, and the mean age of third-year medical students who were lost to follow-up were significantly higher than were those observed among students who were successfully followed-up. However, both subgroups showed similar proportions of smokers and answered similarly the questions regarding formal training, perception of smoking ban, and self-recognition as role models. Moreover, comparisons regarding demographic data, smoking status, and selected answers to the WHO GHPSS between third- and sixth-year medical students who were successfully followed up revealed similar results to those found for the overall sample of third- and sixth-year medical students who completed the survey (Table 1).

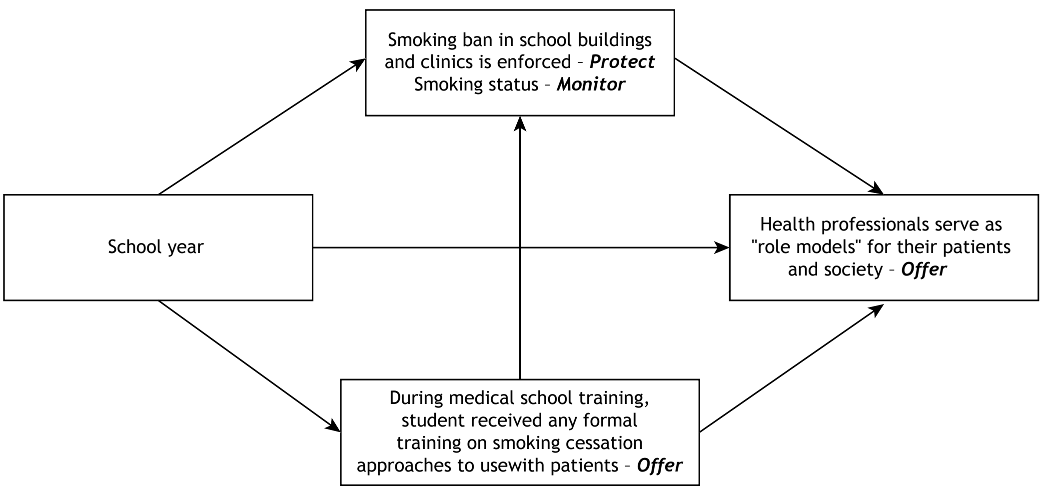

Figure 1. Schematic representation of the mechanisms to explain the relationship between school year and the research questions of interest.

Table 1. Demographic data, smoking status, and selected answers to the WHO Global Health Professions Student Survey of third-year medical students (2008-2012) and sixth-year medical students (2011-2015). University of São Paulo School of Medicine, Brazil.[a]

Variable	School year				p	Adjusted p*
	Third		Sixth			
	N = 556		N = 387			
Male	321	(57.7)	213	(55.5)	0.49	N/A
Tobacco use (Monitor)[b]						
Cigarette smoking	30	(5.4)	26	(6.7)	0.40	0.57
Experimentation with other forms of tobacco[c]	117	(21.0)	92	(23.8)	0.35	0.94
Experimentation with water pipe	241	(43.3)	168	(43.8)	0.83	0.90
University/curriculum (Offer)[b]						
Received any formal training on smoking cessation approaches	126	(22.7)	369	(95.8)	< 0.001	N/A
University/passive smoking (Protect)[b]						
Smoking ban in school buildings and clinics is enforced	326	(59.3)	265	(69.0)	< 0.002	N/A
Health professionals/attitude (Offer)[b]						
Recognize yourself as a role model for patients and the general population	464	(84.5)	347	(89.7)	0.023	N/A

[a]Values expressed as n (%). [b]In accordance with WHO MPOWER policies. [c]Except water pipe. *The overall difference by school year in the prevalence of smoking (or tobacco use) was simultaneously adjusted for age and sex.

Table 3 shows that there was an increase in student perception of being role models (regarding smoking) for patients/society from the third to the sixth year of medical school (crude absolute difference = +6.9%), although that increase was not found when the statistical model was adjusted for other demographic and socioenvironmental variables. Model B suggests that the effect of the school year was primarily mediated by having received formal training on smoking cessation strategies (crude absolute difference = +6.4%). The variable "having knowledge of the compliance with the smoking ban policy on the university campus" was also associated with an increase (crude and adjusted absolute difference) in student perception of being role models for patients and the general population.

We included the entire sample of third-year medical students in the sensitivity analysis (Table 4), and the main conclusions based on Table 3 remained unaltered.

DISCUSSION

From 2008 to 2015, the present study monitored third- and sixth-year medical students at the University of São Paulo School of Medicine on various issues related to smoking, and it revealed that the academic/university environment had a positive and transforming impact on those students.

Sixth-year medical students reported a significant increase in their knowledge of the approach to smoking treatment and in their perception of their role as behavioral models for patients/society, when compared with third-year students (MPOWER **O**ffer strategy).

Formal training on smoking cessation approaches probably had an impact on the increase in self-efficacy and expanded the repertoire of the students on topics related to smoking cessation to be used with smokers in the future (MPOWER **O**ffer strategy). A study involving medical students from Finland revealed that the lack of ability to address smokers appropriately during a clinical consultation stems from the lack of specific training.[13] Moreover, a study conducted in Iraq found that physicians who were smokers and reported having received formal training on smoking cessation during their university education recognized that they could have a more positive impact on the population if they quit smoking.[14] Formal education obtained during the years of medical training is, therefore, essential for the transformation and development of the student into a medical role model, insofar as the vision of his/her role in society expands.[17] Another important point is that the concept that students have of themselves evolves as they come into contact with patients and accumulate more knowledge, feel more confident, and have a greater professional identity.[18,19]

Article 14 of the WHO Framework Convention on Tobacco Control[20] strengthens the importance of reducing the number of current tobacco users through teaching about the treatment of tobacco dependence. One of WHO's global monitoring frameworks for the noncommunicable disease action plan is to reduce tobacco use. To achieve that goal, medical schools

Table 2. Demographic data, smoking status, and selected answers to the WHO Global Health Professions Student Survey of third-year medical students (lost and not lost to follow-up subgroups) and sixth-year medical students (not lost to follow-up). University of São Paulo School of Medicine, Brazil.[a]

Variable	School year		
	Third (2008-2012)[c,d]		Sixth (2011-2015)[d]
	Lost to follow-up n = 353	Not lost to follow-up n = 203	Not lost to follow-up n = 203
Demographic			
Male	62.0%	50.3%	50.3%
Mean age, years	22.5	21.8	24.5
Tobacco use (**M**onitor)[a]			
Cigarette smoking	5.7%	4.9%	5.9%
Experimentation with other forms of tobacco[b]	23.1%	18.0%	17.3%
Experimentation with water pipe	49.7%	33.3%	33.7%
University/curriculum (**O**ffer)[a]			
Received any formal training on smoking cessation approaches	24.4%	19.8%	95.1%
University/passive smoking (**P**rotect)[a]			
Smoking ban in school buildings and clinics is enforced	61.3%	55.7%	63.4%
Health professionals/attitude (**O**ffer)[a]			
Recognize yourself as a role model for patients and the general population	84.7%	84.2%	91.1%

[a]In accordance with WHO MPOWER policies. [b]Except water pipe. [c]Statistically significant differences between the subgroups are indicated as follows: male (p = 0.007); age (p = 0.009); and water pipe experimentation (p < 0.001; p adjusted for sex and age = 0.15), [d]Statistically significant differences between school years among students who were not lost to follow-up are indicated as follows: age (p < 0.001); **O**ffer policy (p < 0.001); and role model (p = 0.033).

Table 3. Crude and adjusted absolute differences in student self-recognition as role models for patients/society among medical students who were successfully followed up, by school year, demographic variable, and socioenvironmental variable.

Variable	CAD[a]		Model A[b] AAD[a]		Model B[c] AAD[a]	
	%	p	%	p	%	p
School year						
Third	Ref		Ref			
Sixth	6.9	0.03	6.3	0.09	1.9	0.70
Sex						
Female	Ref		–	–	–	-
Male	−3.0	0.34	–	–	–	-
Age, years	0.9	0.10	−0.1	0.89	−0.1	0.87
Smoking status						
Nonsmoker	Ref		Ref		Ref	
Smoker	−11.0	0.23	−11.7	0.18	−11.5	0.19
Received any formal training on smoking cessation approaches						
No	Ref		–	–	Ref	
Yes	7.9	0.02	–	–	+6.4	0.14
Smoking ban in school buildings and clinics is enforced						
No	Ref		Ref		Ref	
Yes	7.9	0.02	6.6	0.05	6.7	0.05

CAD: crude absolute difference; and AAD: adjusted absolute difference. [a]Generalized linear model using the binomial family and Gaussian link function. The regression coefficient was the absolute difference in proportions. [b]The overall difference by school year in the proportion of affirmative answers to the question about self-recognition as role models was simultaneously adjusted for age, smoking status, cohort of students, and smoking ban. [c]The overall difference in the proportion of affirmative answers to the question about self-recognition as role models was simultaneously adjusted for age, smoking status, cohort of students, smoking ban, and the question about receiving any formal training on smoking cessation approaches.

Table 4. Crude and adjusted absolute differences in student self-recognition as role models for patients/society among the overall sample of medical students, by school year, demographic variable, and socioenvironmental variable .

Variable	CAD[a]		Model A[b] AAD[a]		Model B[c] AAD[a]	
	%	p	%	p	%	p
School year						
Third	Ref		Ref			
Sixth	6.6	0.009	7.1	0.010	1.6	0.62
Sex						
Female	Ref		-	-	-	-
Male	−2.2	0.39	-	-	-	-
Age, years	0.3	0.099	−0.2	0.69	−0.2	0.79
Smoking status						
Nonsmoker	Ref		Ref		Ref	
Smoker	−8.2	0.21	−8.2	0.19	−8.4	0.18
Received any formal training on smoking cessation approaches						
No	Ref		-	-	Ref	
Yes	5.8	0.049	-	-	6.1	0.075
Smoking ban in school buildings and clinics is enforced						
No	Ref		Ref		Ref	
Yes	6.8	0.011	5.9	0.026	6.0	0.029

CAD: crude absolute difference; and AAD: adjusted absolute difference. [a]Generalized linear model using the binomial family and Gaussian link function. The regression coefficient was the absolute difference in proportions. [b]The overall difference in the proportion of affirmative answers to the question about self-recognition as role models was simultaneously adjusted for age, smoking status, cohort of students, and smoking ban. [c]The overall difference in the proportion of affirmative answers to the question about self-recognition as role models was simultaneously adjusted for age, smoking status, cohort of students, smoking ban, and the question about receiving any formal training on smoking cessation approaches.

will therefore have to do their part in teaching about tobacco control in order to help smokers to quit.[20,21]

At present, smoking cessation treatment involves both behavioral/cognitive counseling (brief or intensive, individual or in group) and pharmacotherapy, and its costs are fully covered to all smokers by the Brazilian Unified Health Care System in primary care facilities or hospitals. In 2019, after a long and arduous process, the National Health Insurance Agency of the Brazilian National Ministry of Health finally approved the inclusion of smoking cessation treatment in private health insurance coverage, benefiting 47 million privately insured people (22% of the total population in Brazil).[22-24]

To the best of our knowledge, this is the first study that evaluated the association between the GHPSS and medical students' self-recognition of their importance as future physicians who will offer their patients help to quit tobacco use and will serve as role models for their patients/society. The reasons for their self-recognition as role models can be a result of a transition process during their medical training, determined not only by formal education methodology but also by socioenvironmental components, such as the smoke-free environment law that came into force in the state of São Paulo in 2009 (MPOWER **P**rotect policy).[12] In fact, the 2019 Report on the Global Tobacco Epidemic[3] emphasizes that when the help to quit smoking comes together with other tobacco control strategies, there is a greater impact.

Our analysis showed that the perception of enforcement of the smoking ban inside the campus (MPOWER **P**rotect policy) also influenced student self-recognition as a model of behavior for patients and the population, regardless of the school year. It is worth mentioning that, in 2009, ninety days prior to the enactment of the Anti-smoking Law[12] that created smoke-free environments and banned the use of any smoking product, derived or not from tobacco, in all public and private enclosed places, the most varied types of communication outlets massively disseminated information about the contents of the law and the necessary changes that should take place.

According to Bandura,[25] the observational paradigm of the process of awareness of becoming a role model is composed of attention, retention, reproduction, and motivation, which in turn is influenced by the behavior, the individual, and the environment. The vast majority of the citizens in the state of São Paulo comply with the smoke-free environment law,[12] which suggests that they understood the benefit of the law for public health. The assessment of students that was conducted between June/July of each year probably revealed the positive impact of a well-conducted public health campaign in the perception of the third- and sixth-year medical students as of 2010. This change in beliefs and behaviors is corroborated by studies conducted in the last decade that demonstrated that disclosure and dissemination of health care knowledge lead to changes in the attitudes of medical professionals and the population in general.[26-29]

The social environmental components, such as the implementation of smoke-free environments in hospital and medical education settings, are important for the development of the student's own image as a future health professional who will serve as a role model for patients and society.[30] A change in the educational environment, such as the enforcement of the smoke-free environment law,[12] should be adopted on a broader scale in the education of medical students as part of the contribution to the construction of a "role model".[31] By means of a cultural change, medical students acquire skills and competences to cope with the new norms and values of his/her community.[8] This concept is known as "community practices"[32] and contributes, together with the years spent in medical school, to the development of the professional identity of the physician.[8]

Although we did not find a statistically significant association between smoking status and self-recognition as a role model, a physician who smokes may be less likely to motivate and advise smokers to quit.[10,11] Our results also cause concern because, although the cigarette smoking rate was low, we found a high proportion of water pipe experimentation (MPOWER **M**onitor policy), despite the knowledge that smoke is not filtered through the water pipe water, which could negatively impact on the MPOWER **O**ffer policy (help to quit tobacco use).[3] Other national and international studies have also found high rates of water pipe experimentation/use among medical students, which poses an additional challenge to increasing the effectiveness of smoking cessation treatment in Brazil and other countries.[33,34]

Our study has some limitations. It was unable to assess the independent effects of policies other than the smoke-free policy implemented during the study period (e.g., in 2011, a new policy for pricing and taxing tobacco products was implemented in Brazil). Another limitation of the present study was that a reduced number of sixth-year medical students attend formal classes, mostly because they work full time in the hospital and have limited activities in the classroom, which hindered contact between students and researchers and reduced student participation in the study. Although approximately 60% of the third-year medical students were lost to follow-up, our analysis including students who were not successfully followed up produced results that were consistent with those students who were, which suggests that our conclusions might be somewhat generalizable.

In conclusion, knowledge of smoking cessation strategies and self-recognition as role models for patients/society increase over the course of medical school and are associated with the successful implementation of smoke-free policies in enclosed places and on the university campus. This will be important to improve smoking cessation treatment in the future.

AUTHOR CONTRIBUTIONS

SRM: planning, interpretation of evidence, writing/revision of preliminary and final versions, and approval of final version. ASS: interpretation of evidence, writing/revision of preliminary and final versions, and approval of final version. MAB: interpretation of evidence. GFP: conception, planning, and interpretation of evidence. RBP and EMSL: conception and planning. RGB: writing/revision of preliminary and final versions. FLAF: conception, planning, and writing/revision of preliminary/final versions. MTF: revision of preliminary and final versions. UPS: conception, planning, interpretation of evidence, and drafting/revision of preliminary and final versions.

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ORIGINAL ARTICLE

Protective mechanical ventilation in patients with risk factors for ARDS: prospective cohort study

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ABSTRACT

Objective: To evaluate the association that protective mechanical ventilation (MV), based on V_T and maximum distending pressure (MDP), has with mortality in patients at risk for ARDS. **Methods:** This was a prospective cohort study conducted in an ICU and including 116 patients on MV who had at least one risk factor for the development of ARDS. Ventilatory parameters were collected twice a day for seven days, and patients were divided into two groups (protective MV and nonprotective MV) based on the MDP (difference between maximum airway pressure and PEEP) or V_T. The outcome measures were 28-day mortality, ICU mortality, and in-hospital mortality. The risk factors associated with the adoption of nonprotective MV were also assessed. **Results:** Nonprotective MV based on V_T and MDP was applied in 49 (42.2%) and 38 (32.8%) of the patients, respectively. Multivariate Cox regression showed that protective MV based on MDP was associated with lower in-hospital mortality (hazard ratio = 0.37; 95% CI: 0.19-0.73) and lower ICU mortality (hazard ratio = 0.40; 95% CI: 0.19-0.85), after adjustment for age, Simplified Acute Physiology Score 3, and vasopressor use, as well as the baseline values for PaO_2/FiO_2 ratio, PEEP, pH, and $PaCO_2$. These associations were not observed when nonprotective MV was based on the V_T. **Conclusions:** The MDP seems to be a useful tool, better than V_T, for adjusting MV in patients at risk for ARDS.

Keywords: Respiration, artificial; Tidal volume; Respiratory distress syndrome, adult.

INTRODUCTION

Although mechanical ventilation (MV) is an essential supportive measure for patients with severe respiratory failure,[1,2] it can cause lung injury characterized by inflammatory infiltrates and hyaline membranes, as well as alveolar and interstitial edema, being designated ventilator-induced lung injury (VILI).[3]

Previously injured lungs, as in ARDS, are more susceptible to VILI,[4] and, in such cases, lung-protective ventilator settings, such as reducing V_T to ≤ 6 mL/kg of predicted body weight and plateau pressure to ≤ 30 cmH_2O, are associated with lower mortality.[5-7] Amato et al.[8] demonstrated that distending pressure (DP, i.e., plateau pressure minus PEEP) correlated better with mortality than did V_T, plateau pressure, or PEEP. This correlation was confirmed by Bellani et al.,[9] and a DP of < 14-15 cmH_2O has been recommended as a lung-protective ventilation strategy in ARDS.[10]

Although experimental studies have shown that VILI can occur in previously normal lungs,[11,12] the impact of lung-protective MV on patients without ARDS is controversial. In a randomized clinical trial in patients without ARDS, Determann et al.[13] showed that low V_T resulted in a lower occurrence of VILI. However, in another randomized clinical trial in patients without ARDS, no differences were found between patients receiving ventilation with a low V_T and those receiving ventilation with a high V_T regarding mortality and duration of MV.[14]

Observational studies have evaluated the impact of DP on mortality in patients without ARDS; however, the results have been conflicting. Although Simonis et al. showed an association between an increased DP and ICU mortality,[15] Schimidt et al. found no association between DP and in-hospital mortality in patients without ARDS.[16] One limitation of these studies was that maximum airway pressure was assumed to be equivalent to plateau pressure in patients receiving pressure-controlled ventilation and was used in order to calculate DP. Maximum airway pressure is necessarily greater than plateau pressure, and we propose that the term maximum DP (MDP) be used in order to refer to the difference between maximum airway pressure and PEEP.

One possible explanation for these conflicting results is that mechanically ventilated patients without ARDS can present with a variety of clinical conditions requiring ventilatory support, all of which can differ in terms of the risk for VILI. Given that VILI ultimately results in an inflammatory lung injury that is similar to ARDS, it is to

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be expected that VILI is more likely to occur in patients without ARDS with one or more risk factors for ARDS than in those with no risk factors for ARDS.[17] The primary objective of this prospective cohort study was to evaluate the association that protective MV (based on V_T and MDP) has with mortality in patients at risk for ARDS. A secondary objective was to identify factors associated with nonprotective MV in these patients.

METHODS

This was a prospective cohort study conducted between May of 2016 and March of 2018 in the ICU of the *Hospital Universitário da Universidade Federal de Juiz de Fora* (HU-UFJF, Federal University of Juiz de Fora University Hospital), located in the city of Juiz de Fora, Brazil. The HU-UFJF ICU is a 9-bed medical-surgical ICU for adult patients. The study followed the principles of the Declaration of Helsinki and was approved by the Human Research Ethics Committee of the HU-UFJF (Ruling no. 2,494,061). Close relatives of the patients gave written informed consent.

Study cohort

The inclusion criteria were being ≥ 18 years of age, having been admitted to the ICU, being on MV, and having at least one of the following risk factors for ARDS: pneumonia, sepsis, shock, aspiration of gastric contents, pancreatitis, blood component transfusion, trauma, pulmonary contusion, and lung injury caused by inhalation or near drowning. The exclusion criteria were as follows: having been diagnosed with ARDS in accordance with the Berlin Definition of ARDS[18] within two days of endotracheal intubation; having been transferred from another hospital while on MV; having been on MV for less than 48 h; and having been started on palliative care by decision of the treatment team.

All patients were ventilated with a Servo-S ventilator (Maquet, Solna, Sweden), initially in pressure-controlled mode. Patients were switched to pressure support ventilation if they were awake and stable, as evaluated by the treatment team.

Variables

Data on baseline clinical and demographic characteristics were collected at ICU admission for the Simplified Acute Physiology Score 3 (SAPS 3) and SOFA, as were data on diagnosis at admission and comorbidities. The day of endotracheal intubation was designated day 0, the following data being recorded: reason for intubation, risk factors for ARDS, the SAPS 3, SOFA scores, predicted body weight—weight = 50.0 + 0.91 × (height in cm − 152.4) for males and weight = 45.5 + 0.91 × (height in cm − 152.4) for females—BMI, ventilatory parameters, and arterial blood gases.

From MV day 1 to MV day 7, ventilatory parameters were collected daily at 8:00 a.m. and 8:00 p.m., as were data on the use of vasopressors, corticosteroids, and neuromuscular blocking agents while on MV. Data on 28-day mortality, ICU mortality, and in-hospital mortality were also collected.

The exposure variable was whether or not protective MV based on V_T was used within the first 7 days of MV. Protective MV based on V_T was considered to have been provided when the V_T was found to be lower than 8 mL/kg of predicted body weight in at least 80% of the 14 measurements performed within the first 7 days of MV. A second exposure variable was whether protective MV based on MDP (difference between maximum airway pressure and PEEP) was used within the first 7 days of MV. Protective MV based on MDP was considered to have been provided when the MDP was found to be lower than 15 cmH_2O in at least 80% of the 14 measurements performed within the first 7 days of MV. MV was also considered to be protective when it met the criteria for protective MV as defined by both the V_T and the MDP.

Outcome measures

The outcome measures were 28-day mortality, in-hospital mortality, and ICU mortality.

Statistical analysis

The results are presented as mean and standard deviation, median and interquartile range, or proportions, as appropriate. For continuous variables with normal distribution, the groups protective MV and nonprotective MV were compared by the Student's t-test; for continuous variables with non-normal distribution, they were compared by the Wilcoxon test, the Shapiro-Wilk test being used in order to determine the distribution of the variables. For categorical variables, the groups were compared by the chi-square test.

Multivariate Cox regression was used in order to estimate the hazard ratio (HR) for 28-day mortality, ICU mortality, and in-hospital mortality as a function of whether or not protective MV had been used. The HR was adjusted for age, SAPS 3, use of vasopressors, the PaO_2/FiO_2 ratio, PEEP, respiratory system compliance (C_{rs}), pH, and $PaCO_2$.

Multivariate logistic regression was performed to analyze factors independently associated with the use of nonprotective MV, all of the variables showing $p < 0.2$ in the univariate analysis being included in the multivariate analysis. The coefficients were estimated by the maximum likelihood method.

Values of $p < 0.05$ were considered statistically significant. All analyses were performed with the Stata statistical package, version 15.1 (StataCorp LP, College Station, TX, USA).

RESULTS

During the study period, 258 patients were admitted to the HU-UFJF ICU. Of those, 148 met the inclusion criteria. Of those, 32 were excluded, the study cohort therefore consisting of 116 patients. The main reason for exclusion was having been started on palliative care by decision of the treatment team. As can be seen in Figure 1, nonprotective MV based on V_T was used in 49 patients (42.2%; 95% CI: 33.5-51.1%) and nonprotective MV based on MDP was used in 38 (32.8%; 95% CI: 24.7-41.9%).

The main baseline characteristics of the patients are summarized in Table 1. The mean age was 59.3 ± 17.7 years, and the SAPS 3 at ICU admission was 49.9 ± 15.8. Major risk factors for ARDS included shock, in 71 patients (61.2%), sepsis, in 68 (58.6%), and pneumonia, in 27 (23.3%); a total of 66 patients (56.9%) had more than one risk factor for ARDS. Table 2 shows the outcomes of patients receiving protective or nonprotective MV based on V_T and MDP.

At baseline, patients receiving protective MV based on V_T had lower severity scores (SAPS 3), higher predicted body weight, higher pH values, and lower FiO_2 than did those receiving nonprotective MV (Table 1). Protective MV based on V_T was not associated with lower in-hospital mortality, ICU mortality, or 28-day mortality (Tables 3 and 4). Given that sample size was not initially calculated, the power of the study to detect an association between protective MV based on V_T and ICU mortality was calculated. On the basis of the number of patients included in the study (N = 116) and the results obtained (HR = 0.72), with $p < 0.05$ being considered significant, the power of the study to detect an association between protective MV based on V_T and ICU mortality was 39%. The following variables were independently associated with nonprotective MV based on the V_T: the SAPS 3 at admission, predicted body weight, and the PaO_2/FiO_2 ratio (Table 5).

Patients receiving protective MV based on MDP had higher C_{rs}, better gas exchange (higher PaO_2/FiO_2 and lower $PaCO_2$), and higher pH values, as well as requiring lower FiO_2 and PEEP (Table 1). After adjustment for covariates, protective MV based on MDP was associated with lower in-hospital mortality, ICU mortality, and 28-day mortality (Tables 3 and 4). On the basis of the number of patients included in the study (N = 116) and the results obtained (HR = 0.68), with $p < 0.05$ being considered significant, the power of the study to detect an association of protective MV based on MDP with mortality was 43%. The following variables were independently associated with nonprotective MV based on the MDP: pneumonia as the reason for initiating MV, C_{rs}, the PaO_2/FiO_2 ratio, and pH (Table 5).

When protective MV was defined on the basis of both the V_T and the MDP, it was significantly associated with 28-day mortality, although not with in-hospital mortality or ICU mortality (Tables 3 and 4).

DISCUSSION

In the present study, no association was found between lower mortality and protective MV based on a V_T of < 8 mL/kg of predicted body weight in more than 80% of the measurements performed within the first 7 days of ventilatory support in patients at risk for ARDS. However, when protective MV was defined on the basis of an MDP of < 15 cmH_2O, it was associated with lower in-hospital mortality, ICU mortality, and 28-day mortality.

Although it is well established that protective MV reduces mortality in patients with ARDS,[6,7] the benefits of protective MV in patients without ARDS remain controversial. In a meta-analysis of randomized clinical trials and observational studies conducted in ICUs or during major surgery, protective MV with low V_T was associated with better clinical outcomes in patients without ARDS, including lower mortality and lower occurrence of lung infection and injury.[19] However, in a clinical trial of patients without ARDS, no differences in mortality (ICU mortality, in-hospital

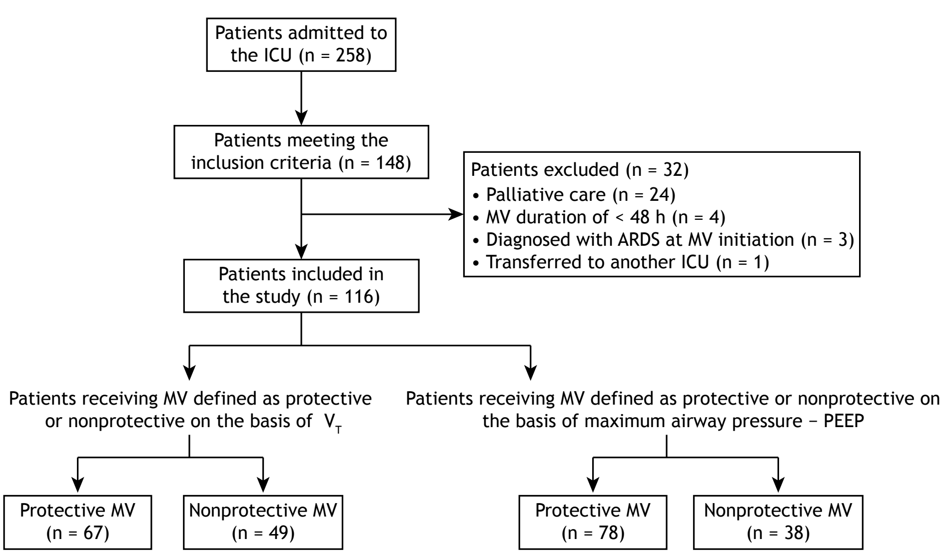

Figure 1. Cohort study flow chart. MV: mechanical ventilation.

Table 1. Baseline characteristics of patients receiving protective or nonprotective mechanical ventilation.[a]

		Group					
		V_T			MDP		
	Total sample (N = 116)	Protective MV (n = 67)	Nonprotective MV (n = 49)	p	Protective MV (n = 78)	Nonprotective MV (n = 38)	p
Age, years	59.3 ± 17.7	57.0 ± 18.2	62.3 ± 16.7	0.108	57.6 ± 18.6	62.6 ± 15.2	0.152
Males	65 (56.0)	44 (65.7)	21 (42.9)	0.140	47 (60.3)	18 (47.4)	0.189
SAPS 3 at admission	49.9 ±15.8	46.8 ± 15.2	54.3 ± 15.8	0.011	48.7 ± 15.8	52.4 ± 15.9	0.247
SOFA at admission	7.8 ± 3.7	7.7 ± 3.5	8.0 ± 3.9	0.741	7.7 ± 3.7	8.0 ± 3.6	0.684
SAPS 3 at intubation	51.2 ± 14.8	47.9 ± 14.3	55.7 ± 14.2	0.004	50.0 ± 14.8	53.6 ± 14.6	0.219
SOFA at intubation	8.3 ± 3.3	8.2 ± 3.2	8.5 ± 3.4	0.592	8.2 ± 3.3	8.5 ± 3.3	0.724
BMI, kg/m^2	22.5 [19.0-27.0]	22.3 [19.6-26.3]	23.3 [18.0-28.3]	0.789	22.2 [18.8-25.6]	23.6 [20.9-28.3]	0.171
Predicted body weight, kg	58.5 ± 10.3	61.7 ± 9.1	54.2 ± 10.5	< 0.001	58.9 ± 10.7	57.7 ± 9.8	0.549
Reason for ICU admission				0.872			0.715
Clinical	95 (81.9)	55 (82.1)	40 (81.6)		63 (80.8)	32 (84.2)	
Elective surgery	13 (11.2)	8 (11.9)	5 (10.2)		10 (12.8)	3 (7.9)	
Urgent surgery	8 (6.9)	4 (6.0)	4 (8.2)		5 (6.4)	3 (7.9)	
Risk factor for ARDS							
Pneumonia	27 (23.3)	16 (23.9)	11 (22.5)	0.857	14 (17.9)	13 (34.2)	0.052
Sepsis	68 (58.6)	38 (56.7)	30 (61.2)	0.626	47 (60.3)	21 (55.3)	0.608
Shock	71 (61.2)	37 (55.2)	34 (69.4)	0.122	46 (59.0)	25 (65.8)	0.480
Aspiration	4 (3.5)	4 (5.9)	0 (0.0)	0.082	3 (3.9)	1 (2.6)	0.737
Blood product transfusion	21 (18.1)	10 (14.9)	11 (22.5)	0.371	14 (18.0)	7 (18.4)	0.951
Other	10 (8.6)	6 (8.9)	4 (8.2)	0.881	8 (10.3)	2 (5.3)	0.368
Number of risk factors				0.399			0.464
1	50 (43.1)	32 (47.8)	18 (36.7)		34 (44.0)	16 (42.1)	
2	47 (40.5)	26 (38.8)	21 (42.9)		33 (42.3)	14 (36.8)	
3	18 (15.5)	8 (11.9)	10 (20.4)		11 (14.1)	7 (18.4)	
4	1 (0.9)	1 (1.5)	0 (0.0)		0 (0.0)	1 (1.4)	
MV (day 0)							
FiO_2	0.5 [0.4-0.6]	0.45 [0.4-0.6]	0.5 [0.4-0.7]	0.027	0.4 [0.4-0.5]	0.6 [0.5-0.7]	<0.001
FR, breaths/min	18 [16-22]	20 [16-22]	17 [16-20]	0.049	18 [16-21]	18 [16-22]	0.608
V_T/predicted body weight, mL/kg	7.5 ± 1.4	6.9 ± 1.1	8.3 ± 1.4	< 0.001	7.5 ± 1.5	7.4 ± 1.4	0.617
MDP, cmH_2O	14.5 ± 3.4	14.3 ± 3.4	14.8 ± 3.5	0.447	13.5 ± 3.0	16.6 ± 4.1	<0.001
Paw_{max}, cmH_2O	20.6 ± 4.5	20.5 ± 4.7	21.0 ± 4.4	0.565	19.3 ± 3.7	23.5 ± 5.0	<0.001
PEEP, cmH_2O	5 [5-7]	5 [5-6]	6 [5-7]	0.117	5 [5-6]	6 [5-7]	0.019
C_{rs}, mL/cmH_2O	31.8 ± 10.3	31.5 ± 9.8	32.2 ± 11.0	0.712	33.7 ± 10.1	27.7 ± 9.5	<0.001
Arterial blood gas analysis (day 0):							
pH	7.34 ± 0.11	7.36 ± 0.1	7.32 ± 0.1	0.032	7.36 ± 0.11	7.30 ± 0.10	0.005
$PaCO_2$, mmHg	289.0 ± 104.0	301.8 ± 96.0	272.5 ± 112.1	0.134	320.0 ± 98.0	224.0 ± 85.0	<0.001
$PaCO_2$, mmHg	38.5 ± 11.6	38.7 ± 10.6	38.2 ± 12.9	0.803	36.2 ± 9.1	43.3 ±14.4	0.002

MDP: maximum distending pressure; SAPS 3: Simplified Acute Physiology Score 3; MV: mechanical ventilation; Paw_{max}: maximum airway pressure; and C_{rs}: respiratory system compliance. [a]Values expressed as n (%), mean ± SD, or median [IQR].

Table 2. Outcomes of patients receiving protective or nonprotective mechanical ventilation.[a]

Variable	Total sample (n = 116)	Group					
		V_T			MDP		
		Protective MV (n = 67)	Nonprotective MV (n = 49)	p	Protective MV (n = 78)	Nonprotective MV (n = 38)	p
Use of vasopressors	100 (86.2)	56 (83.6)	44 (89.8)	0.338	65 (83.3)	35 (92.1)	0.198
Use of corticosteroids	90 (77.6)	49 (73.1)	41 (83.7)	0.179	57 (73.1)	33 (86.8)	0.095
Use of neuromuscular blocking agents	19 (16.4)	11 (16.4)	8 (16.3)	0.990	7 (9.0)	12 (31.6)	0.002
28-day mortality	35 (30.2)	14 (20.9)	21 (42.9)	0.011	19 (24.4)	16 (42.1)	0.051
ICU mortality	47 (40.5)	22 (32.9)	25 (51.0)	0.049	23 (29.5)	24 (63.2)	0.001
In-hospital mortality	59 (50.9)	28 (41.8)	31 (63.3)	0.22	30 (38.5)	29 (76.3)	< 0.001

MDP: maximum distending pressure; and MV: mechanical ventilation. [a]Values expressed as n (%).

Table 3. Univariate Cox regression for the association of mortality with protective mechanical ventilation based on V_T, on maximum distending pressure, and on both.

Outcome	Protective MV based on					
	V_T[a]		MDP[b]		Both the V_T and the MDP	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
In-hospital mortality	0.63 (0.37-1.05)	0.079	0.60 (0.36-1.01)	0.053	0.46 (0.29-0.93)	0.03
ICU mortality	0.72 (0.40-1.28)	0.261	0.49 (0.27-0.88)	0.189	0.60 (0.30-1.21)	0.151
28-day mortality	0.44 (0.22-0.86)	0.017	0.56 (0.29-1.11)	0.096	0.38 (0.17-0.83)	0.016

MV: mechanical ventilation; MDP: maximum distending pressure; and HR: hazard ratio. [a]Protective MV based on V_T: a V_T of < 8 mL/kg of predicted body weight in at least 80% of the 14 measurements performed within the first seven days of MV. [b]Protective MV based on MDP: an MDP of < 15 cmH_2O in at least 80% of the 14 measurements performed within the first seven days of MV.

Table 4. Multivariate Cox regression for the association of mortality with protective mechanical ventilation based on V_T, on maximum distending pressure, and on both.[a]

Outcome	Protective MV based on					
	V_T[b]		MDP[c]		Both the V_T and the MDP	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
In-hospital mortality	0.75 (0.43-1.32)	0.320	0.48 (0.26-0.90)	0.022	0.53 (0.28-1.01)	0.055
ICU mortality	0.78 (0.42-1.47)	0.443	0.45 (0.24-0.90)	0.023	0.59 (0.28-1.25)	0.151
28-day mortality	0.53 (0.24-1.16)	0.113	0.41 (0.18-0.94)	0.036	0.40 (0.17-0.94)	0.036

MV: mechanical ventilation; MDP: maximum distending pressure; and HR: hazard ratio. [a]Model adjusted for age, Simplified Acute Physiology Score 3, use of vasopressors, PaO_2/FiO_2, PEEP, respiratory system compliance, pH, and $PaCO_2$. [b]Protective MV based on V_T: a V_T of < 8 mL/kg of predicted body weight in at least 80% of the 14 measurements performed within the first seven days of MV. [c]Protective MV based on MDP: an MDP of < 15 cmH_2O in at least 80% of the 14 measurements performed within the first seven days of MV.

mortality, 28-day mortality, or 90-day mortality), duration of MV, or ICU length of stay were found between patients randomized to MV with low V_T (4-6 mL/kg of predicted body weight) and those randomized to MV with high V_T (10 mL/kg of predicted body weight).[14] In an observational study of a cohort of 935 patients without ARDS,[16] no correlations were found between V_T and mortality. These results are consistent with ours and constitute evidence against the use of low V_T in mechanically ventilated patients without ARDS.

One possible explanation for the lack of association between lower V_T and better outcomes in patients without ARDS is that such patients have higher C_{rs}, which can reduce the risk of injury even if they receive MV with high V_T. Therefore, DP (or MDP, as in our study) might be better than V_T to adjust MV for lung-protective ventilation in patients without ARDS. DP is calculated by dividing V_T by static compliance of the respiratory system.[8] Therefore, whenever compliance is reduced, translating to greater pulmonary involvement, V_T should be reduced for protective MV based on the DP. A randomized clinical trial[14] corroborated this hypothesis, showing no differences between MV with low V_T and MV with intermediate V_T regarding the outcomes of patients without ARDS, with the levels of DP in both groups being protective against VILI (11 cmH_2O in the low V_T group and 13 cmH_2O in the intermediate V_T group).

In our study, protective MV based on the MDP correlated with lower mortality, suggesting that MDP is an important parameter to be considered for protective MV in patients without ARDS. The association between protective MV and mortality was found to be worse

Table 5. Factors associated with nonprotective mechanical ventilation based on both the V_T and the maximum distending pressure.

Factor	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p	OR (95% CI)	p
V_T				
Age	1.02 (1.00-1.04)	0.109		
Male sex	0.39 (0.18-0.84)	0.015		
SAPS 3	1.03 (1.01-1.06)	0.014	1.05 (1.02-1.08)	0.002
Predicted body weight	0.92 (0.89-0.96)	< 0.001	0.91 (0.86-0.95)	< 0.001
PaO_2/FiO_2	1.00 (0.99-1.00)	0.135	0.99 (0.99-1.00)	0.020
pH	0.96 (0.93-0.99)	0.035		
Use of corticosteroids	1.88 (0.74-4.77)	0.183		
MDP				
Age	1.01 (0.99-1.04)	0.153		
Male sex	0.60 (0.27-1.30)	0.191		
BMI	1.05 (0.98-1.11)	0.162		
Pneumonia	2.38 (0.98-5.76)	0.055	3.23 (1.07-9.71)	0.037
PEEP	1.25 (0.10-1.56)	0.052		
C_{rs}	0.93 (0.88-0.98)	0.004	0.94 (0.89-0.99)	0.029
PaO_2/FiO_2	0.99 (0.98-0.99)	< 0.001	0.99 (0.98-0.99)	< 0.001
pH	0.95 (0.91-0.99)	0.007	0.95 (0.90-0.99)	0.017
$PaCO_2$	1.06 (1.02-1.10)	0.004		
Use of corticosteroids	2.43 (0.84-7.06)	0.102		
Use of neuromuscular blocking agents	4.68.(1.66-13.18)	0.003		
Use of vasopressors	2.33 (0.62-8.74)	0.209		

SAPS 3: Simplified Acute Physiology Score 3; MDP: maximum distending pressure; and C_{rs}: respiratory system compliance.

when MV was defined as protective on the basis of both the V_T and the MDP, the addition of V_T therefore being unnecessary. Our results are consistent with those of other studies[16,20] showing correlations between MDP and the outcomes of patients without ARDS. In a study showing no correlation between V_T and mortality, a positive correlation was found between MDP and ICU mortality.[16] In an observational study of a cohort of 986 patients receiving MV because of an acute neurological condition, Tejerina et al. demonstrated that increased mortality correlated with increased MDP but not with increased V_T.[20]

We decided to use the term MDP in order to differentiate it from DP, which was initially correlated with better outcomes in ARDS in the study by Amato et al.[8] DP is calculated as the difference between plateau pressure, which is measured at the end of an inspiratory pause, and PEEP. Some authors have used end-inspiratory airway pressure during pressure-controlled MV instead of plateau pressure for calculating DP.[15,16,20] Although they are similar or even the same in some cases, especially when there is no significant increase in airway resistance, they are not necessarily always the same. However, MDP will always be equal to or greater than DP and is therefore a useful parameter for monitoring VILI.

To our knowledge, this is the first prospective study analyzing the risk factors associated with the adoption of nonprotective MV in patients at risk for ARDS. The factors associated with nonprotective MV based on the V_T were those related to greater patient severity (the SAPS 3 and the PaO_2/FiO_2 ratio) and lower predicted body weight. The association between nonprotective MV and greater patient severity was likely due to priority being given to stabilizing arterial blood gas levels in these patients, possibly to the detriment of protective MV. The association between nonprotective MV and lower predicted body weight was likely due to an inadequate estimate of predicted body weight in shorter patients, given that it is calculated on the basis of patient height. It should be noted that an inappropriate V_T setting based on predicted body weight is more likely to occur in women, as indicated by the results of univariate analysis. The factors associated with nonprotective MV based on the MDP were those related to more severe lung disease (pneumonia, lower C_{rs}, and lower PaO_2/FiO_2) and greater ventilatory demand (lower pH values). These results suggest that not enough attention has been paid to MDP for protective MV, with the MDP increasing when lung mechanics are altered or when there is a need to compensate for acidosis.

Our study has several strengths. First, V_T and MDP were measured twice a day during the first 7 days of MV in order to define MV as protective or nonprotective. Previous observational studies of the correlations of V_T and DP with mortality in patients without ARDS have collected ventilator settings on a single day, usually the first day of MV.[14,15,20] This single assessment, particularly in the case of DP, may have been much more reflective of the severity of the initial lung disease and its impact on patient outcomes. We believe that our 7-day measurements of V_T and MDP more accurately reflect the correlation of the ventilatory strategy used with the occurrence of VILI and its impact on mortality. In addition, we evaluated the association between nonprotective MV and mortality in a specific group of patients without ARDS, i.e., those with one or more risk factors for developing ARDS. Such patients have worse outcomes (e.g., pulmonary complications and increased mortality) than do those without risk factors for ARDS.[14,21] Therefore, among patients without ARDS, those with one or more risk factors for ARDS represent a subgroup of patients in whom a lung-protective ventilation strategy is most relevant.

Some limitations of our study should be noted. During the measurements of MDP, particularly in patients receiving pressure support ventilation, we did not consider the possibility of patient inspiratory effort increasing transpulmonary pressure, which is associated with VILI. This limitation is inevitable when esophageal pressure is not monitored in patients making inspiratory efforts. Given the observational nature of our study, it cannot be stated that the correlation between MDP and mortality indicates causality; that is, it cannot be stated that nonprotective MV based on the MDP resulted in increased mortality. Despite multivariate analysis to adjust for potential confounders, a higher MDP may have represented greater patient severity of illness, thus explaining its association with mortality. The sample size may have been insufficient to detect associations between V_T and mortality, given that the power of the study to detect such associations was 39%. However, the fact that an association was found between MDP and mortality—the power of the study to detect such an association being 43%—suggests that MDP is better than V_T to adjust MV for lung-protective ventilation. Because this was a single-center study, our results should be extrapolated with caution.

In conclusion, an increased MDP during the first 7 days of MV was associated with increased mortality, although an increased V_T was not. Therefore, MDP is a parameter that should be considered in mechanically ventilated patients at risk for ARDS. Factors associated with nonprotective MV include lower PaO_2/FiO_2, lower C_{rs}, pneumonia as the reason for initiating MV, higher severity scores, acidosis, and lower predicted body weight. In the presence of one or more of these factors, MV settings should be adjusted to avoid harmful parameters.

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Vitamin D: association with eosinophil counts and IgE levels in children with asthma

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ABSTRACT

In this cross-sectional study, we investigated the relationship that levels of vitamin D had with eosinophil counts and IgE levels in 26 children with asthma (6-12 years of age) in the city of Londrina, Brazil. Vitamin D levels were found to correlate significantly, albeit moderately, with age ($r = -0.51$) and eosinophilia ($r = -0.49$), although not with IgE levels ($r = -0.12$). When we stratified the sample into two groups by the median vitamin D level (< or ≥ 24 ng/mL), we found that those in the < 24 ng/mL group were older, had higher eosinophil counts, and had higher IgE levels. To our knowledge, this is the first study to show an association between low levels of vitamin D and more pronounced eosinophilia in children with asthma in Brazil.

Keywords: Vitamin D; Asthma; Eosinophils; Eosinophilia; Child.

Inflammation via Th2 lymphocytes is the most common asthma profile in childhood, characterized by the presence of eosinophilia and increased levels of IgE, which are related to the improvement of the disease with the use of corticosteroids.[1-3]

Vitamin D, a liposoluble micronutrient[4] that acts through the vitamin D receptor (VDR),[5] can influence the immunological cascade of asthma by suppressing the response of T2-high lymphocytes and reducing the production of IL-5, thereby decreasing the eosinophil counts and IgE levels.[6] Vitamin D is usually not present in the diet of most people, including that of most Brazilians.[2,7-9] Combined with insufficient sun exposure, that can lead to vitamin D deficiency.

In Brazil, although most people live in regions with adequate sun exposure, vitamin D insufficiency is a common problem that also affects children and is associated with an increased incidence of poorly controlled asthma symptoms.[8,9] In a previous study, involving children with asthma and vitamin D insufficiency, vitamin D supplementation improved asthma control and diminished the risk of exacerbations.[4] Eosinophil counts and IgE levels can also be higher in individuals with vitamin D insufficiency than in those with sufficient levels of the vitamin.[6,10] However, it is questionable whether the reference levels of vitamin D used worldwide (< 20 ng/dL being designated deficient and 20-30 ng/dL being designated insufficient) are applicable as references for all individuals, because the clinical characteristics, place of residence, age, and life habits are not taken into consideration.[9-11]

The relationships that vitamin D levels have with eosinophilia and IgE have not been explored in-depth in children with asthma in Brazil. Despite those affected being subject to clinical specificities and to their own levels of sun exposure, it has been hypothesized that vitamin D levels are associated with those aspects in children in Brazil, as has been observed in populations in other parts of the world. Therefore, the objective of the present exploratory study was to analyze vitamin D levels and their association with eosinophil counts and IgE levels in a sample of schoolchildren with asthma.

The present study was carried out at the Pediatric Pulmonology Outpatient Clinic of Londrina State University, located in the city of Londrina, Brazil. It was a preliminary, exploratory study with an analytical cross-sectional design. The sample was composed of consecutive pediatric patients seen at the outpatient clinic between May and August of 2019 (autumn and winter months), residing in Londrina or the surrounding area. Written informed consent was obtained from the legal guardian of each participant. The project was approved by the human research ethics committee of the institution (Reference no. 3.093.047/2018).

The inclusion criteria were as follows: being 6-12 years of age, being followed at the outpatient clinic, and having received a clinical diagnosis of asthma, in accordance with the GINA criteria[1]; currently using

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inhaled corticosteroids with no restrictions on the duration of use; being clinically stable, defined as not having needed to use oral corticosteroids to treat an asthma crisis during the last month; not having taken vitamin D supplementation in the previous month; absence of any other pulmonary pathologies, cerebral palsy, gastroesophageal reflux disease, or dysphagia; and having been treated with an antiparasitic agent within the last 12 months. The following exclusion criteria were applied: having experienced an asthma exacerbation that required hospitalization for more than one day or the use of an oral corticosteroid; presenting with comorbidities; using medications that could interfere with the metabolism of vitamin D (e.g., anticonvulsants and systemic antifungal drugs); and no blood sample having been obtained for the quantification of vitamin D.

Patients who met the inclusion criteria, as identified by clinical evaluation, were assessed once. The method of evaluating the serum levels of vitamin D has been described previously,[12,13] reflecting contributions from all sources of this vitamin (i.e., through diet and sun exposure).[14] Previous studies have also described the methods for evaluating serum eosinophils,[3,13] IgE,[15] and the level of asthma control,[1] as well as for diagnosing allergic rhinitis,[16] and performing spirometry.[17,18] The tapering of the inhaled corticosteroid doses and their standardization in budesonide-equivalent doses were as described in the GINA guidelines.[1]

The sample size was determined with a correlation sample size calculator made (http://www.sample-size.net/correlation-sample-size/). Using an alpha of 0.05 and a beta of 0.20, in order to achieve a > 0.60 correlation between the levels of vitamin D and the eosinophils count, we found that the minimum sample required was 19 patients.

In the statistical analysis, the Shapiro-Wilk test was used to analyze the normality of data distribution, the data being expressed as mean and standard deviation or as median and interquartile interval. For analytical purposes, given that the median values measured for vitamin D were not consonant with the reference values typically proposed, the patients were stratified into two groups according to their serum vitamin D levels: those whose level was equal to or above the median for the study sample (24 ng/mL); and those whose level was below that. The median was chosen because, in small samples, it is considered to be more representative. The two groups were compared by using the unpaired Student's t-test or the Mann-Whitney test for continuous variables and the chi-square test for categorical variables. The correlations were evaluated by Spearman's coefficient. The statistical analysis was performed with the IBM SPSS Statistics software package, version 22.0 (IBM Corporation, Armonk, NY, USA). The level of statistical significance was set at $p < 0.05$.

The initial study sample included 27 patients. However, in one case, it was not possible to collect a blood sample for the quantification of the vitamin D level. Therefore, the final sample comprised 26 patients. The baseline characteristics of the patients are described in Table 1. On average, the patients in the sample presented with BMIs within the normal range and vitamin D levels below those considered appropriate, as well as increased IgE levels and eosinophil counts.

Table 1. Characteristics of the patients included in the study (N = 26).[a]

Variable	Result
Age, years	9.5 (7.0-11.0)
Male/female gender, n/n	19/7
BMI, kg/m^2	20 ± 4
Allergic rhinitis	< 100%
Secondhand smoke	< 38%
Uncontrolled asthma	< 35%
Daily dose of inhaled corticosteroid, µg	400 (200-400)
Vitamin D, ng/mL	24 (19-31)
Total IgE, IU/mL	706 (515-1,583)
Eosinophils, %	9.5 ± 6.7
Eosinophils, cells/µL	653 ± 471
FEV_1, % predicted	90 ± 9
Post-BD FEV_1, % predicted	105 ± 14
FEV_1/FVC	78 ± 7
FEV_1/FVC post-BD	84 ± 3
$FEF_{25-75\%}$, % predicted	96 ± 23
Post-BD $FEF_{25-75\%}$, % predicted	136 ± 36

BD: bronchodilator. [a]Values expressed as mean ± SD or median (interquartile interval), except where otherwise indicated.

In comparison with the patients in the ≥ 24 ng/mL vitamin D group, those in the < 24 ng/mL group were older, had higher absolute eosinophil counts, and had higher IgE levels (Table 2). No other significant or borderline statistical differences were observed between the two groups. In the sample as a whole, vitamin D levels showed moderate but statistically significant correlations with age ($r = -0.51$) and with the absolute eosinophil count ($r = -0.49$), although not with the IgE levels ($r = -0.12$; $p = 0.66$). No other significant correlations were observed among the variables studied.

To our knowledge, this is the first study to show that low vitamin D levels are associated with higher absolute eosinophil counts and higher IgE levels in children with asthma in Brazil. However, our results should be interpreted with caution, given that they still do not allow the inference of causality. An association between vitamin D level and age has been previously observed in children and adolescents,[10] although not in children in Brazil. This could be due to lifestyle (such as getting less sun exposure) and to the increased risk of chronic and inflammatory diseases, which increase the metabolism of vitamin D.[8,9]

The role that vitamin D plays at points in the inflammatory cascade in asthma patients is the subject of various ongoing discussions, the outcomes of which

Table 2. Comparison between the groups stratified by the median vitamin D level (24 ng/mL).[a]

Variable	Vitamin D level		p
	< 24 ng/mL (n = 13)	≥ 24 ng/mL (n = 13)	
Age, years	10 (9-11)	8 (7-10)	0.019
Male/female, n/n	9/4	10/3	0.658
BMI, kg/m^2	20 (17-23)	17 (16-23)	0.479
Daily dose of inhaled corticosteroid, µg	400 (200-400)	400 (200-400)	0.880
Uncontrolled asthma	38%	30%	0.999
Secondhand smoke	46%	31%	0.688
Vitamin D, ng/mL	19 ± 4	30 ± 4	< 0.001
Eosinophils, %	11 ± 6	8 ± 7	0.351
Eosinophils, cells/µL	918 ± 464	448 ± 382	0.042
Total IgE, IU/mL	961 (696-2,283)	621 (325-940)	0.046
FVC, % predicted	101 ± 14	108 ± 6	0.548
FEV_1, % predicted	89 ± 11	91 ± 8	0.990
FEF_{25-75}, % predicted	96 ± 23	93 ± 20	0.905

[a]Values expressed as mean ± SD or median (interquartile interval), except where indicated.

have been discrepant. One study of children with asthma (7-14 years of age) in Brazil did not quantify eosinophils but found an inverse association between the levels of IgE and those of vitamin D,[(11)] whereas another study of children with asthma (6-14 years of age) in Costa Rica showed that vitamin D levels correlated significantly with IgE levels but not with eosinophil counts.[(10)]

In response to corticosteroids, vitamin D restores the capacity of the T cells to secrete IL-10 (a powerful anti-inflammatory cytokine),[(10)] thus exerting an immunomodulatory effect[(19)] and indirectly diminishing the production of IgE,[(1,20)] given that IgE does not have a VDR and is produced by B lymphocytes. Hypothetically, that would explain why there is not a more robust correlation between vitamin D and IgE, in contrast to what has been observed for eosinophils, which have the VDR[(20)] and are produced directly by the T2-high lymphocytes. Given that vitamin D can prolong the survival of eosinophils and increase the expression of membrane receptors that inhibit their apoptosis,[(20)] there is less need to produce new eosinophils in this scenario, which is a possible explanation for the association between vitamin D and eosinophils.

In view of the median vitamin D level found in our sample (24 ng/mL), the internationally accepted cutoff points for vitamin D may not be applicable to children with asthma in Brazil. It is noteworthy that the vitamin D values generally suggested as sufficient, insufficient, and deficient have been based primarily on bone health,[(9)] involving presumably healthy people,[(10)] however without considering the specificities related to sun exposure and age.

The limitations of the present study include the relatively small sample size (which might not be representative of the population of children with asthma and precluded multiple regression analysis for the study of independent associations) and the cross-sectional design, which prevented us from establishing causality. Therefore, large, multicenter cohort studies involving nutritional surveys are warranted in order to confirm or refute our findings.

In conclusion, to our knowledge, this is the first study to show an association between vitamin D levels and eosinophil counts in children with asthma in Brazil. However, we were unable to establish a causal relationship between the two. Our findings also suggest that the vitamin D values commonly used are not applicable to children with asthma in Brazil.

AUTHOR CONTRIBUTIONS

CLCGA: study conception and design; data collection; analysis and interpretation of the results; and drafting of the manuscript. JMO, AR, and KCF: analysis and interpretation of the results; and revision of the manuscript. FP: study conception and design; analysis and interpretation of the results; revision of the manuscript; and final approval of the version to be submitted.

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Efficiency of different protocols for oral hygiene combined with the use of chlorhexidine in the prevention of ventilator-associated pneumonia

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ABSTRACT

Objective: In ICU patients on mechanical ventilation (MV), ventilator-associated pneumonia (VAP) is a common infection. However, such infection can be prevented through oral care protocols. The objective of this study was to compare the efficiency of the use of chlorhexidine and oral hygiene protocols (brushing and clinical procedures) with that of the use of chlorhexidine alone (intervention group and control group, respectively) in decreasing the prevalence of VAP in patients ≥ 18 years of age admitted to the ICU and requiring MV. **Methods:** In this systematic review and meta-analysis, studies were identified through searches of various national and international databases, as well as of the gray literature, and were selected in accordance with eligibility criteria. **Results:** We evaluated six studies, involving a collective total of 1,276 patients. We classified the risk of bias as low in three studies, high in two, and uncertain in one; among the six risk domains evaluated, a low risk of bias was predominant in five. The results for random risks were similar in terms of direction and statistical magnitude—chi-square = 6.34; risk difference: −0.06 (95% CI: −0.11 to −0.02); I^2 = 21%; p = 0.007. There was a decrease in the prevalence of VAP in the intervention group (n = 1,276) included in the meta-analysis. **Conclusions:** Protocols that include the mechanical removal of oral biofilm in combination with the use of chlorhexidine can reduce the incidence of VAP among ICU patients requiring MV.

Keywords: Intensive care units; Pneumonia, ventilator-associated; Oral hygiene; Respiration, artificial.

INTRODUCTION

Mechanical ventilation (MV) is a support method for the treatment of patients with severe chronic or acute respiratory insufficiency.(1) Ventilator-associated pneumonia (VAP) is a pulmonary infection that develops ≥ 48 h after hospital admission in patients on MV (via tracheostomy or endotracheal intubation). Among all nosocomial infections, VAP has the greatest negative impact on patient outcomes and health care costs.(2)

Prevention strategies for VAP include interventions such as elevating the head of the patient, administering antibiotics prophylactically, limiting the duration of MV, and discontinuing sedation. Oral hygiene has been considered an essential component of VAP prevention and, with standardized application, can significantly reduce the rate of respiratory tract infections due to microbial colonization.(3)

Mouthwashes are efficient in reducing oral microbiota, and those that contain chlorhexidine are considered the gold standard, but there are many adverse effects associated with the use of chlorhexidine. Therefore, there is a tendency to search for mouthwashes that are as efficient as those with chlorhexidine, but with fewer adverse effects.(4)

Pharmacological control of bacterial plaque through the use of chlorhexidine is practical and is widely accepted among health professionals.(5) However, mechanical cleaning might be the most efficient method to reduce pathogenic agents in the biofilm.(6)

The objective of this systematic review and meta-analysis was to determine whether, in ICU patients, protocols involving the use of oral hygiene techniques (mechanical removal of biofilm) together with the use of chlorhexidine are more effective in decreasing the incidence of VAP than are those involving the use of chlorhexidine alone. As a secondary objective, we compared the protocols to determine whether there were differences in terms of the length of the ICU stay or in-hospital mortality.

METHODS

Protocol and registration

The present systematic review was conducted in accordance with the criteria from Preferred Reporting

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Items for Systematic Review and Meta-Analysis[7] and registered with the International Prospective Register of Systematic Reviews (Registration no. CRD42018083932).

Research information and search strategy

The descriptors were selected in accordance with the DeCS and MeSH lists of descriptors, and the questions were defined in accordance with the strategy known as PICO: Population—adult ICU patients (≥ 18 years of age) on MV; Intervention—different protocols involving oral hygiene combined with the use of chlorhexidine; Comparison—protocols involving the use of chlorhexidine alone; and Outcome—efficacy in reducing the incidence of VAP.

We performed searches of the following databases: PubMed (MedLine), the Brazilian Library of Dentistry, LILACS, the Nursing Database of the Brazilian Virtual Library of Health, SciELO, and the Cochrane Library (Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trials); for the gray literature, we used the Brazilian Institute of Information in Science and Technology Digital Library of Theses and Dissertations. The search terms included the following descriptors, as well as their plural forms and synonyms—"Intensive Care Unit", "Oral Hygiene", "Ventilator Associated Pneumonia", and "Randomized Clinical Trial"—in conjunction with Boolean operators (AND/OR). Searches were adapted in accordance with the particularities of each database. The following search strategy was used: "intensive care units"[All Fields] OR "ITU"[All Fields] OR "ITC"[All Fields] OR "intensive care centers"[All Fields] OR "intensive care center"[All Fields] AND "dentistry"[All Fields] OR "oral hygiene"[All Fields] OR "oral health"[All Fields] OR "care oral"[All Fields] OR "dental"[All Fields] AND "ventilator associated pneumonia"[All Fields] AND ("trial"[All Fields] OR "study trial"[All Fields] OR "clinical study"[All Fields] OR "randomized clinical study"[All Fields] OR "randomized clinical trial"[All Fields]). For the gray literature, in addition to the aforementioned database, manual search was also considered. There were no restrictions regarding the language or year of publication.

Eligibility criteria

The inclusion criteria were as follows: design—randomized clinical trials (RCTs); population—adult ICU patients (≥ 18 years of age) on MV; intervention—oral hygiene protocols (mechanical removal of biofilm) combined with the use of chlorhexidine; control—use of chlorhexidine only; and outcome measure—efficacy in reducing the incidence of VAP. Studies that evaluated patients already diagnosed with VAP, edentulous patients, or pregnant patients were excluded.

Study selection and collection

The studies identified in the databases were transferred to the reference manager EndNote Web (Clarivate, Philadelphia, PA, USA) for storage and exclusion of duplicates. Two reviewers, working independently, evaluated the titles and abstracts of the studies, applying the eligibility criteria, and a third reviewer evaluated any discrepant results. The potentially eligible studies (articles and theses) were then included in the second phase for a full-text reading, especially if the title and abstract did not provide enough information to include the study out of hand. Any disagreements were resolved through discussion with the third reviewer. Only the studies in which there were complete data on primary and secondary outcome measures were included in the meta-analysis.

Synthesis and presentation of data

The studies included were examined independently, and the relevant information was extracted to evaluate the quality of each study and synthesize the data. The details of the studies are shown in Table 1. Only the information available in the articles was considered. The data were presented as follows: author/year; country; sample size; intervention; control; and outcome measures (primary and secondary). We evaluated the incidence of VAP, as the primary outcome measure, by calculating absolute and relative frequencies. We also evaluated the secondary outcome measures length of ICU stay, by calculating the mean and standard deviation, and in-hospital mortality, by calculating the absolute frequency.

We extracted data on the study design, patient population, intervention, comparison, and clinical results. The main result of interest was prevention of VAP. Other results of interest were length of ICU stay and in-hospital mortality.

Evaluations of risk of bias and summarization

Although RCTs are the type of clinical study with the highest level of evidence, they are quite prone to biases, whether due to the arbitrariness of investigators in the selection of the sample and gauging of the variables analyzed or to the difficulty in controlling other factors that could influence the clinical outcome. Although there are several tools to evaluate the susceptibility to biases in RCTs, we used the Review Manager program, version 5.1 (RevMan 5; Cochrane Collaboration, Oxford, UK).

Quantitative analysis

The values for the frequency of VAP in ICU patients on MV were obtained from the studies selected. The results were divided into two groups: the intervention group—those obtained with protocols involving oral hygiene (brushing or clinical procedures) in combination with chlorhexidine; and the positive control group—those obtained with protocols involving the use of chlorhexidine only. For the meta-analysis, we chose the Review Manager program, version 5.3, with a significance level of 5%. In the comparison of the groups, the effect size defined was the difference between the absolute prevalences (difference between

Table 1. Organization and presentation of data taken from the studies included in the qualitative and quantitative analyses.

Study/country	Sample	Groups		Outcome measures	
	N	Intervention	Control	Primary	Secondary
Bellíssimo-Rodrigues et al.[9]/Brazil	254	Tooth brushing, tongue scraping, calculus removal, atraumatic restorative treatment, tooth extraction, and irrigation with chlorhexidine at 0.12% or 2.0%, depending on the level of patient consciousness, 3 times a day (n = 127)	Cleaning with gauze wrapped onto a tongue depressor, followed by rinsing with chlorhexidine at 0.12% or 2.0%, 3 times a day (n = 127)	Prevalence of VAP Absolute frequency: IG: 18/127; CG: 8/127 Relative frequency: IG: 8.%; CG 18.% (RR = 0.38; 95% CI: 0.16-0.93; p = 0.030)	Length of ICU stay, days: IG: 10.7 ± 10.6; CG: 11.3 ± 9.0 (p = 0.225) Mortality associated with lower respiratory tract infection: IG: 5/127; CG 8/127 (RR = 0.61; 95% CI: 0.19-1.92; p = 0.393)
				The IG had more favorable results in reducing VAP than did the CG (p < 0.05). There were no significant differences between the groups in terms of the length of ICU stay on MV and in-hospital mortality.	
Félix et al.[10]/Brazil	58	Tooth brushing with a toothbrush soaked in 0.12% chlorhexidine, 3 times a day (n = 30)	Cleaning with gauze soaked in 0.12% chlorhexidine, 3 times a day (n = 28)	Prevalence of VAP Absolute frequency: IG: 1/30; CG: 3/28 Relative frequency: IG: 3.3%; CG: 10.7% (p = 0.344)	NR
				Neither protocol resulted in a significant decrease in the prevalence of VAP	
de Lacerda Vidal et al.[11]/Brazil	213	Tooth brushing with chlorhexidine gel at 0.12%, 2 times a day (n = 105)	Irrigation with and suction extraction of chlorhexidine at 0.12%, 2 times a day (n = 108)	Prevalence of VAP Absolute frequency: IG: 88/105; CG: 80/108 Relative frequency: IG: 37.8%; CG: 62.2% (RR = 1.81; 95% CI: 0.93-3.57; p = 0.084)	Length of ICU stay, days IG = 8.7± 9.0; CG = 11.1 ± 7.6 (p = 0.018) In-hospital mortality: IG: 20/105 (42.5%); CG: 27/108 (57.5%) (RR = 1.41; 95% CI: 0.73-2.70; p = 0.2)
				The IG showed a significant reduction in the length of ICU stay on MV (p < 0.05), although there were no statistical differences between the groups in terms of the decrease of VAP prevalence or in-hospital mortality	

Continued ▸

Table 1. Continued...

Study/country	Sample	Groups		Outcome measures	
	N	Intervention	Control	Primary	Secondary
Lorente et al.[12]/Spain	436	Brushing teeth and tongue for 90 s + gauze soaked in 20 mL of 0.12% chlorhexidine + irrigation of 10 mL of 0.12% chlorhexidine in the oral cavity for 30 s, 3 times a day (n = 217)	Cleaning with gauze soaked in 20 mL of 0.12% chlorhexidine + irrigation of 10 mL of 0.12% chlorhexidine in the oral cavity for 30 s, 3 times a day (n = 219)	Prevalence of VAP Absolute frequency: IG: 21/217; CG: 24/219 Relative frequency: IG: 9.7%; CG: 11.0% (p = 0.75)	Length of ICU stay, days: IG: 12.07 ± 15.55; CG: 13.04 ± 17.27 (p = 0.54) In-hospital mortality: IG: 62/217 (28.6%); CG: 69/219 (31.5%) (p = 0.53)
				There were no significant differences between the IG and CG in terms of the decrease in VAP prevalence, length of ICU stay, or in-hospital mortality.	
Nasiriani et al.[13]/Iran	168	Tooth brushing with a soft toothbrush with distilled water plus application of a cotton swab saturated in 0.12% chlorhexidine on the tongue, 2 times a day (n = 84)	Use of saline solution and application of chlorhexidine on the tongue with a cotton swab soaked in the solution, 2 times a day (n = 84)	Prevalence of VAP Absolute frequency: IG: 25/84; CG: 40/84 Relative frequency: IG: 29.8%; CG: 47.6% (p = 0.02)	NR
				The prevalence of VAP in intubated ICU patients was lower in the IG (p < 0.05).	
Pobo et al.[14]/USA	147	Electric toothbrush + use of 0.12% chlorhexidine, 3 times a day (n = 74)	Use of 0.12% chlorhexidine, 3 times a day (n = 73)	Prevalence of VAP Absolute frequency: IG: 15/74; CG: 18/73 Relative frequency: IG: 20.3%; CG: 24.7% (OR: 0.78; 95% CI: 0.36-1.65; p = 0.56)	Length of ICU stay, days: IG: 8.9 ± 5.8; CG: 9.8 ± 6.1 (p = 0.45) In-hospital mortality General: 39/147 (26.5%) IG: 21.6%; CG: 31.5% (p = 0.19)
				There were no significant differences between the IG and CG in terms of the decrease in VAP prevalence, length of ICU stay, or in-hospital mortality.	

IG: intervention group; CG: control group; VAP: ventilator-associated pneumonia; MV: mechanical ventilation; NR: not reported; and RR: relative risk.

risks).[8] Fixed- and random-effects models were used in order to analyze the heterogeneity in the two models. The heterogeneity was evaluated with the chi-square method, and the I^2 value was calculated. The I^2 statistic (range, 0-100) was used in order to analyze the variations of heterogeneity: an $I^2 > 75$ indicates significant heterogeneity.

RESULTS

Research and selection of studies

In total, 89 articles were identified and inserted into the reference manager. After the removal of duplicates, 66 studies remained. Of those, 21 were selected for the first phase of title and abstract reading. On the basis of the eligibility criteria, 15 articles were excluded: 4 because they included infants and children, 3 because they included edentulous patients, and 8 because they did not have a positive CG. Therefore, we included 6 studies in the qualitative review, including those same 6 studies in the meta-analysis (Figure 1). All of the studies included were published between 2009 and 2017.

Characteristics of the patient sample

The studies included in the present systematic review evaluated a collective total of 1,276 adult ICU patients on MV and comprised 3 studies conducted in Brazil,[9-11] 1 conducted in Spain,[12] 1 conducted in Iran,[13] and 1 conducted in the USA.[14] The participants included 770 males and 506 females. All of the participants were ≥ 18 years of age, and the mean age varied between 45 and 63 years. The main reasons for admitting the patients to the ICU were coronary diseases, diabetes, respiratory diseases, neurological diseases, and neoplasms.

Types of intervention and gauging scale

In the 6 studies included, oral hygiene routines were performed (Table 1): three times a day in 4 of the studies[9,10,12,14]; and twice a day in 2.[11,13]

Chlorhexidine was used in all of the studies included, although the concentration varied. The concentration used was 0.12% for all patients in 4 studies,[10-12,14] whereas the authors of 1 study adjusted the concentration from 0.12% in conscious patients to 0.2% in unconscious patients[9] and those of another study did not report the concentration.[13]

In the intervention group, various tooth brushing techniques were employed: brushing with an electric toothbrush[14]; brushing with distilled water[13]; brushing with a toothbrush saturated in chlorhexidine[10]; and brushing before the application of chlorhexidine.[11] Bellíssimo-Rodrigues et al.[9] employed a protocol involving tooth brushing, tongue scraping, removal of calculi, atraumatic restorative treatment, dental extraction, and rinsing with chlorhexidine. Lorente et al.[12] evaluated an oral hygiene protocol involving tooth brushing and cleaning with gauze soaked in 20 mL of 0.12% chlorhexidine, followed by 30-s irrigation of the oral and oropharyngeal area with 10 mL of 0.12% chlorhexidine, which was then extracted by suction.

The oral hygiene conditions were evaluated by different methods. In one study,[13] the Quigley-Hein plaque index, as modified by Turesky,[15] was used. In the remaining studies,[9,10,11,14] the evaluation method was not clearly described, the exception being the study conducted by Lorente et al.,[12] who specifically stated that no such evaluation was performed.

Incidence of VAP

One study[13] showed that the incidence of VAP in was significantly lower in the intervention group than in the control group; in another study,[9] it was concluded that the dental care protocol evaluated was safe and effective in preventing VAP. Two studies[10,11] showed that the incidence of VAP was low after the application of the two oral hygiene techniques evaluated, with no significant differences between the two groups. However, another two studies[12,14] showed that other oral hygiene methods involving the use of chlorhexidine were not effective in preventing VAP.

In-hospital mortality

In relation to the reduction of in-hospital mortality, no significant difference between the groups was found in the study conducted by Belíssimo-Rodrigues et al.[9] However, the number of patients who died from VAP was 38.1% lower in the intervention group than in the control group. In another study,[11] in-hospital mortality was significantly lower in the intervention group than in the control group. Nevertheless, in three studies,[12-14] no significant differences were found in terms of in-hospital mortality, whereas in one study,[10] the difference in mortality between the groups was not mentioned.

Length of ICU stay

In relation to the length of ICU stay, one study[11] showed that it was shorter among the intervention group patients, although the difference was not statistically significant. Three studies[12-14] showed no significant differences related to the length of ICU stay between the intervention group and control group, whereas the length of ICU stay was not mentioned in two other studies.[9,10]

Publication bias

All of the studies were included in the evaluation of risk of bias.[16] This evaluation generally showed a predominantly low risk of bias in five domains; a high risk of bias was predominant in only one domain (blinding between patients and professionals; Figure 2). In the classification of individual risk of bias, three studies showed a low risk of bias,[9,10,13] and two other studies were considered to have a high risk of bias[12,14]; only one study was classified as having an uncertain risk of bias,[11] as shown in Figure 3.

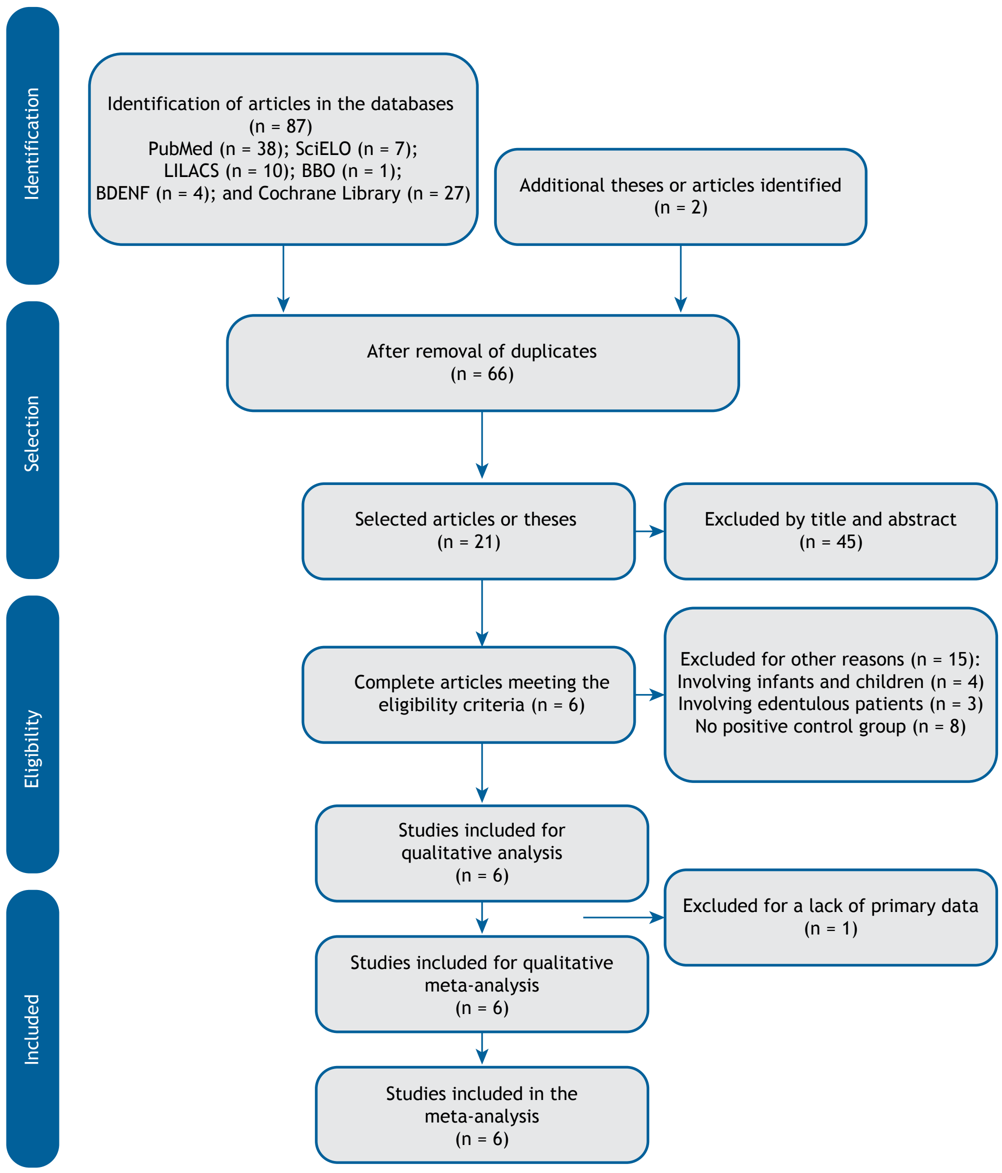

Figure 1. Flow chart of the study selection process.BBO: *Biblioteca Brasileira de Odontologia* (Brazilian Library of Dentistry); and BDENF: *Base de Dados de Enfermagem* (Nursing Database [of the Brazilian Virtual Library of Health]).

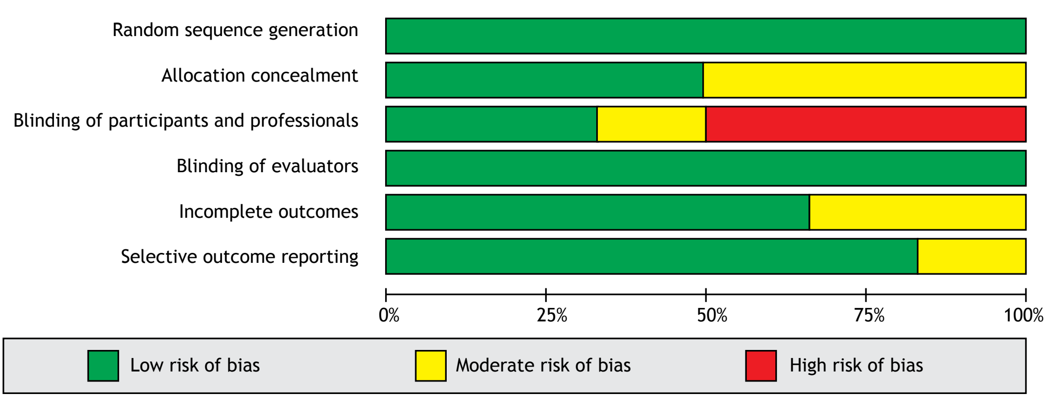

Figure 2. Risks of bias.

Meta-analysis

All of the studies were included in the meta-analysis,[9-14] comprising a collective sample of 1,276 patients. In the comparison between the intervention group and control group in relation to the prevalence of VAP, the synthesis of the analysis showed that the incidence of VAP was lower in the intervention group than in the control group (p = 0.007). Random-effects models (Figure 4) and fixed-effects models (Figure 5) were employed in the meta-analysis. The results for random risks were similar in direction and statistical magnitude—chi-square = 6.34; risk difference: −0.06 (95% CI: −0.11 to −0.02); I^2 = 21%; p = 0.007—the analysis favoring the intervention group over the control group in terms of the decrease in VAP prevalence among ICU patients on MV.

	Random sequence generation	Allocation concealment	Blinding of participants and professionals	Blinding of evaluators	Incomplete outcomes	Selective outcome reporting
Belíssimo-Rodrigues et al.[9]	+	+	–	+	+	+
Félix et al.[10]	+	?	–	+	+	+
de Lacerda Vidal et al.[11]	+	+	+	+	+	+
Lorente et al.[12]	+	?	?	+	?	+
Nasiriani et al.[13]	+	?	+	+	+	+
Pobo et al.[14]	+	+	+	+	?	?

\+ Low risk – High risk ? Uncertain risk

Figure 3. Summary of the risks of bias.

DISCUSSION

The results of the present meta-analysis allow us to state that mechanical removal of biofilm combined with the use of chlorhexidine was more effective in reducing the incidence of VAP than were other oral hygiene protocols. All of the studies showed a decrease in the incidence of VAP, although only two studies[9,13] showed significant differences between the intervention group and control group. The four other studies[10-12,14] showed no statistically significant differences.

There is scientific evidence that the use of chlorhexidine in different formulations (solution or gel) reduces the incidence of VAP from 25% to approximately 19%.[14] However, there is insufficient evidence regarding the impact that mechanical removal of biofilm (with manual brushing, brushing with an electric toothbrush, or gauze) has on that incidence.[12]

Regarding in-hospital mortality, five studies[9,11-14] showed no statistically significant differences. However, two of those studies[9,11] reported reductions in the mortality rate related to VAP. In relation to the length of ICU stay, four studies[9,12-14] showed no significant differences between the groups. Only one study[11] showed such a difference, the length of stay being significantly shorter in the intervention group.

There is no convincing evidence that the use of chlorhexidine is associated with differences in in-hospital mortality, duration of MV, or length of ICU stay.[14] The mechanical removal of microorganisms can increase the efficacy of the effects of chlorhexidine on the remaining bacteria or diminish bacterial growth.[11] The meta-analysis showed that additional methods of hygiene (mechanical removal of biofilm) combined with the use of chlorhexidine are more effective in preventing VAP than is the use of chlorhexidine alone.

Study or subgroup	Intervention Event	Intervention Weight	Control Event	Control Total	Control Weight	M-H risk difference, Fixed-effects, 95% CI
Lorente et al.[12]	21	217	24	219	34.2%	-0.01 (-0.07. 0.04)
Pobo et al.[14]	15	74	18	73	11.5%	-0.04 (-0.18. 0.09)
Félix et al.[10]	1	30	3	28	4.5%	-0.07 (-0.21. 0.06)
Belíssimo-Rodrigues et al.[9]	8	127	18	127	19.9%	-0.08 (-0.15.-0.00)
de Lacerda Vidal et al.[11]	17	105	28	108	16.7%	-0.10 (-0.21. 0.06)
Nasiriani et al.[13]	25	84	40	84	13.2%	-0.18 (-0.32. -0.03)
Total (95% CI)		**637**		**639**	**100%**	**-0.07 (-0.11. -0.03)**
Total events		87		131		

Heterogeneity: x^2 = 6.34, df = 5 (p = 0.27); I^2 = 21%

Test for total effect: Z = 3.38 (p = 0.007)

M-H risk difference, Fixed-effects, 95% CI

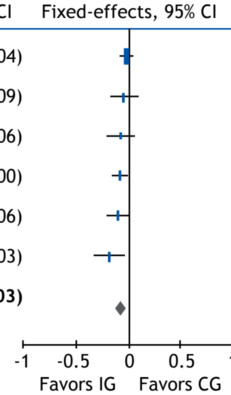

Figure 4. Comparison between the intervention and control groups in relation to the decrease in the prevalence of ventilator-associated pneumonia, fixed-effects model. M-H: Mantel-Haenszel (method); df: degrees of freedom; IG: intervention group; and CG: control group.

Study or subgroup	Intervention Event	Intervention Weight	Control Event	Control Total	Weight	M-H risk difference, Fixed-effects, 95% CI
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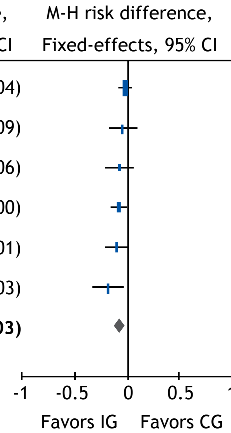
de Lacerda Vidal et al.[11]	17	105	28	108	13.7%	-0.10 (-0.21. 0.01)
Nasiriani et al.[13]	25	84	40	84	8.3%	-0.18 (-0.32. -0.03)
Total (95% CI)		**637**		**639**	**100%**	**-0.06 (-0.11. -0.03)**
Total events		87		131		



Heterogeneity: $T^2 = 0.00$. $X^2 = 6.34$, df = 5 ($p = 0.27$); $I^2 = 21\%$

Test for total effect: $Z = 3.38$ ($p = 0.007$)

Figure 5. Comparison between the intervention and control groups in relation to the decrease in the prevalence of ventilator-associated pneumonia, random-effects model. M-H: Mantel-Haenszel (method); df: degrees of freedom; IG: intervention group; and CG: control group.

Our study has some limitations. There were differences across studies in terms of the proposed methods of oral hygiene, such as use of manual or electric toothbrushes, as well as the use of gauze, immersion of the toothbrush in distilled water, tongue scraping, and single versus multiple daily cleanings. The microbiological data to determine the relationship between VAP and the in-hospital mortality rate were not analyzed in the studies included in our meta-analysis. That limitation raises questions about the potential use of antibiotics, with the appearance of resistance, unnecessary adverse effects, and toxicity of those medications. There were no data regarding the oral microbiota and its contribution to the occurrence of VAP. In addition, strategies such as optimizing the time of intervention and personalizing the intensity of the individualization of risk should be adopted. Future studies adopting the same protocol for RCTs could be conducted in such a way that those adverse effects are minimized.

We conclude that ICU patients on MV get more benefit when various protocols for mechanical removal of biofilm (brushing or scraping) are combined with the concomitant use of chlorhexidine to reduce the incidence of VAP.

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https://dx.doi.org/10.36416/1806-3756/e20200267 REVIEW ARTICLE

Environmental air pollution: respiratory effects

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ABSTRACT

Environmental air pollution is a major risk factor for morbidity and mortality worldwide. Environmental air pollution has a direct impact on human health, being responsible for an increase in the incidence of and number of deaths due to cardiopulmonary, neoplastic, and metabolic diseases; it also contributes to global warming and the consequent climate change associated with extreme events and environmental imbalances. In this review, we present articles that show the impact that exposure to different sources and types of air pollutants has on the respiratory system; we present the acute effects—such as increases in symptoms and in the number of emergency room visits, hospitalizations, and deaths—and the chronic effects—such as increases in the incidence of asthma, COPD, and lung cancer, as well as a rapid decline in lung function. The effects of air pollution in more susceptible populations and the effects associated with physical exercise in polluted environments are also presented and discussed. Finally, we present the major studies on the subject conducted in Brazil. Health care and disease prevention services should be aware of this important risk factor in order to counsel more susceptible individuals about protective measures that can facilitate their treatment, as well as promoting the adoption of environmental measures that contribute to the reduction of such emissions.

Keywords: Air pollution; Particulate matter; Respiratory tract diseases; Pulmonary disease, chronic obstructive; Asthma; Respiratory tract infections; Lung neoplasms.

INTRODUCTION

A major problem in the world today is air pollution, not only because of its impact on climate change but also because of its impact on public and individual health, being an important risk factor for increased morbidity and mortality.

Although exposure to air pollution has records that date back more than 20 centuries ago, until the well-known episodes of a sudden increase in pollutants that occurred in the Meuse Valley (Belgium, 1930), in Donora (Pennsylvania, USA, 1948), and above all in London (United Kingdom, 1952), studies on the effects of exposure to air pollutants were restricted to work environments and to exposure to toxic agents used in wars.[(1)] It was only from the mid-20th century onward that the subject began to be studied more and more,[(2)] with the first document on the effects of air pollution on health, prepared by the WHO and published in 1958, recommending that pollutant levels be reduced for health protection.[(3,4)]

Air pollution is estimated to have been responsible for approximately 5 million deaths worldwide in 2017, 70% of which being caused by outdoor environmental air pollution. Environmental and household air pollution jointly rank fifth among the five leading risk factors for death worldwide (Table 1).[(5)]

AIR POLLUTION AND ITS MAJOR SOURCES

The majority of emissions of pollutants are a result of human activity. Currently, the main sources of pollution in urban areas are motor vehicles and industries.[(6)] In some countries, including Brazil, the main source of environmental pollution originating from non-urban areas is the burning of biomass (sugarcane fields, pastures, savanna, and forests). Natural emissions, such as those from dust storms in large desert areas, those from accidental fires, and nitrogen oxides (NO_x) emissions from lightning, may contribute secondarily to the generation of air pollutants.[(6,7)]

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Pollutants are classified as either primary or secondary. Primary pollutants are those emitted directly into the atmosphere by industries, thermoelectric power plants, and motor vehicles powered by fuels. Primary pollutants include sulfur dioxide (SO_2); nitrogen oxides (NO_x: NO and NO_2); particulate matter (PM)—total suspended particles less than 10 µm in aerodynamic diameter (PM_{10}) and less than 2.5 µm in aerodynamic diameter ($PM_{2.5}$)—; and carbon monoxide (CO). In some countries, volatile organic compounds (VOCs) and metals are also monitored. Fine and ultrafine particles, since they have a higher surface/mass ratio and can be transferred to the systemic circulation, have a more marked effect.[8] Secondary pollutants are those formed from chemical reactions induced by NO_x-catalyzed photochemical oxidation of VOCs, which, in the presence of ultraviolet rays from sunlight, give rise to ozone.[9] Other secondary pollutants are formed through a process of nucleation and condensation of gaseous pollutants (NO_2 and SO_2) and acid mists, such as NO_x and secondary PM, formed by sulfates and nitrates.[1,7,10]

Exposure to air pollution varies widely across countries, regions, cities, and households. A study based on 2017 data estimates that 42% of people were exposed to fine PM ($PM_{2.5}$) above concentrations considered to be of minimal risk and 43% of those people were exposed to ozone worldwide.[5]

IMPACT ON HEALTH

Globally, most deaths and years of life lost due to premature death or lived with disability (disability-adjusted life years) that are secondary to air pollution exposure are a result of cardiopulmonary disease, lung cancer, or type 2 diabetes (Table 2).[5] A study using a novel approach[11] reported values that were higher than those calculated by the Global Burden of Disease (GBD) models[12]: an estimated 8.8 million deaths globally in 2015[11] versus 4.24 million.[12] In addition, the loss of life expectancy was reported to be 2.9 years worldwide in 2015.[13] In two of the aforementioned studies, the number of environmental air pollution-related deaths in 2015 in Brazil was estimated to be 52,300[12] and 102,000,[11] environmental air pollution being the ninth leading risk factor for mortality.[12]

Why and how air pollution has an impact on health: mechanisms involved in respiratory effects

The damage caused by particulate and gaseous pollutants depends on the inhaled concentration of

Table 1. Major risk factors for, and their impact on, morbidity and mortality worldwide in 2017 according to the Global Burden of Disease 2017 Risk Factor Collaborators.[5]

Risk factors	Deaths × 1,000 (95% CI)	DALYs × 1,000 (95% CI)	Global ranking
Diet (all causes)	10,900 (10,100-11,700)	255,000 (234,000-274,000)	1
Hypertension	10,400 (9,400-11,500)	218,000 (198,000-237,000)	2
Smoking (active + environmental + smokeless)	8,100 (7,800-8,420)	213,000 (201,000-227,000)	3
Elevated fasting blood glucose levels	6,530 (5,230-8,230)	171,000 (144,000-201,000)	4
Air pollution (total)	4,900 (4,400-5,400)	147,000 (132,000-162,000)	5
Environmental air pollution ($PM_{2.5}$)	2,940 (2,500-3,360)	83,000 (71,400-94,300)	
Environmental air pollution (ozone)	472 (177-768)	7,370 (2,740-12,000)	
Household air pollution	1,640 (1,400-1,930)	59,500 (50,800-68,900)	

$PM_{2.5}$: fine particulate matter < 2.5 µm in aerodynamic diameter; DALYs: disability-adjusted life years (the sum of the number of years of life lost due to premature death and the number of years lived with limitation/disability). In air pollution-related deaths and air pollution-related DALYs, the sum of the separate impacts of the pollutants is slightly higher than the sum of their combined impact.

Table 2. Estimates of deaths and disease burden associated with air pollution: global data for 2017 according to the Global Burden of Disease 2017 Risk Factor Collaborators.[5]

Pollutants and diseases	Environmental air pollution: $PM_{2.5}$		Household air pollution	
	Deaths × 1,000 (95% CI)	DALYs × 1,000 (95% CI)	Deaths × 1,000 (95% CI)	DALYs × 1,000 (95% CI)
COPD[a]	1,105 (583-1,606)	23,070 (13,040-32,800)	362 (248-482)	9,370 (6,480-12,400)
Ischemic heart disease	977 (839-1,120)	21,900 (18,900-25,400)	410 (344- 490)	10,200 (8,450-12,100)
Ischemic brain disease	445 (343-552)	10,510 (8,189-13,020)	231 (178-293)	5,761 (4,493-7,417)
Respiratory infections	433 (343-527)	18,500 (14,400-23,400)	459 (367-552)	25,900 (20,300-31,300)
Lung cancer	265 (183-351)	5,860 (4,050-7,730)	85 (60-113)	1,990 (1,410-2,640)
Type 2 diabetes	184 (123-227)	10,500 (6,700-13,900)	92 (63-113)	4,750 (3,110-6,190)
Cataracts	-	-	-	1,440 (732-2,250)
Total	3,412 (2,677-4,168)	147,000 (132,000-162,000)	1,640 (1,400-1,930)	59,500 (50,800-68,900)

$PM_{2.5}$: fine particulate matter < 2.5 µm in aerodynamic diameter; DALYs: disability-adjusted life years (the sum of the number of years of life lost due to premature death and the number of years lived with limitation/disability). [a]Ozone was responsible for 472,000 (95% CI: 177,000 to 768,000) deaths and 7.37 million (95% CI: 2.74 to 12.00 million) DALYs.

such pollutants, the defenses of the respiratory system, and the solubility of gaseous pollutants. The possible mechanisms involved in cardiorespiratory effects include inflammation and oxidative stress induced by reactive oxygen and nitrogen species (RONS) generated by inhaled pollutants.[14,15] Recent studies suggest a relevant role for inhaled environmentally persistent free radicals (EPFR) produced by combustion of catechols, phenols, and hydroquinones, which can remain in the air for up to 21 days.[16]

Chronic or acute inhalation of PM, O_3, and EPFR generates RONS, which trigger an inflammatory process and amplify it through the endogenous production of more RONS. If RONS production overcomes antioxidant defenses, there is activation of the mitogen-activated protein kinase (MAPK) complex, involved in the activation of nuclear transcription factors, such as NF-κB and AP-1, which stimulate the synthesis of RNA and the production of pro-inflammatory cytokines IL-8 and TNF-α, possibly inducing the formation of DNA adducts.[14,17] Air pollution has also been associated with epigenetic effects that, although potentially reversible without the occurrence of mutations, can produce changes in DNA expression, potentiating the inflammatory effects of pollutants.[8]

Air pollution has also been associated with reduced function of regulatory T lymphocytes, increased IgE levels, and increased production of CD4+ and CD8+ T lymphocytes, along with a greater Th2 response to stimuli by antigens in polluted environments, which would be associated with diseases such as rhinitis and asthma.[6,8]

Air pollution: respiratory effects

Air pollution is associated with various health effects, in addition to respiratory effects (Figure 1). Acute respiratory effects are those associated with recent exposure (hours or days), whereas chronic ones are a result of prolonged exposure, usually longer than 6 months.

With regard to acute effects, there is a consistent association between increased pollutant levels and increased numbers of emergency room visits, hospitalizations, and deaths, especially among

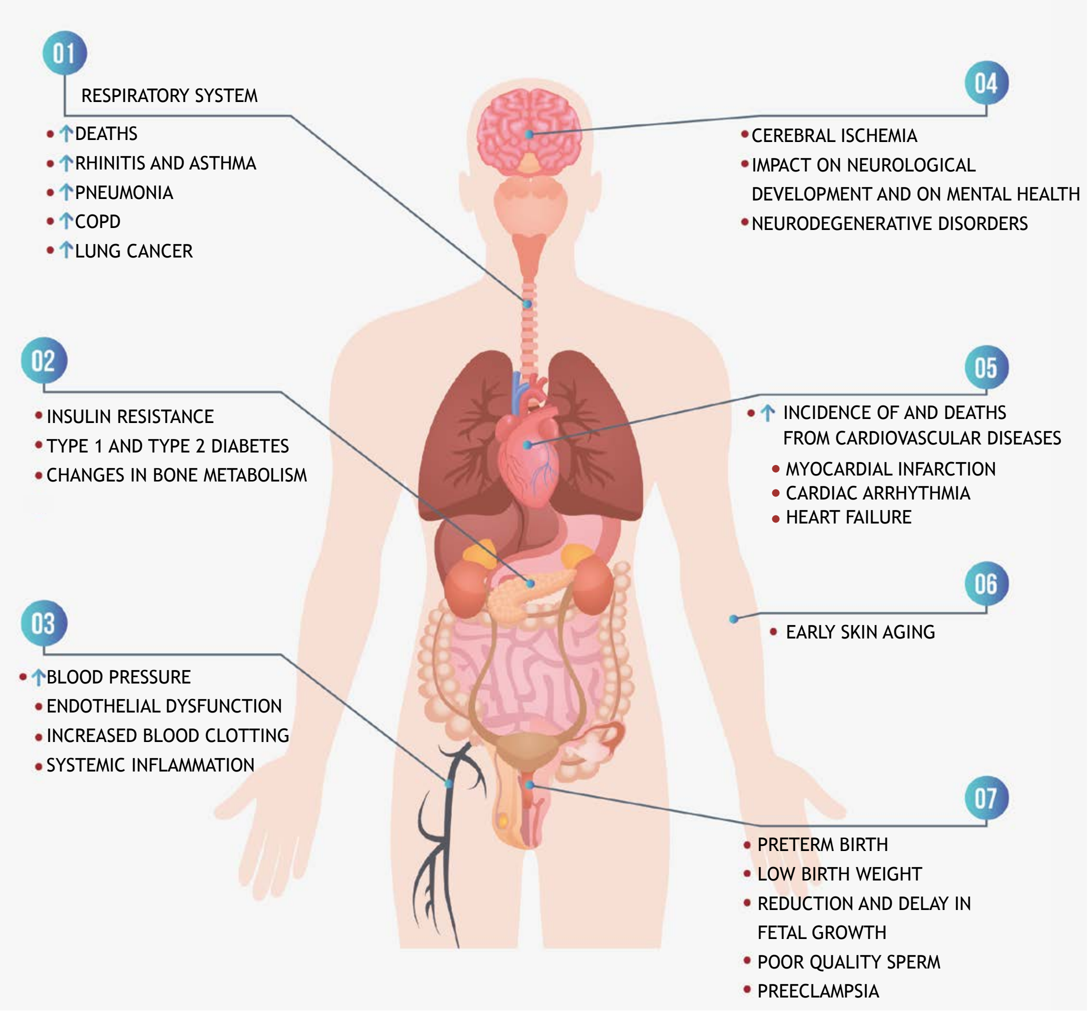

Figure 1. A representation of diseases and changes associated with air pollution. Adapted from Peters et al.[26]

individuals with chronic respiratory diseases, children, and elderly individuals.[18] A study involving 112 cities in the USA found a 1.68% increase in mortality due to respiratory disease for every 10 μg/m^3 increase in $PM_{2.5}$ concentration.[19] A systematic review and meta-analysis of 110 time-series studies conducted in several regions of the world revealed a 1.51% increase in mortality from respiratory diseases for every 10 μg/m^3 increase in $PM_{2.5}$ concentration.[20] In addition, a study conducted in Latin America[21] revealed a 2% increase in the risk of mortality from respiratory and cardiovascular diseases for every 10 μg/m^3 increase in $PM_{2.5}$ concentration, which is in line with the findings of studies conducted in Europe and North America.

The effects of chronic exposure have been associated with increased overall mortality from respiratory diseases, increased incidence of asthma and COPD, increased incidence of and mortality from lung cancer, reduced lung function, and a deficit in lung development during childhood.[22,23] One of the first studies on the subject, conducted in six major cities in the USA, revealed that the risk of death from cardiopulmonary diseases was 26% higher among individuals living in more polluted cities than among those living in less polluted cities.[24] These findings have been confirmed in other studies, including a prospective study involving 500,000 adults from all 50 U.S. states that revealed 9% and 18% increases in the risk of mortality from cardiopulmonary diseases and lung cancer, respectively, that were associated with a 10-μg/m^3 increase in $PM_{2.5}$ concentration.[25]

Pollution and rhinitis

A growing number of studies show an association between environmental air pollution and increased incidence and exacerbation of rhinitis. Authors suggest that genetic factors alone do not appear to be sufficient to justify the increase observed in the prevalence and exacerbation of allergic diseases, in particular, eczema, rhinitis and asthma. Exposure to PM_{10} and $PM_{2.5}$ appears as a factor that has a major impact in increasing the prevalence of these diseases, especially in children and adolescents.[6,27]

Pollution and asthma

Exposure to pollutants such as PM, NO_2, ozone, and carbon, as well as to motor vehicle traffic-related air pollution, is associated with a higher number of exacerbations, hospitalizations, and deaths in patients with asthma.[6,28,29]

One of the first studies evaluating the acute effects of air pollution, which involved 3,676 children from 12 locations in the state of California, USA,[30] showed that children with asthma who were exposed to NO_2, PM_{10}, and $PM_{2.5}$ had a higher prevalence of respiratory symptoms and a greater need for medication than did children without asthma. The most significant association was with exposure to NO_2, with a 2.7 times higher prevalence of symptoms for every 24 ppb increase in NO_2 concentration. A study conducted in Hubei province, China, with 4,454 individuals who died from asthma between 2013 and 2018 found increases of 7%, 9%, and 11% in mortality that were associated with $PM_{2.5}$, O_3, and NO_2, respectively.[31]

In recent years, studies have revealed that air pollution is also associated with an increased incidence of asthma, especially in children and adolescents,[6,23,32-34] with less robust data on adults.[35,36] One of the first prospective studies on the subject, also conducted in California, showed an association between chronic exposure to ozone and an increased incidence of asthma.[37] Another study evaluated the global incidence of air pollution-related asthma. For 2015, 4 milllion new cases of asthma (13% of global incidence) were estimated to be associated with exposure to NO_2 in children and young people under 18 years of age, 150,000 of which were in Brazil and Paraguay (aggregate data).[38] In adults, a study conducted in Australia showed that individuals exposed to NO_2 for at least 5 years and those living less than 200 m from a major road were at an increased risk of developing asthma and experiencing a marked decline in lung function.[39]

Pollution and COPD

Since the 1990s, epidemiological studies have shown an association between air pollution and acute respiratory events in individuals with COPD, with an increased number of exacerbations, emergency room visits, hospitalizations, and deaths.[40] One of the first studies on the subject, which evaluated hospitalizations secondary to COPD exacerbation that were associated with exposure to pollutants, found that, for every 10 μm/m^3 increase in PM_{10} concentration, there was a 2.5% increase in hospitalizations. A recent study[41] involving 303,887 individuals in the United Kingdom revealed that a 5 μg/m^3 increase in $PM_{2.5}$ concentration was associated with 83 mL and 62 mL reductions in FEV_1 and FVC, respectively, as well as with a 52% increase in COPD prevalence.

More recent studies suggest that exposure to pollutants is associated with an increased incidence of COPD.[23,41] A cohort study conducted in Norway involving 57,000 individuals found an 8% increase in COPD incidence that was associated with a 5.8 μg/m^3 increase in NO_2 concentration.[42] Another recently published cohort study,[43] involving 7,071 individuals in six U.S. metropolitan regions between 2000 and 2018, found an increased percentage of areas of pulmonary emphysema, as assessed by HRCT, that were associated with exposure to O_3, $PM_{2.5}$, NO_x, and carbon particles. A study analyzing 2017 data estimated that 1.1 million COPD deaths were attributable to air pollution worldwide,[5] representing 34.6% of all COPD deaths in that year.[44]

Pollution and lung function

In recent years, evidence has been accumulating on the effects of air pollution on lung function, confirming the findings of earlier studies.[45,46] The effects of air pollution appear to be more marked during the first years of life, including during the intrauterine period. Jedrychowski et al.[47] evaluated maternal exposure to $PM_{2.5}$ during the second trimester of pregnancy and found lower FEV_1 and FVC values (differences of 87 mL and 91 mL, respectively) at 5 years of age in children whose mothers had higher exposure to $PM_{2.5}$. In the city of Guangzhou, China, a study of highly polluted areas (an annual average PM_{10} concentration between 80 and 96 μg/m³) showed that higher levels of pollution are associated with a reduction in the growth rate of $FEF_{25-75\%}$ and FEV_1 in boys.[48]

A prospective study[49] that followed children from age 10 to age 18 years in 12 cities in California found a reduction in the total growth of FEV_1 that was associated with $PM_{2.5}$, NO_2, acid vapor, and carbon particles. The proportion of young individuals who, at age 18 years, had an FEV_1 of less than 80% of the predicted value was 4.9 times higher (a prevalence of 7.9%) in the communities with the highest levels of $PM_{2.5}$ than in the communities with the lowest levels.

A study conducted in the city of São Paulo, Brazil, involving taxi drivers and traffic controllers revealed that exposure to high levels of $PM_{2.5}$ was associated with a nonsignificant reduction in FEV_1 and FVC, but there was a significant increase in $FEF_{25-75\%}$, suggesting possible interstitial changes due to exposure to polllutants.[50]

Pollution and respiratory infections

Exposure to air pollutants increases the risk of upper and lower airway infections. Exposure to PM was responsible for 433,000 deaths from respiratory infections globally in 2017, especially affecting children and elderly individuals.[5] A systematic review estimated a 12% increase in the risk of pneumonia in children for every annual average increase of 10 μg/m³ in $PM_{2.5}$ concentration.[51] In line with this, a systematic review and meta-analysis using six European cohorts and involving 16,000 children showed an up to 30% increase in NO_2 exposure-related risk of pneumonia.[35]

Current studies suggest a possible contributing effect of air pollution on the spread of SARS-CoV-2 (COVID-19). A study conducted in Italy revealed that, in cities where the concentrations of air pollutants were higher before the epidemic, there was an accelerated spread of the virus, as well as a higher number of infected individuals, when compared with less polluted cities.[52,53] A recently published study that characterized, with the use of satellites, the global concentration of $PM_{2.5}$ and its anthropogenic fraction, estimated that exposure to PM would have contributed 15% (95% CI: 7-33%) to global COVID-19 mortality, being an important cofactor for increasing the risk of COVID-19 morbidity and mortality.[54,55]

Pollution and lung cancer

The International Agency for Research on Cancer considers environmental air pollution carcinogenic to humans, because it increases the risk of lung cancer.[56] Although a positive association has also been found between exposure to this type of pollution and bladder cancer, a causal relationship has yet to be established. According to global data,[5] an estimated 2.16 million new cases of lung cancer and 1.88 million lung cancer deaths occurred in 2017, lung cancer being the leading cause of cancer death among men and the third leading cause of cancer death among women. It is estimated that 14% (n = 265,000) of lung cancer deaths are attributable to environmental air pollution,[5] a proportion that ranges from 1% to 25% across countries. The mean risk for developing lung cancer ranges across studies from 20% to 30% for a 10 μg/m³ increase in PM_{10} concentration and a 5 μg/m³ increase in $PM_{2.5}$ concentration.[56,57]

Air pollution can induce genotoxic effects that include formation of DNA adducts, breaks in DNA strands, and damage to DNA bases due to oxidation, genetic mutations, chromosomal damage to somatic cells, gametic mutations, and oncogenic transformation. Molecular epidemiological studies in humans reveal associations between the frequencies of DNA damage (such as adducts in lymphocytes) and cytogenetic damage (such as chromosomal translocations and micronuclei) and exposures to PM and/or carcinogenic polycyclic aromatic hydrocarbons. Multiple proven effects lend plausibility to the association between air pollution and lung cancer development through a direct effect, as well as to tumor development via oxidative stress and persistent inflammation.[56]

Pollution and physical exercise

Low physical activity is an important risk factor for mortality and was associated with 1.26 million deaths in 2017. Regular mild- to moderate-intensity exercise contributes to reducing or delaying the onset of chronic diseases by up to 10 years.[58]

Exercising in air-polluted environments can have health consequences in susceptible populations, such as children, the elderly, and individuals with chronic diseases, as well as resulting in poorer physical performance in athletes.[59,60] A study conducted in communities with high ozone concentrations in California[61] found that the risk of developing asthma was 3.3 times higher in children playing three or more sports per week than in children playing no sports. Sports had no effect in cities with low ozone concentrations.

In healthy individuals, the respiratory effects of air pollution do not appear to be significant.[62] A study conducted in London, United Kingdom,[63] compared changes over time in lung function and sputum inflammatory markers in adults with asthma who walked for 2 h in a park and, on a separate occasion, along a busy traffic street. Participants with asthma showed a significant decline in lung function and an increase in inflammatory markers after walking along a busy traffic street.[63] A study with a similar design that compared healthy individuals, individuals with

COPD, and individuals with stable coronary disease revealed that, in all participants, walking for 2 h in a park led to an increase in lung function, an increase that was absent or reduced after walking along a busy traffic street.[59] Studies in humans[59] and studies using mathematical models[64,65] have shown that, for healthy individuals and even for individuals with chronic diseases, mild-to-moderate exercise in polluted environments, even where pollution levels are above the reference values recommended by the WHO,[7] has beneficial effects that override the effects of inhalation of an increased load of pollutants. Therefore, the balance of studies suggests that mild-to-moderate exercise is beneficial even in polluted places.[8,60,64,65]

Other pulmonary conditions

Recent studies have shown an association of exposure to air pollution with sleep apnea,[8] increased risk of bronchiolitis obliterans, increased risk of death in lung transplant recipients,[66] and increased risk of progression to interstitial lung disease.[67]

SUSCEPTIBLE/VULNERABLE POPULATIONS

Intrinsic and extrinsic factors increase the vulnerability and/or susceptibility of individuals to the adverse effects of air pollutants. In addition to age, having a preexisting chronic disease, such as asthma, COPD, pulmonary fibrosis, arrhythmias, hypertension, ischemic heart disease, diabetes, autoimmune diseases, and obesity, makes individuals more vulnerable.[8,68]

Individuals with poor socioeconomic status are most vulnerable, since they are likely to be exposed for longer periods on their way to work and tend to live closer to industrial areas. In addition, they live in overcrowded households, in areas without appropriate green spaces, and have diets poor in fruits and vegetables, which are rich in antioxidants.[8,68]

Pregnant women

Exposure to air pollutants during pregnancy can compromise fetal development and cause intrauterine growth restriction, prematurity, low birth weight, congenital anomalies, and intrauterine and perinatal death.[8,69]

Intense cell proliferation, physiological immaturity, accelerated organ development, and changes in metabolism increase the fetus' susceptibility to inhalation of air pollutants by the mother, and the mother in turn can have her respiratory system compromised by the action of pollutants, which can thereby affect the transport of oxygen and nutrients across the placenta. Exposure to high concentrations of PM is associated with placental inflammation, abnormal trophoblastic invasion, and decreased placental angiogenesis, impacting fetal development.[69]

Children

Worldwide, 93% of children live in environments in which air pollutant concentrations are above those recommended by the WHO.[70] The WHO estimates that one in every four deaths of children under 5 years of age is directly or indirectly related to environmental risks.[70] Global analyses for 2015 estimated the number of deaths from respiratory infections resulting from exposure to environmental air pollution among children aged 5 years or younger to be 727,000.[71] Children have higher minute ventilation and higher basal metabolic rates and engage in more physical activity than do adults, as well as spending more time outdoors.

The fact that children's immune system is not fully developed increases their susceptibility to respiratory infections.[8,70] Inside the womb, fetuses can be affected by pollutants inhaled by the mother, with can have health consequences in adulthood, such as an increased risk of asthma.[8,70,72]

Elderly individuals

The elderly population is growing because of increased life expectancy and steadily declining birth rates. In 2013, elderly individuals aged 80 years or older represented 14% of the world population.

Elderly individuals are susceptible to the adverse effects of exposure to air pollutants because they have a less efficient immune system (immunosenescence) and a progressive decline in lung function, which can lead to decreased exercise tolerance. Wu et al.,[73] in a study conducted in Beijing, China, observed a greater increase in hospitalizations for air pollution-related pneumonia in the elderly compared with younger age groups. A cohort study conducted in the USA[74] that used Medicare data showed that, between 2000 and 2012, acute exposures to fine PM and ozone during the warmest seasons of the year (spring and summer) were associated with an increased risk of all-cause mortality among elderly individuals. The same effect was observed even on days with concentrations below the air quality limits set by the U.S. Environmental Protection Agency.

Genetic susceptibility

The production of free radicals and the induction of inflammatory response by pollutants in the respiratory system can be neutralized by the antioxidant agents present in the aqueous layer lining the respiratory epithelium—glutathione S-transferase (GST), superoxide dismutase, catalase, tocopherol, ascorbic acid, and uric acid—which can prevent oxidative stress and represent the first line of defense against the adverse effects of pollutants. Polymorphisms in genes responsible for controlling oxidative stress (*NQO1*, *GSTM1*, and *GSTP1*) and in inflammatory genes (*TNF*) alter the presence and intensity of respiratory symptoms and change lung function and the risk of developing asthma in response to pollutants.[75]

Of the antioxidant agents present in the respiratory epithelium, the GST family is considered one of the most important, being represented by three major classes of enzymes: GSTM1; GSTP1; and GSTT1.[76]

Polymorphisms in genes encoding the enzymes of the GST family can change the expression or function of these enzymes in the lung tissue, resulting in different responses to inflammation and oxidative stress and, consequently, in increased susceptibility to the adverse effects of air pollutants.[76] A study conducted by Prado et al.[77] found a marked loss of lung function in sugarcane workers exposed to air pollution who had deletions in the *GSTM1* and *GSTT1* genes.

Studies have also revealed the epigenetic effect of exposure to PM, an effect that can override genetic susceptibility. Altered epigenetic regulation of white blood cells and various other tissue cells, especially PM-induced changes in DNA methylation, appears to contribute to the health effects associated with air pollution.[23]

BRAZIL: RELEVANT STUDIES ON THE EFFECTS OF AIR POLLUTION

Since the late 1970s, the effects of air pollutants, from both vehicular and industrial sources and from biomass burning, have been systematically studied in Brazil.

Air pollution from fossil fuel burning

Over the past 30 years, 170 studies on the subject conducted in Brazil have been published. From 1975 onward, the Air Pollution Experimental Laboratory of the University of São Paulo School of Medicine Department of Pathology, in the city of São Paulo, located in the state of São Paulo, Brazil, carried out experimental and epidemiological studies to assess the adverse effects of exposure to air pollutants. The first study exposed rats to the environmental air in the city of São Paulo and to the environmental air in the city of Atibaia, also located in the state of São Paulo and where the air, at the time, was considered cleaner. After 6 months of exposure, there were changes in mucus rheological properties, destruction of cilia, and, consequently, increased bacterial colonization of the respiratory epithelium, all of which led to the death of 50% of the rats exposed to the air in the city of São Paulo.[78] In parallel, using models from ecological time series studies, another study showed that daily increases in NO_x concentration were associated with increased mortality from respiratory diseases in children aged 5 years or younger in the city of São Paulo.[79] Another study by the group showed that lung autopsy samples from residents of the city of Guarulhos, located in the state of São Paulo and where pollution levels were high at the time of the study, presented more evidence of histopathologic damage than did those from residents of the cities of Ourinhos and Ribeirão Preto, also located in the state of São Paulo but where pollution levels were lower, even after controlling for smoking.[80]

In another study, mice were exposed to different concentrations of inhaled fine PM, and even those exposed to low concentrations showed oxidative stress, inflammation, and lung tissue damage.[81]

Ecological time series studies have shown associations between increased emergency room visits in children with respiratory diseases and increased air pollution[82]; between increased hospitalizations for respiratory diseases in children and adolescents and increased concentrations of PM_{10} and SO_2[83]; and between increased emergency room visits due to pneumonia and influenza,[84] as well as due to asthma and COPD[85,86] in adults and increased air pollution.

A study conducted on workers exposed to environmental air pollution in the city of São Paulo, located in the state of São Paulo, Brazil, revealed that, those with the highest level of exposure had a reduction in FVC compared with those with the lowest level of exposure.[50] Chart 1 summarizes the major studies on the respiratory impact of urban air pollution conducted in Brazil.

Air pollution from biomass burning

Over the past 20 years, studies conducted in Brazil have assessed the impacts that forest fires (especially in the Brazilian Amazon) and pre-harvest sugarcane burning (especially in the state of São Paulo) have on the health of the exposed population (Chart 2).

Studies conducted in urban areas located in sugarcane producing regions in the state of São Paulo have shown that, during the sugarcane burning season, there were increases in emergency room visits for inhalation therapy[87] and for pneumonia,[88] as well as an increase in hospitalizations of children and elderly individuals for all respiratory diseases,[89] specifically for asthma.[90] In Monte Aprazível, a town in the state of São Paulo, rhinitis prevalence increased and lung function decreased in children during the sugarcane burning season.[91] Another study revealed that, during manual harvesting of burnt cane, workers had exacerbated respiratory symptoms, reduced lung function, reduced antioxidant enzyme activity, and increased oxidative stress markers.[77] In another group of sugarcane workers, it was found that, during the sugarcane burning season, there were changes in mucus properties and impairment of nasal mucociliary clearance.[92]

Emissions from fires in the Amazon region can be transported long distances and, in addition to affecting the global climate,[93] can impact the health of children and the elderly.[94,95] Studies conducted in the state of Mato Grosso have shown that increased exposure to PM contributed to increased hospitalizations of children less than 5 years of age due to respiratory diseases[96] and to acute decreases in PEF.[97]

In an experimental study in mice, animals received repeated intranasal instillation of PM from different sources, and PM from biomass burning were found to be more toxic than PM from vehicular traffic.[98]

FINAL CONSIDERATIONS

Environmental air pollution affects billions of people every day worldwide, having a major impact on

Chart 1. Major studies on air pollution, predominantly from vehicular and industrial sources, and respiratory diseases conducted in Brazil.

Authors	Population and setting	Outcome	Exposure	Results
Sobral[100]	Children in the city of São Paulo, located in the state of São Paulo	Respiratory diseases	Air pollution	Increased respiratory diseases in more polluted areas
Saldiva et al.[78]	Rats in the cities of São Paulo and Atibaia, both located in the state of São Paulo	Changes in the mucociliary system	Environmental air in the two cities	Changes in the mucus and cilia and increased mortality from respiratory diseases in the city of São Paulo
Saldiva et al.[79]	Children aged 5 years or younger in the city of São Paulo	Mortality from respiratory diseases	Measured primary pollutants	An association between NOx and increased mortality
Saldiva et al.[101]	Elderly individuals > 65 years old in the greater metropolitan area of São Paulo	Mortality from respiratory diseases	PM_{10}, NO_x, SO_2, and CO	Increased deaths associated with increased air pollutant levels
Souza et al.[80]	Autopsy in individuals who died a violent death. Smokers in the city of Ourinhos (mean, 31 years) and nonsmokers in the city of Guarulhos (mean, 26 years), both located in the state of São Paulo	Lung histopathologic changes	Tobacco and air pollution	Comparison of lung injury between nonsmokers in the more polluted city (Guarulhos) and smokers in the less polluted city (Ourinhos)
Lin et al.[82]	Children and adolescents in the city São Paulo	Emergency room visits	Measured air pollutants	Increased visits associated with PM_{10} and O_3
Braga et al.[83]	Children aged 12 years or younger in the city of São Paulo	Hospitalizations for respiratory diseases	PM_{10}, SO_2, NO_2, CO, and O_3	An association between hospitalization and air pollutants
Braga et al.[102]	Individuals aged 19 years or younger in the city of São Paulo	Hospitalizations for respiratory diseases	PM_{10}, SO_2, NO_2, CO, and O_3	An increased risk in children ≤ 2 years and adolescents aged 14 to 19 years
Conceição et al.[103]	Children aged 5 years or younger in the city of São Paulo	Mortality from respiratory diseases	Primary and secondary pollutants	A mortality increase associated with increases in CO, SO_2, and PM_{10}
Martins et al.[104]	Elderly individuals in the city of São Paulo	Mortality from respiratory diseases	Primary and secondary pollutants	An association between PM_{10} and increased numbers of deaths; more deaths in those with a lower socioeconomic status
Mauad et al.[105]	Mice in the city of São Paulo	Lung development	Air pollution	Exposure to PM and decreases in inspiratory and expiratory lung volumes
Arbex et al.[86]	Adults and elderly individuals in the city of São Paulo	Emergency room visits	Air pollutants	Increased visits by elderly individuals and women
Riva et al.[81]	Mice (an experimental study)	Inflammatory changes in the lung	Inhaled fine PM	Low concentrations of $PM_{2.5}$ induce oxidative stress and inflammation in the lung.
Santos et al.[50]	Workers exposed to environmental air pollution	Lung function	Individual exposure to $PM_{2.5}$	Reduced FVC and increased $FEF_{25-75\%}$
Gouveia et al.[106]	Individuals of all ages and children less than 5 years old	Hospitalizations for respiratory diseases	PM_{10}	Increased hospitalizations in all age groups and in children less than 5 years old
de Barros Mendes Lopes et al.[107]	Mice: exposure during pregnancy and after birth (São Paulo)	Lung formation and growth	$PM_{2.5}$	Exposure leads to a reduced number of alveoli and impaired lung function in adult mice.

PM_{10}: particulate matter with an aerodynamic diameter less than 10 µm; $PM_{2.5}$: particulate matter with an aerodynamic diameter less than 2.5 µm; and NO_x: nitrogen oxides.

morbidity and mortality, as well as contributing to global warming.

The presence of chronic systemic diseases increases the susceptibility of individuals to the adverse effects of air pollutants, manifesting from mild forms of illness to death, which occurs in patients with increased susceptibility. Recent studies show that exposure to air pollutants can cause asthma, COPD, and lung

Chart 2. Major studies on air pollution, especially from biomass burning, and respiratory diseases conducted in Brazil.

Authors	Population and setting	Outcome	Exposure	Results
Arbex et al.[87]	Population in the city of Araraquara, located in the state of São Paulo	Use of medication by the population (inhalation therapy)	TSP	Increased visits for inhalation therapy during the sugarcane burning season
Cançado et al.[89]	Children and elderly individuals in the city of Piracicaba, located in the state of São Paulo	Hospitalization for respiratory disease	$PM_{2.5}$, PM_{10}	Increased hospitalizations on more polluted days; major effects during the sugarcane burning season
Arbex et al.[90]	Population in the city of Araraquara	Hospitalization for asthma	TSP	Increased hospitalizations on more polluted days and during the sugarcane burning season; a 50% increase in hospitalizations during the sugarcane burning season
do Carmo et al.[94]	Children and elderly individuals in Alta Floresta, a town in the state of Mato Grosso	Outpatient treatment for respiratory disease	$PM_{2.5}$ from forest burning	Increased visits by children but not by elderly individuals
Ignotti et al.[95]	Children and elderly individuals in microregions of the Brazilian Amazon	Hospitalization for respiratory disease	$PM_{2.5}$ > 80 μg/m^3	Increased hospitalizations in children and elderly individuals
Rodrigues et al.[108]	Elderly individuals in the Brazilian Amazon	Hospitalization for asthma	Dry season vs. wet season	Hospitalization rates are three times higher during the dry season than during the wet season.
Riguera et al.[91]	Schoolchildren aged 10 to 14 years in Monte Aprazível, a town in the state of São Paulo	Asthma and rhinitis symptoms, PEF	$PM_{2.5}$ and black carbon	Increased symptoms of asthma and rhinitis; a higher prevalence of rhinitis during the sugarcane burning season; decreased PEF
Goto et al.[92]	Sugarcane workers in Cerquilho, a town in the state of São Paulo	Mucociliary clearance	Sugarcane burning	Impaired clearance and changes in mucus properties
Prado et al.[77]	Sugarcane workers and residents of Mendonça, a town in the state of São Paulo	Lung function, respiratory symptoms, oxidative stress markers	Sugarcane burning	Reduced lung function, increased respiratory symptoms, and increased oxidative stress during the harvest season
Silva et al.[96]	Children and elderly individuals in the city of Cuiabá, located in the state of Mato Grosso	Hospitalization	$PM_{2.5}$	Increased hospitalizations in children but not in elderly individuals
Arbex et al.[88]	Population in the city of Araraquara	Emergency room visit for pneumonia	TSP	An increased effect of exposure during the sugarcane burning season
Jacobson et al.[97]	Schoolchildren aged 6 to 15 years in the city of Tangará da Serra, located in the state of Mato Grosso	Lung function	PM_{10} and $PM_{2.5}$	Decreases in PEF
Mazzoli-Rocha et al.[98]	Mice, cities of São Paulo and Araraquara, both located in the state of São Paulo	Lung resistance, lung elastance, and lung inflammation	Repeated instillation of PM	PM from sugarcane burning is more toxic than is PM from vehicular sources.
de Oliveira Alves et al.[109]	Lung cells, the Amazon region	Cell toxicity	PM during burning in the Amazon forest	Increased levels of reactive oxygen species, inflammatory cytokines, DNA damage, apoptosis, and necrosis

TSP: total suspended particles; PM_{10}: particulate matter with an aerodynamic diameter less than 10 μm; and $PM_{2.5}$: particulate matter with an aerodynamic diameter less than 2.5 μm.

cancer. Exposure of pregnant women to air pollutants has serious adverse effects on the fetus that, if not lethal, can result in compromised health in childhood, adolescence, adulthood, and old age. Regular physical exercise can contribute to minimizing the effects of air pollution.

The most effective measures for reducing the impact of air pollution on human health are those related to reducing emissions. Expansion of public transportation, the use of cleaner fuels in vehicles, industries, and households, as well as a change in building construction standards, which require a lot of energy, are feasible and necessary measures to reduce global warming and its direct effects on human health.[99] It is estimated that reducing emission levels to those recommended by the WHO and the Paris Agreement can lead to up to 60% decrease in pollution-related deaths annually.[11] In this context, physicians should be able to inform and advise the population about healthy eating habits, regular physical exercise, and chronic disease control. Physicians should also contribute to strengthening the necessary measures to reduce emissions in favor of environmental recovery. The current SARS-CoV-2 virus pandemic, which follows the SARS and MERS outbreaks in 2000 and 2012, respectively, shows that we cannot adopt a passive behavior regarding environmental imbalances caused by the way the planet is developed and occupied.

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Pulmonology approach in the investigation of chronic unexplained dyspnea

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ABSTRACT

Chronic unexplained dyspnea and exercise intolerance represent common, distressing symptoms in outpatients. Clinical history taking and physical examination are the mainstays for diagnostic evaluation. However, the cause of dyspnea may remain elusive even after comprehensive diagnostic evaluation—basic laboratory analyses; chest imaging; pulmonary function testing; and cardiac testing. At that point (and frequently before), patients are usually referred to a pulmonologist, who is expected to be the main physician to solve this conundrum. In this context, cardiopulmonary exercise testing (CPET), to assess physiological and sensory responses from rest to peak exercise, provides a unique opportunity to unmask the mechanisms of the underlying dyspnea and their interactions with a broad spectrum of disorders. However, CPET is underused in clinical practice, possibly due to operational issues (equipment costs, limited availability, and poor remuneration) and limited medical education regarding the method. To counter the latter shortcoming, we aspire to provide a pragmatic strategy for interpreting CPET results. Clustering findings of exercise response allows the characterization of patterns that permit the clinician to narrow the list of possible diagnoses rather than pinpointing a specific etiology. We present a proposal for a diagnostic workup and some illustrative cases assessed by CPET. Given that airway hyperresponsiveness and pulmonary vascular disorders, which are within the purview of pulmonology, are common causes of chronic unexplained dyspnea, we also aim to describe the role of bronchial challenge tests and the diagnostic reasoning for investigating the pulmonary circulation in this context.

Keywords: Dyspnea; Exercise test; Bronchial provocation tests; Vascular diseases.

INTRODUCTION

Dyspnea is a common and distressing symptom. Population-based studies have shown that the prevalence of mild-to-moderate dyspnea is 9-37% among community-dwelling adults.[1] Higher dyspnea scores were associated with decrements in health status and physical activity in subjects with COPD,[2] and the magnitude of dyspnea can be more discriminating than the functional staging of disease severity (based on FEV_1) concerning survival[3] and health-related quality of life.[4] Dyspnea has been shown to be a better predictor of mortality than has angina in patients referred for cardiac stress testing[5] and was associated with a higher risk of mortality when compared with asymptomatic population-based subjects.[6]

There is no definitive classification of dyspnea according to its duration. Dyspnea is usually considered acute when it lasts over hours to days and is considered chronic when it lasts for more than 4 to 8 weeks.[7,8] Multiple conditions can cause chronic dyspnea. Although clinical history taking and physical examination are often insufficient to unequivocally identify the etiology(ies), they remain the mainstays of the diagnostic evaluation, providing guidance to narrow the possibilities and to select appropriate tests. Together with initial examinations, the potential underlying cause(s) can usually be identified in a significant proportion of cases. In two previous seminal studies by Pratter et al.[8,9] investigating chronic dyspnea in clinical practice, approximately half of the participants were considered as having their diagnosis defined based on clinical history taking, physical examination, chest X-ray, and spirometry. Respiratory and cardiac disorders made up the most common etiologies. Dyspnea that remains unexplained after this initial testing sequence represents a major diagnostic challenge. In fact, the cause of dyspnea may remain elusive even after aggressive evaluation.[10,11] Such cases are frequently referred to various different specialists who may conduct the investigation of dyspnea with different—and sometimes contrasting—approaches, and quite often there is no effective communication and collaboration among them. This situation generally results in repeated medical appointments and diagnostic testing, treatments being delayed while the cause of

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dyspnea is being investigated, and, in the end, it frequently remains "unexplained".[12]

There is no consensus definition, but unexplained dyspnea or dyspnea of unknown origin could be characterized as persistent dyspnea (for at least 3 months) that is clinically and significantly severe (modified Medical Research Council scale score ≥ 2) and remains unexplained after thorough clinical assessment, basic biochemical testing, complete blood count, thyroid function testing, pulmonary function testing, and chest imaging (Figure 1; initial evaluation).[13] Again, although the definition is questionable, the concept of disproportionate or out-of-proportion dyspnea emerges, that is, when a patient has mild abnormalities relative to resting cardiac and pulmonary function testing or imaging findings that do not convincingly explain the severity of dyspnea, at least as expected based on clinical experience and the literature available.[13] Given the epidemiological importance of cardiopulmonary diseases in this context[8,14] and the widespread availability of "advanced" lung function testing, cardiovascular testing, and CT of the chest, it is our impression, based on clinical practice and the literature available,[10-14] that chronic dyspnea is only assumed to be unexplained if the results of those tests are inconclusive (Figure 1; advanced evaluation). In this context, we suggest that HRCT of the chest should be performed using inspiratory/expiratory maneuvers (to detect expiratory dynamic airway collapse, and regional air trapping). Specific studies in this setting are scarce, probably due to the complexity to gather such cases and provide an unequivocal final diagnosis. Those cases account for about 15% of all chronic dyspnea cases and are usually reported in the literature as being treated in multidisciplinary specialized centers.[7,15,16]

Our intention is not to describe the diagnostic criteria to confirm all potential etiologies of chronic dyspnea. Instead, the overarching objective of the current review is to present the clinical utility of cardiopulmonary exercise testing (CPET) in the evaluation of chronic dyspnea by describing the syndromic patterns related to exercise responses and by indicating a set of different etiological possibilities. Furthermore, given the low specificity and sensitivity of clinical evaluation to detect airway hyperresponsiveness (AHR)[17,18] and pulmonary vascular diseases,[14] the frequency of these conditions causing chronic unexplained dyspnea being high (Table 1), as well as the frequent inconclusive results from spirometry, lung volume measurements, DLCO, and CT of the chest in this context, specific tests to diagnose these conditions should be considered (Figure 1; specific evaluation). Therefore, we also aim to describe the role of bronchial challenge tests (BCTs) and the reasoning for the evaluation of pulmonary circulation in the diagnostic

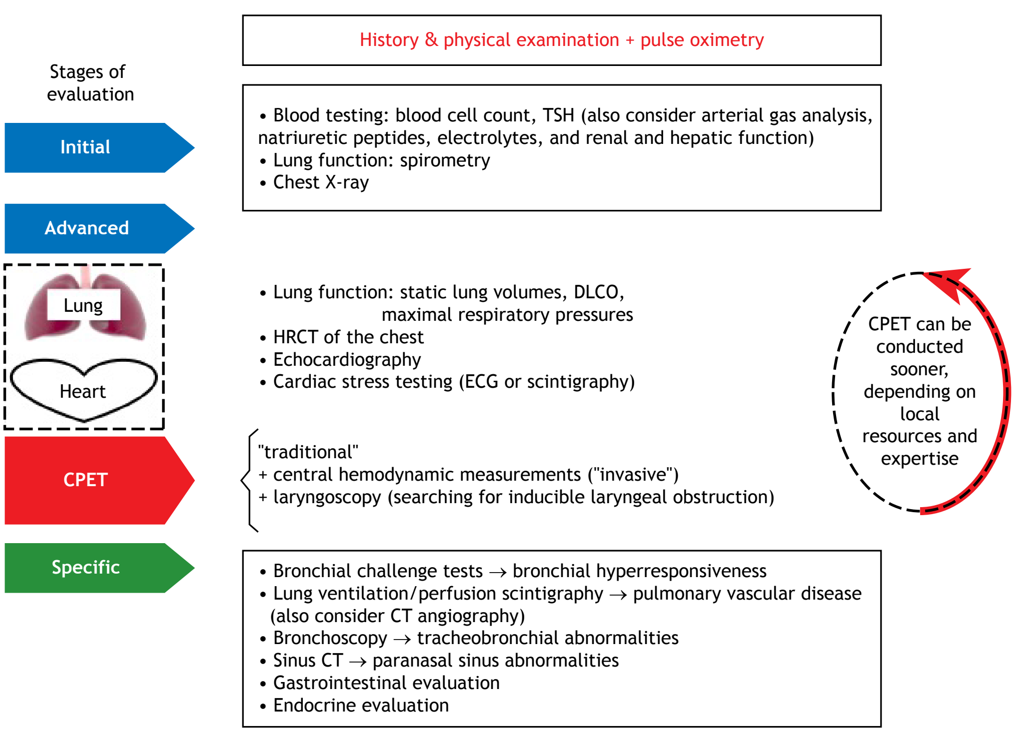

Figure 1. Suggested workup for the investigation of chronic dyspnea. The stages are based on the complexity of the tests and the epidemiology of the most common underlying diseases. Note that the sequence can be modified on the basis of the clinical impression and local resource availability. ECG: electrocardiogram; and CPET: cardiopulmonary exercise testing.

Table 1. Major etiologies identified in studies on chronic unexplained dyspnea. Cardiopulmonary diseases comprise two-thirds of the underlying causes.

Etiology	Prevalence, %
Respiratory	
"Unspecified" airway disease	25-37
Asthma	16-29
Airway hyperresponsiveness	25
Pulmonary vascular disease	5- 17
COPD	9-14
Interstitial lung disease	7-14
Other	2-9
Cardiocirculatory	
Chronic (systolic or diastolic) heart failure	6-17
Ischemic heart disease	5
Other	8
Noncardiopulmonary diseases (less common)	
Obesity	16
Dysfunctional breathing	5-32
Deconditioning	3-28
Myopathies	1-24
Dysautonomia	21
Miscellaneous	2-7

Information extracted from references.[7-9,10,12]

workup to unveil the cause(s) of chronic unexplained or disproportionate dyspnea.

CPET

Multiple causes, such as exercise-induced disorders not manifested at rest, exaggerated dyspnea from common conditions (obesity, adverse events of medications), skeletal muscle disease, psychogenic dyspnea (unexplained by organic dysfunction), and rare miscellaneous conditions, should be considered in the face of chronic unexplained dyspnea.[12,13] In other words, chronic unexplained dyspnea might be caused by conditions presenting with greater complexity, unusual presentations of common diseases, or rare disorders, or might even have a psychogenic origin. CPET is a safe procedure that can identify specific physiological abnormalities of the integrated cardiopulmonary, neuromuscular, and sensory systems that contribute to persistent perceived respiratory discomfort. Also of utmost importance is the objective assessment of aerobic capacity and exercise tolerance, as well as of physiological and sensory dynamic responses to exercise. Given the possible dissociation between the perception of dyspnea during activities of daily living and that perception objectively measured during an exercise test,[19] as well as the complex neurophysiology of breathlessness and the influence of psychological and cultural factors,[20] CPET frequently uncovers a preserved exercise capacity and normal responses to exercise, reassuring the patient and the medical team that a relevant organic abnormality is not present. Caution should be considered regarding incipient pathological conditions that lead to a decrement in exercise capacity without reducing peak measurements below the lower limit of normality or that cause abnormal submaximal responses. This can be suspected if a subject whose physical fitness was previously good/excellent complains about exercise intolerance with no evident reason (e.g., reduction or interruption of the physical activity) and is controlled by repeating the CPET (one or more times) during follow-up.

Based on the most common causes of chronic unexplained dyspnea (Table 1),[7-9,10,12] we consider that when the etiology of dyspnea remains elusive after the initial evaluation (Figure 1), and the patient's medical history and physical examination point out to no specific direction, CPET is uniquely poised to unveil the main physiological system(s) that could be related to the perception of dyspnea and to measure exercise tolerance objectively, as well as the perception of dyspnea for a given workload or ventilation, or, in the best scenario, to indicate the absence of physiological impairment. In various circumstances, CPET is not diagnostic *per se*, but it can uncover patterns of physiological dysfunction, guide further investigation(s), or reassure that no significant cardiopulmonary or other underlying disease is explicit at that moment. Therefore, CPET might guide the investigation and could avoid unnecessary tests and costs. Because there are multiple and combined causes of dyspnea and no cogent scientific evidence to dictate the sequence of evaluation, it seems that good practice follows the clinical impression based on medical history taking, physical examination, and availability of local resources and expertise (Figure 1). After the "supposed" cause(s) of dyspnea is/are identified, it is crucial to consider the response to the treatment(s) employed (e.g., weight loss, exercise training, use of inhaled corticosteroids, etc.), which, if subjectively and objectively effective, reinforces the diagnosis(es) being considered.

CPET is usually performed using a cycle ergometer or a treadmill, although cycling is more frequently used in the setting of chronic respiratory diseases and investigation of dyspnea. The most commonly used protocol includes a resting steady-state period of a few minutes, followed by 2-3 min of unloaded pedaling and, thereafter, a rapidly incremental continuous "ramp" or 1-2-min stepwise increases in the work rate (WR) until exhaustion.[21] Breath-by-breath responses should be recorded and presented in both numerical (tabular report) and graphical formats at average time intervals of 10-20 s.[22] Modern equipment allows routine serial inspiratory capacity (IC) measurements during exercise to track operating lung volumes.[23]

Due to overlapping responses during exercise across disease states, CPET may provide pathognomonic information in rare circumstances; however, it is more realistic to recognize that CPET shortens the list of differential diagnoses. Based on clustering findings, we can derive a syndromic approach indicative of: a) ("normal") physiological responses; b) oxygen delivery/utilization mismatch; c) mechanical ventilatory impairment; d) impaired pulmonary gas exchange/altered ventilatory control; e) obesity; and f) dysfunctional breathing/hyperventilation disorder (Table 2). These patterns of exercise responses must be integrated with the clinical impression based on medical history taking and previous investigations, allowing a specific diagnosis or guiding the next diagnostic steps.[22] Eventually, "conventional" CPET might indicate exercise-related abnormalities; however, it might still be insufficiently discriminative to point out a specific disorder. If metabolic myopathies, exercise-induced pulmonary hypertension (PH), or heart failure with preserved ejection fraction are suspected, invasive CPET (including central hemodynamic assessment via a pulmonary artery catheter and arterial blood gas

Table 2. Key cardiopulmonary exercise test findings in relation to different patterns of abnormality and potential etiologies.

Pattern	Finding	Differential diagnosis
O_2 delivery/utilization mismatch	⇓ peak $\dot{V}O_2$ ⇓ lactate threshold ⇓ $\Delta\dot{V}O_2/\Delta WR$ ⇑ $\Delta HR/\Delta\dot{V}O_2$ ⇓ $\dot{V}O_2/HR$ Flat or decreasing $\dot{V}O_2/HR$ trajectory	Chronic (systolic or diastolic) heart failure Pulmonary vascular disease Ischemic coronary disease Heart valve disease Severe sedentariness Peripheral muscle dysfunction Endocrine/metabolic disorder Anemia
Mechanical ventilatory impairment	⇓ peak $\dot{V}O_2$ ⇑ peak $\dot{V}_E/MVV$ ⇑ peak V_T/IC ⇑ peak EILV/TLC Constraint to V_T expansion ⇑ peak f and f/V_T Decrement in IC as $\dot{V}_E$ increases ⇑ dyspnea-WR and dyspnea-$\dot{V}_E$ relationships	COPD Interstitial lung disease Other persistent airflow obstructive disorders: asthma with airway remodeling, cystic fibrosis, bronchiectasis Chest wall disease Respiratory muscle dysfunction
Impaired gas exchange/altered ventilatory control	⇓ peak $\dot{V}O_2$ ⇑ $\dot{V}_E/\dot{V}CO_2$ metrics Significant SpO_2 decrement ⇑ dyspnea-WR but unaltered dyspnea-$\dot{V}_E$ relationship	Chronic (systolic or diastolic) heart failure Pulmonary vascular disease Lung V/Q mismatch disorders: COPD, interstitial lung disease
Obesity	Preserved peak $\dot{V}O_2$ (% of predicted) ⇓ peak WR ⇑ $\dot{V}O_2$ and $\dot{V}_E$ for a given WR ⇑ symptoms for a given WR	
Dysfunctional breathing	Erratic breathing pattern: surges of ⇓ and ⇑ V_T in a background of fast f Large fluctuations in $\dot{V}_E/\dot{V}CO_2$ ⇑ $\dot{V}_E/\dot{V}CO_2$ slope ⇑ RER (usually at rest)	

Peak: at peak exercise; $\dot{V}O_2$: oxygen uptake; WR: work rate; $\dot{V}_E$: minute ventilation; MVV: maximum voluntary ventilation; IC: inspiratory capacity; EILV: end-inspiratory lung volume; f: breathing frequency; $\dot{V}CO_2$: carbon dioxide output; V/Q: ventilation/perfusion; and RER: respiratory exchange ratio.

analysis via a radial catheter) might be indicated.[24] Another less common cause of unexplained chronic dyspnea that can be investigated with an "adapted" CPET is exercise-induced laryngeal obstruction.[25] Exercise protocols vary, but what is crucial is the ability to promote sustained high-intensity efforts for as long as necessary to induce the symptoms. Continuous laryngoscopy during exercise uses a flexible laryngoscope fixed to a head apparatus, which allows real-time visualization of the larynx throughout the study.[25]

Physiological responses to exercise

The normal response is characterized by ventilatory, circulatory, and metabolic trajectories throughout and at peak exercise within thresholds derived from sedentary healthy populations adjusted for sex and age (Table 3).[18] Table 3 should also be used in order to check abnormalities regarding each parameter, which will allow the characterization of abnormal exercise response patterns described below.

A submaximal test is suspected when no main physiological domain reaches critical values at the end of exercise to constrain exercise continuity[26]:

a) metabolic domain: carbon dioxide output ($\dot{V}CO_2$)/oxygen uptake ($\dot{V}O_2$), i.e. respiratory exchange ratio > 1.05; and/or b) cardiovascular domain: HR > 85% of the predicted value; and/or c) ventilatory domain: minute ventilation ($\dot{V}_E$)/maximum voluntary ventilation (MVV) > 0.80—MVV usually being estimated as FEV_1 × 35-40—; V_T/IC > 0.70[27]; and/or end-inspiratory lung volume (EILV)/TLC > 0.9.[28]

CPET is considered "nonphysiologically" limited when none of the above thresholds are reached. In that case, reasons for exercise interruption should be pursued, and CPET should be repeated if the limitation can be relieved: e.g., better hydration for dry throat, analgesics for orthopedic pain, improvement of the seat comfort, familiarization with the cycling equipment, etc.

Oxygen delivery/utilization mismatch

This pattern involves an imbalance between O_2 delivery and the energetic needs of the working muscles. Although this pattern implies compromised vascular transport of O_2 (reduced cardiac output or convective peripheral O_2 delivery in the arterial system) in the majority of the clinical situations, low arterial O_2 content and metabolic dysfunction of skeletal muscles (severe sedentariness or myopathies) might produce a similar pattern of responses making it impractical to differentiate between such conditions based on CPET alone. The cluster of findings indicative of this pattern includes:

a) low $\dot{V}O_2$ at peak exercise (Figure 2A) and at lactate threshold (Figure 2B)—the latter figure demonstrates the noninvasive estimation of the lactate threshold by the V-slope method[29]:

Table 3. Reference parameters for clinical interpretation of cardiopulmonary exercise testing derived from healthy sedentary subjects.

Parameter	Age, years							
	20		40		60		80	
	Male	Female	Male	Female	Male	Female	Male	Female
Metabolic								
Peak $\dot{V}O_2$ (% predicted)	> 83	> 83	> 83	> 83	> 83	> 83	> 83	> 83
$\Delta\dot{V}O_2/\Delta WR$ (mL/min/W)	> 9.0	> 8.5	> 9.0	> 8.5	> 9.0	> 8.5	> 9.0	> 8.5
$\dot{V}O_2$ at LT (peak $\dot{V}O_2$ % predicted)	> 35	> 40	> 40	> 40	> 45	> 50	> 55	> 60
Cardiovascular								
Peak HR (bpm)	>175	> 170	> 160	> 155	> 150	> 145	> 130	> 125
O_2 pulse (mL/min/beat)	> 12	> 10	> 10	> 8	> 9	> 7	> 7	> 6
$\Delta HR/\Delta\dot{V}O_2$ (beat/L/min)	< 60	< 85	< 70	< 90	< 80	< 100	< 90	< 105
Ventilatory/gas exchange								
Peak $\dot{V}_E$ /MVV	< 0.80	< 0.75	< 0.80	< 0.75	< 0.80	< 0.75	< 0.80	< 0.75
Peak $\dot{V}_E$ /MVV at LT	< 0.35	< 0.40	< 0.40	< 0.40	< 0.45	< 0.45	< 0.50	< 0.50
$\Delta\dot{V}_E/\Delta\dot{V}CO_2$	< 26	< 28	< 28	< 30	< 30	< 32	< 32	< 32
$\dot{V}_E/\dot{V}CO_2$ nadir	< 30	< 32	< 32	< 34	< 32	< 34	< 34	< 34
Peak *f* (breaths/min)	< 50	< 50	< 50	< 50	< 45	< 50	< 45	< 45
Peak f/V_T	< 28	< 30	< 28	< 30	< 28	< 35	< 30	< 40
Peak V_T/IC	< 0.70	< 0.75	< 0.70	< 0.75	< 0.70	< 0.75	< 0.70	< 0.75
$P_{ET}CO_2$ at LT (mmHg)	> 43	> 41	> 41	> 40	> 39	> 39	> 37	> 37
Peak SpO_2 (%)	> 93	> 93	> 93	> 93	> 93	> 93	> 93	> 93
SpO_2 rest-peak (%)	< 5	< 5	< 5	< 5	< 5	< 5	< 5	< 5

Reproduced with permission of the European Respiratory Society.[22] Peak: at peak exercise; $\dot{V}O_2$: oxygen uptake; WR: work rate; LT: lactate threshold; $\dot{V}_E$: minute ventilation; MVV: maximum voluntary ventilation; $\dot{V}CO_2$: carbon dioxide output; *f*: breathing frequency; IC: inspiratory capacity; and $P_{ET}CO_2$: end-tidal carbon dioxide pressur.

the inflection in the $\dot{V}CO_2$ rate of increment as a function of $\dot{V}O_2$ corresponds to the point where there is a progressive accumulation of lactate as the workload intensifies;

b) a slower increment of $\dot{V}O_2$ by incremental WR ($\downarrow\Delta\dot{V}O_2/\Delta WR$; Figure 2A);

c) low reserve to increase cardiac output at the expense of stroke volume, resulting in an exaggerated increase in HR to increments in $\dot{V}O_2$ ($\uparrow\Delta HR/\Delta\dot{V}O_2$) and, consequently, low $\dot{V}O_2$ for a given HR during submaximal and peak exercise ($\downarrow\dot{V}O_2/HR = O_2$ pulse; Figure 2C)—a flattened or decreasing O_2 pulse trajectory during incremental CPET was more commonly found in conditions associated with impaired stroke volume, that is, cardiocirculatory dysfunction.[30,31]

Mechanical ventilatory impairment

Conceptually, this pattern occurs when mechanical abnormalities of the interface between the lung and the thorax compromise the adequate ventilation required to a given metabolic demand. The classical approach is to assess how close ventilation is to its ceiling, i.e., measured peak $\dot{V}_E$ in relation to the estimated maximum ventilatory capacity. A rough guide to this maximum is provided by MVV: peak $\dot{V}_E$/MVV above a certain threshold (Table 2) has been used to indicate "ventilatory limitation" (Figure 3A).[32] However, this ratio correlates poorly with exertional dyspnea in individual subjects with both obstructive and restrictive ventilatory defects.[33] Several dyspneic patients with COPD, mainly those with mild-to-moderate FEV_1 reduction,[34] stop exercising and show a preserved $\dot{V}_E$/MVV ratio, but there is unequivocal evidence of constrained ventilatory mechanics according to parameters of operating lung volumes during exercise.[35] Conversely, a peak $\dot{V}_E$ close to MVV may occur in an otherwise fit subject who can exercise up to high workloads.[36] Therefore, a $\dot{V}_E$/MVV ratio above the upper limit of normal should be valued to indicate low ventilatory reserve in the context of reduced exercise capacity; however, a high ratio in fit subjects or a low value in subjects with impaired peak $\dot{V}O_2$ should not be considered as proof of the presence or absence of mechanical ventilatory abnormalities, respectively. There is convincing evidence that dyspnea increases when the mechanical output of respiratory muscles becomes uncoupled from increases in neural respiratory drive.[33,37] Accordingly, indexes of neuromuscular uncoupling have revealed the contribution of impaired ventilation to exertional dyspnea and exercise tolerance better than has peak $\dot{V}_E$/MVV.[27,28] In practice, neuromechanical coupling is searched by means of serial measurements of V_T and IC across the CPET. The difference between EILV and

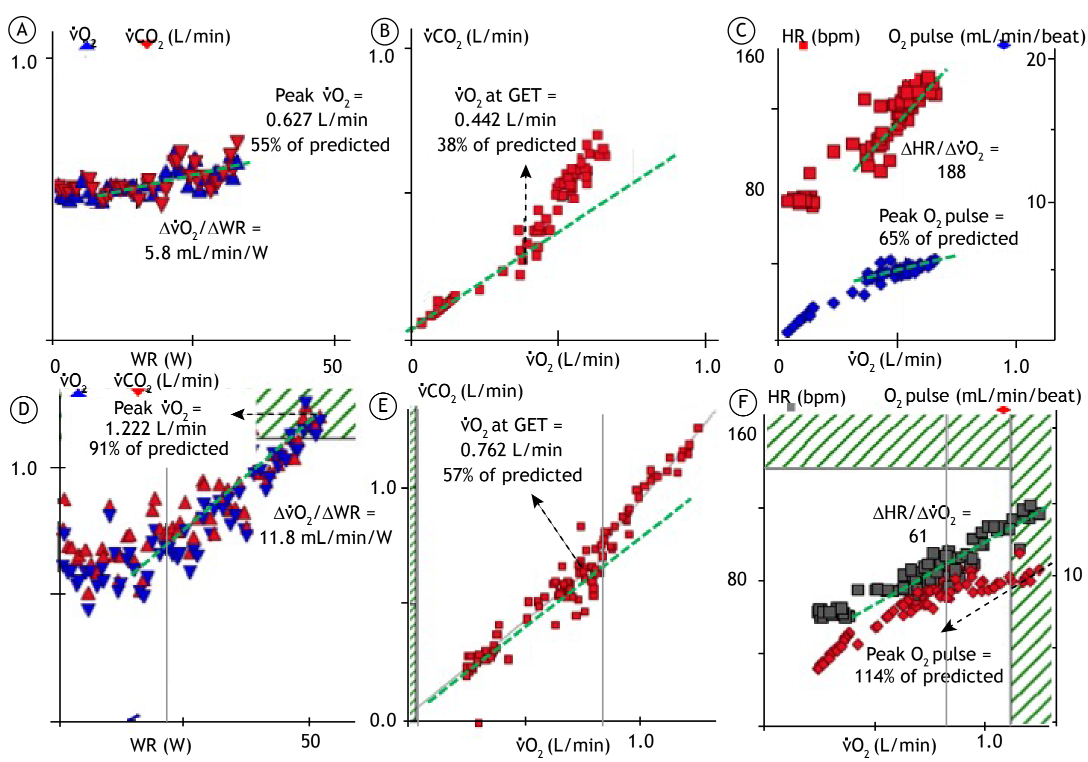

Figure 2. Selected panels from incremental cardiopulmonary exercise test to evaluate metabolic and cardiocirculatory responses. In A-C, a 52-year-old woman with a normal BMI and chronic heart failure due to reduced ejection fraction shows a typical pattern of O_2 delivery/utilization mismatch. See text for further details. In D-F, sex- and age-matched physiological responses in a healthy subject. $\dot{V}O_2$: oxygen uptake; $\dot{V}CO_2$: carbon dioxide output; peak: at peak exercise; WR: work rate; and GET: gas exchange threshold.

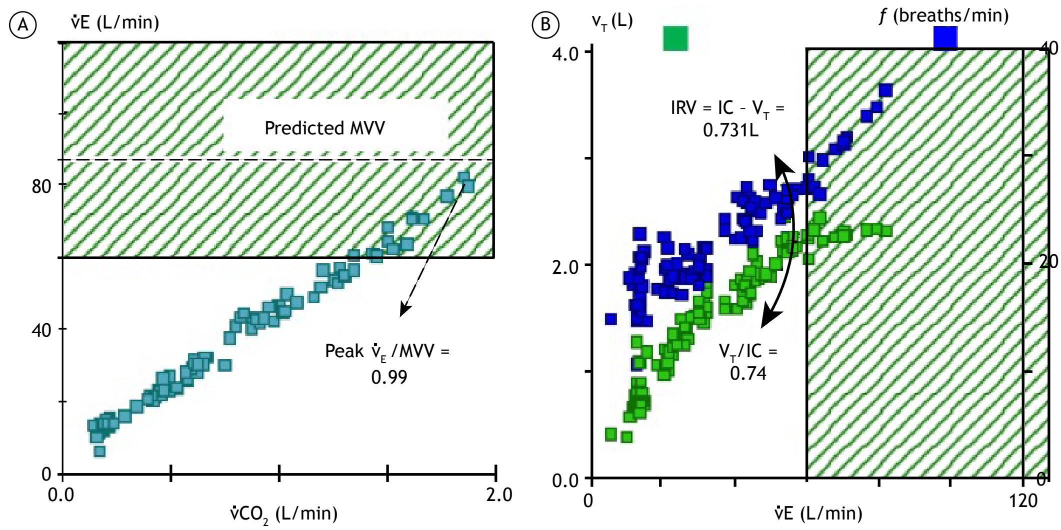

Figure 3. Selected panels to assess ventilatory responses to incremental exercise. In A, the traditional approach to assess ventilatory limitation in which peak minute ventilation ($\dot{V}_E$) almost "touches" the theoretical roof to ventilate—maximum voluntary ventilation (MVV) being calculated as $FEV_1 \times 37.5$—in a middle-aged man with COPD (53 years old; FEV_1 = 56% of the predicted value; FEV_1/FVC ratio = 0.5). In B, when the tidal volume (V_T) reaches a critical proportion (≈70%) of the inspiratory capacity (IC) during cycling exercise close to TLC—inspiratory reserve volume (IRV) < 0.5-1.0 L—V_T expansion is constrained, and any increment in $\dot{V}_E$ mainly occurs at the expense of a faster breathing frequency (*f*). $\dot{V}CO_2$: carbon dioxide output.

TLC dictates the position of V_T on the sigmoid-shaped pressure-volume relationship of the respiratory system. Independently of exercise-induced reduction in IC,[33,38] when the V_T/IC ratio reaches approximately 0.7, the EILV/TLC ratio is > 0.9, or the inspiratory reserve volume (IRV), calculated as IRV = IC − V_T, is < 0.5-1.0 L below TLC during exercise at relatively low workloads, critical mechanical constraints are present and usually mark the point at which dyspnea abruptly rises toward intolerable levels in subjects with different respiratory diseases.[33,38-41] At this point, there is usually a constraint to V_T expansion and, as the exercise continues, any increment in $\dot{V}_E$ happens at the expense of an exaggerated increase in the breathing frequency (*f*; Figure 3B).

Impaired gas exchange/altered ventilatory control

From a practical perspective, these two pathophysiological mechanisms are intrinsically connected, resulting in characteristic responses to exercise. An insufficient decrease in the fraction of breath that is wasted—dead space (V_D)—calculated as V_D/V_T > 0.15-0.20—due to reduced perfusion in relation to alveolar ventilation—ventilation/perfusion (V/Q) mismatch—and/or a low $PaCO_2$ set point at the central control of ventilation results in an increased $\dot{V}_E/\dot{V}CO_2$ ratio, which can be assessed by different metrics (Figure 4).[42] Therefore, the so-called "ventilatory inefficiency" (↑$\dot{V}_E/\dot{V}CO_2$) more commonly reflects poor intrapulmonary gas-exchange efficiency.[43] Examples of high $\dot{V}_E/\dot{V}CO_2$ include aging, increased pulmonary artery resistance, pulmonary vascular disorders, congestive heart failure, wasted ventilation in lung diseases—COPD or interstitial lung disease (ILD)—and extraneous sources that activate ventilation (muscle ergoreceptor overactivity, pulmonary C-fiber receptors, or mechanoreceptors), which can exist in the context of all of the abovementioned conditions.[13] Of note, the $\dot{V}_E/\dot{V}CO_2$ slope (i.e., $\dot{V}_E$ plotted as a function of $\dot{V}CO_2$) increases only if the ventilatory pump is free from mechanical constraints and may even decrease if an obstructive airway disease worsens.[44] Accordingly, caution should be taken not to discard impaired gas exchange in patients with advanced obstructive lung disease and a preserved $\dot{V}_E/\dot{V}CO_2$ slope. In this context, evaluating the intercept of the $\dot{V}_E/\dot{V}CO_2$ slope might represent an alternative for estimating the presence of ventilatory inefficiency.[45]

Other findings in patients with significantly impaired gas exchange include exercise-induced hypoxemia (altered $PaCO_2$ in some circumstances) and an enlarged alveolar-arterial O_2 tension gradient (> 20 mmHg). Although mild-to-moderate decrements in PaO_2 might be missed when oxyhemoglobin saturation is measured by pulse oximetry (SpO_2), this is the parameter usually available in practice (Figure 4A). Exertional oxygen desaturation is not a formal feature in healthy subjects unless they are extremely well trained or are exercising at low inspired O_2 tension (high altitude). Therefore, SpO_2 remains greater than 93% and does not decrease during exercise by more than 4% (Table 3). Low SpO_2 (< 88%) stimulates peripheral chemoreceptors and increases inspiratory neural drive and dyspnea. Exercise-related O_2 desaturation usually implies disorders with a preponderance of alveoli

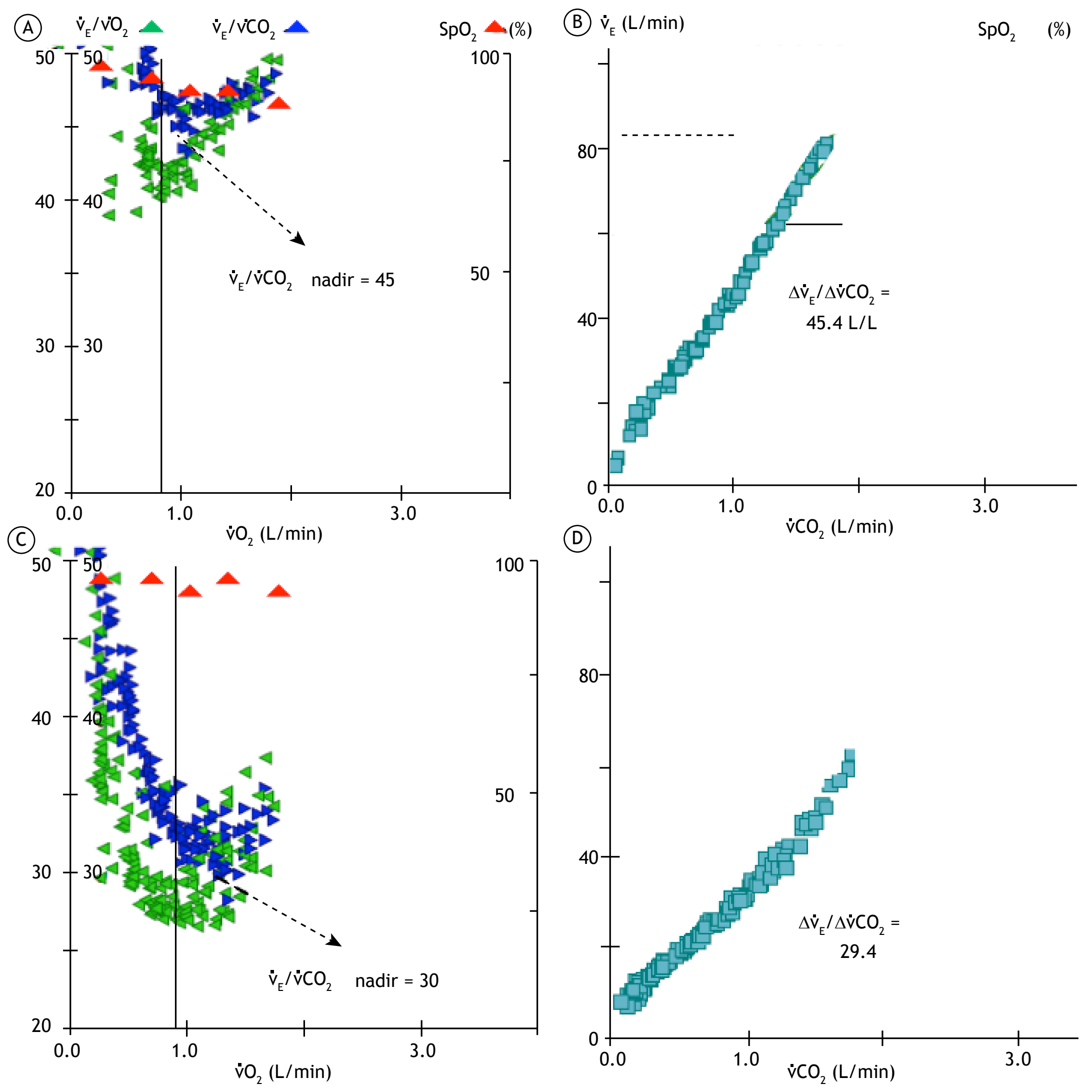

Figure 4. In A, a 50-year-old male with pulmonary arterial hypertension demonstrates gas exchange impairment (significant O_2 desaturation) and altered ventilatory control (excessive exercise ventilation). Ventilatory equivalents for O_2 uptake ($\dot{V}_E/\dot{V}O_2$) and carbon dioxide output ($\dot{V}_E/\dot{V}CO_2$), and arterial oxygen saturation by pulse oximetry (SpO_2) plotted against O_2 uptake during incremental cycle exercise are used to assess gas exchange and ventilatory control. In B, higher ventilation for the metabolic demand can also be observed as steep ventilation ($\dot{V}_E$) versus $\dot{V}CO_2$ increment. In C and D, physiological responses in a sex- and age-matched healthy subject.

presenting with low V/Q ratios, which are commonly associated with low mixed venous O_2 saturation. Other less common causes are right-to-left shunt and alveolar hypoventilation.[13]

Surprisingly, the major complaint that brings such unexplained cases to medical attention (i.e., dyspnea) is virtually neglected in most international guidelines and clinical laboratories nowadays. Given that CPET measures a multitude of physiological responses that are important for the genesis of dyspnea, it seems natural that special attention should be given to the measurement and interpretation of this symptom. In the absence of mechanical ventilatory constraints, an increased reflex chemostimulation[42] translates into excessive ventilatory response that is proportional to the metabolic demand.[35] Therefore, when an increased drive to breathe can be coupled with the act of ventilating, patients tend to report higher dyspnea for a given workload due to a higher need to ventilate but similar (or slightly increased) dyspnea for the level of ventilation when compared with normal subjects.[46] Conversely, dynamic mechanical ventilatory constraints lead to higher perception of dyspnea as a function of both WR and ventilation (Figure 5).[13,41] Thus, evaluating the intensity of dyspnea as a function of WR and ventilatory demand and compare it with a reference frame obtained from healthy subjects[47] might be useful to discriminate between an increased drive to breathe and mechanical ventilatory impairment as the main pathogenesis of dyspnea.

In summary, the presence of impaired gas exchange and altered ventilatory control will infrequently occur in isolation (except during an incipient disorder) from at least one of the other two abnormal patterns—O_2 delivery/utilization mismatch and/or mechanical ventilatory impairment. The clinician receiving the CPET results can restrict the list of possible diseases according to the presence of one or more abnormal patterns in conjunction with the whole medical history of the patient available up to that point[13,22]:

a) Isolated O_2 delivery/utilization mismatch: chronic (systolic or diastolic) heart failure; other cardiocirculatory abnormalities (ischemic coronary or valve disease); extreme sedentariness; skeletal myopathy; endocrine/metabolic disorders, and anemia
b) O_2 delivery/utilization mismatch plus impaired gas exchange/altered ventilatory control: chronic (systolic or diastolic) heart failure; other cardiocirculatory abnormalities; and pulmonary vascular disease (especially if associated with O_2 desaturation)
c) Mechanical ventilatory impairment with or without impaired gas exchange/altered ventilatory control: COPD; other persistent obstructive airway diseases (remodeled asthma, cystic fibrosis, bronchiectasis, or bronchiolitis); exercise-induced obstructive airway disease (asthma), ILD (usually associated with O_2 desaturation); chest wall disease; and isolated respiratory muscle dysfunction

It must be recognized that not all features typical of a given pattern will necessarily be present in every subject and that the final diagnosis of each disease continues being based on defined criteria provided in specific guidelines for each condition.

Obesity

Obesity represents a unique challenge to ventilatory control during exercise due to the increased metabolic demand to displace a large mass against gravity, the increased work of breathing due to thick chest wall, and altered breathing mechanics.[48] Although such a challenge can go unnoticed in several adapted obese subjects, some can report distressing dyspnea. Despite the fact that the diagnosis of obesity is obvious from resting measurements (height and weight), CPET may be useful to measure exercise capacity and symptoms objectively and to demonstrate the typical exercise response of obese subjects: preserved or even increased aerobic capacity (expressed as % of predicted) despite poor exercise tolerance (low peak WR); exaggerated symptoms; and absence of the abovementioned abnormal exercise response patterns.

The increased metabolic demand ($\dot{V}O_2$ and $\dot{V}CO_2$) to a given WR is accompanied by proportionally higher cardiovascular and ventilatory responses. The rate of increase in $\dot{V}O_2$ as a function of WR ($\Delta\dot{V}O_2/\Delta WR$), however, remains normal, indicating preserved aerobic efficiency. Starting from a high resting $\dot{V}O_2$, there is an upward and parallel shift of $\dot{V}O_2$ as work increases, with peak $\dot{V}O_2$ reaching normal or near-normal values despite a low peak WR. Due to the increased metabolic demand, obese subjects also tend to report higher leg discomfort and dyspnea for the level of external WR than do nonobese subjects.[22] Finally, the negative effect of reduced chest compliance seems to be counterbalanced by a lower end-expiratory lung volume due to increased intra-abdominal pressure, resulting in a greater volume available for tidal expansion (i.e., IC). Consequently, there is a downward shift in the operating lung volumes and relatively large inspiratory reserve volumes at exercise cessation, which is in contrast to what is observed in the mechanical-ventilatory impairment pattern.[49]

Caution should be taken regarding the obesity hypoventilation syndrome[50] in morbidly obese (BMI > 40 kg/m²)[51] subjects, who may present with exaggerated abnormalities in ventilatory control and mechanical ventilatory response, respectivelyy.

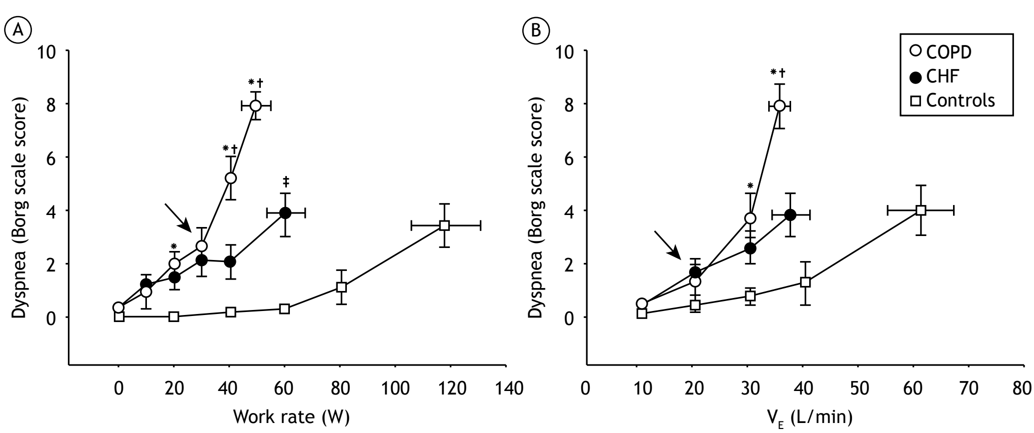

Figure 5. Perception of dyspnea (Borg scale score) as a function of work rate (in A) and minute ventilation ($\dot{V}_E$; in B) during incremental cardiopulmonary exercise test in subjects with COPD, subjects with chronic heart failure (CHF), and sex- and age-matched controls. The arrows indicate the upward inflections in the dyspnea score found in the COPD group that can be characteristically observed both against work rate and ventilation increment. Reproduced with permission of the European Respiratory Society.[41] *COPD vs. controls ($p < 0.05$). †COPD vs. CHF ($p < 0.05$). ‡CHF vs. controls at standardized submaximal or at peak exercise ($p < 0.05$).

Dysfunctional breathing/hyperventilation disorder

Last, but not least, up to one third of the subjects referred for CPET for the investigation of unexplained dyspnea may present with a dysfunctional breathing pattern and/or signals of hyperventilation.[8,10] Albeit not new,[52] given the lack of a formal definition and a gold standard diagnostic method,[53] this condition remains poorly understood and is usually underdiagnosed.[54] Dysfunctional breathing is a wide term describing a group of breathing disorders in subjects with chronic changes in their breathing pattern, resulting in dyspnea and other nonrespiratory symptoms in the absence of, or in excess of, a respiratory disease. Various other terms have been used interchangeably in the literature, including functional breathing disorder, breathing pattern disorder, and behavioral or psychogenic breathlessness. Even though hyperventilation syndrome is often used synonymously with dysfunctional breathing, the former is just one type of the latter, and hyperventilation (i.e., reduced $PaCO_2$) is not necessarily seen in dysfunctional breathing.[53] Before establishing a diagnosis of dysfunctional breathing, organic diseases must be excluded. When common investigations for chronic dyspnea have normal or inconclusive results, CPET seems to be uniquely poised to determine whether breathlessness can be explained (or not) by the presence of any of the aforementioned abnormal exercise response patterns that are indicative of an organic disease. If not, further investigations are required to confirm the presence of dysfunctional breathing (see a detailed description of those methods in this reference).[53] Nevertheless, the exercise responses during CPET can indicate the presence of dysfunctional breathing[22]:

a) chaotic breathing, consisting in surges of low and high V_T in a background of fast *f*
b) clear dissociation between ventilation and metabolic demand represented by large variations in $\dot{V}_E/\dot{V}CO_2$ associated with noncyclic fluctuations of end-tidal O_2 and CO_2 pressures
c) high respiratory exchange ratio at rest (frequently but not always) and a steep $\dot{V}_E/\dot{V}CO_2$ slope
d) high perception of dyspnea for a given WR (a frame of reference for assessing the magnitude of exertional dyspnea during incremental cycle ergometry has been recently published),[47] possibly associated with classical symptoms of hyperventilation (tingling, perioral numbness, and dizziness)

Dysfunctional breathing may occur in the context of a coexistent respiratory disease. There is a close link with asthma, but this is less evident regarding COPD and ILD. Therefore, it is important to identify objective evidence of these conditions and optimize treatment as soon as possible before attributing symptoms mainly (or uniquely) to dysfunctional breathing.[53] In addition, close follow-up is recommended in order to investigate the development of commonly associated conditions (especially asthma[55] or other causes of AHR) or some infrequent and difficult-to-diagnose alternative abnormalities (e.g., neuromuscular disease, respiratory muscle weakness,[56,57] and inducible laryngeal obstruction).[25]

BCTs or bronchial provocation tests

AHR is a common diagnosis in the context of unexplained dyspnea[9,10,14] and is defined as an increased sensitivity and exaggerated response to non-allergenic stimuli that cause airway narrowing. Although most commonly associated with asthma, AHR is also seen in other obstructive or inflammatory airway diseases, it is common in athletes, and it sometimes occurs in patients with heart failure.[17,58] The magnitude of AHR might increase during exacerbations of underlying diseases, decrease with the use of anti-inflammatory medication, or be absent during asymptomatic periods.[17] BCTs are most often indicated to exclude or confirm the diagnosis of asthma, which can be easily achieved by the clinical history taking, presence of wheezing, and appropriate response to therapy. In this context, reversible airflow obstruction on spirometry is confirmatory. However, spirometry is not always performed when the symptoms are present and may be inconclusive, especially in patients with normal or near-normal lung function. Therefore, BCTs emerge as important tools to unveil AHR as a potential cause of chronic unexplained dyspnea.

In clinical practice, the most common BCTs involve the direct stimulus of the muscarinic receptors on airway smooth muscle using methacholine or the indirect hyperosmolar stimulus due to water loss caused by airway drying and cooling through exercise.[17] In the setting of ongoing clinical symptoms, a negative result of a methacholine BCT, which has higher sensitivity than the indirect method, can be most helpful in making AHR improbable. Exercise BCTs are best indicated when the history of the patient suggests that this type of stimulus triggers clinical complaints. In contrast to the methacholine BCT, exercise BCTs stimulate inflammatory mediators and mechanisms involved in clinical asthma. Therefore, exercise BCTs have higher specificity, but they are less sensitive for the diagnosis of asthma and are preferable when the intention is to confirm asthma, rather than exclude it. Although the recommended exercise protocol to detect AHR is a high-intensity, constant-load test (90% of predicted maximum HR or 60% of MVV for the last 4 min of an overall 6-8 min exercise test),[59] spirometric measurements obtained at 5, 10, 15, and 20 min after a rapid incremental WR protocol (duration: 8-12 min) showed to be as useful in diagnosing AHR in susceptible subjects (≈90% of positive and negative predictive values).[60]

Pulmonary circulation assessment

In previous studies, pulmonary vascular diseases are causes of unexplained dyspnea in 5-17% of the patients, mostly being secondary to PH or thromboembolic disease (Table 1).[14,61] Those patients often have an unremarkable physical examination. Abnormalities on chest X-rays and on electrocardiograms generally occur only in advanced disease. It is important to highlight that an isolated reduction in DLCO (and normal spirometry) can be a clue for early pulmonary vascular disease when other signs are missing.[62]

The symptoms of PH are nonspecific and mainly related to progressive right ventricular dysfunction. Initial symptoms are typically induced by exercise and include shortness of breath, fatigue, weakness, angina, and syncope, which might be modified by other diseases that cause or are associated with PH as well as by other concurrent diseases.[63] At presentation, almost all patients with PH report dyspnea, which is most often severe and long lasting. In the French National Registry, the majority of the patients with PH had severe symptoms in the initial assessment, 75% of whom presenting with New York Heart Association functional class III or IV, and the delay between the onset of symptoms and the diagnosis was 27 months.[64] Echocardiography, which allows the determination of tricuspid regurgitation velocity and the assessment of other signs of right ventricular dysfunction, is the first test in the diagnostic workup of PH.[65] If the echocardiographic probability of PH is low but clinical suspicion is high, CPET is indicated. In the context of high pre-test probability, O_2 delivery/utilization mismatch plus impaired gas exchange is highly suggestive of PH. In the appropriate clinical context, if the echocardiographic probability of PH is intermediate or high, patients should undergo right heart catheterization. Occasionally, some patients may have normal right heart catheterization results at rest, and PH is detected only during invasive CPET, being defined as mean pulmonary arterial pressure ≥ 30 mmHg, cardiac output < 10 L/min, and total pulmonary resistance ≥ 3 Wood units at peak exercise.[66]

In prospective studies, the incidence of chronic thromboembolic pulmonary hypertension (CTEPH) after symptomatic acute pulmonary embolism is reported to range from 0.4% to 6.2%.[67] An important prerequisite to confirm this diagnosis is adequate anticoagulation for at least 3 months. About 75% of the patients with CTEPH have previously confirmed venous thromboembolic event(s). V/Q lung scintigraphy remains the screening test for CTEPH because its accuracy is higher than that of CT angiography. In the future, modern dual-energy CT angiography can become the major test, because it allows the evaluation of anatomical and functional perfusion aspects simultaneously. Different from acute pulmonary embolism with low clinical suspicion when a low D-dimer level has a high negative predictive value, D-dimer alone cannot be used to rule out CTEPH in patients with PH.[68]

Chronic thromboembolic disease (CTED) is characterized by presenting with similar symptoms and perfusion defects similar as to those of CTEPH, but no PH at rest. Exercise intolerance in patients with CTED has been attributed either to exercise-induced PH, showing an increased slope of the pulmonary arterial pressure-flow relationship, or to high dead space ventilation (increased $\dot{V}_E/\dot{V}CO_2$).[69] New/worsened dyspnea and persistent perfusion defects are often encountered after acute pulmonary embolism in 30% and 30-50% of the patients, respectively, hindering the diagnosis of CTED.[70] CPET and echocardiography are recommended to recognize patients in whom symptoms are secondary to (nonvascular) lung disease, left heart disease, obesity, or physical deconditioning. Selected symptomatic patients with CTED may benefit from pulmonary endarterectomy.[71]

Pulmonary arteriovenous malformations are structurally abnormal vessels that provide direct capillary-free communication between pulmonary and systemic circulations (hence, an anatomic right-to-left shunt). Those malformations may be related to hereditary hemorrhagic telangiectasia. Patients complain of dyspnea in 14-51% of the cases.[72] Saline contrast echocardiography is the recommended initial screening test when pulmonary arteriovenous malformations are suspected. The circulatory transit of microbubbles generated by intravenously injected agitated saline contrast is detected by the image of bubbles arriving in the left heart or in the systemic circulation. Positive screening can be confirmed with unenhanced thin-slice (1-2 mm) multidetector CT of the chest and CT pulmonary angiography, being considered the gold standard to confirm the diagnosis. Hepatopulmonary syndrome is another type of intrapulmonary shunt that causes dyspnea, as well as occasional findings of platypnea-orthodeoxia.

Chronic dyspnea is an unusual presentation of pulmonary vasculitis. The clinical picture is more acute and has other clinical and laboratory signs of extrapulmonary manifestations. The diagnosis is made by autoantibody findings and histopathological analysis.[73] Neoplasms of pulmonary vasculature are extremely rare, and the diagnosis can be suspected during the investigation of CTEPH or lung masses.[74]

FINAL CONSIDERATIONS

We showed that CPET can identify physiological abnormalities involving cardiopulmonary, neuromuscular, and sensory systems that can be clustered into patterns of exercise response that are useful for a pragmatic interpretation during the investigation of chronic unexplained or out-of-proportion dyspnea. These clusters of findings should be analyzed in conjunction with the patient's medical history and the results of other complementary tests (i.e., pre-test likelihood of a disease) in order to restrict the list of possible diagnoses, indicate the next step(s), or, hopefully, reach a final diagnosis. In addition, practical issues of BCTs and pulmonary circulation assessment, as well as the spectrum of suspected lung vascular diseases, should be closely acknowledged by pulmonologists dealing with unresolved cases of chronic dyspnea. In selected cases, patients should be evaluated in specialized centers that use advanced/specific methods of investigation.

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LETTER TO THE EDITOR

Agreement among four portable wireless pulse oximeters and in-office evaluation of peripheral oxygen saturation

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TO THE EDITOR:

Early diagnosis is essential in the medical practice. Measured via pulse oximetry, SpO_2 is currently considered as the "fifth vital sign" because it shows not only the values of respiratory function but also the presence, amplitude, and frequency of the pulse.(1,2)

During the coronavirus pandemic, the measurement of SpO_2 with portable wireless pulse oximeters has garnered considerable attention as an important vital sign in the early detection of hypoxemia, thereby facilitating the clinical decision-making process.(3,4)

The use of portable pulse oximetry is well-established in the hospital environment. The use of portable wireless pulse oximeters in office visits is growing rapidly, and some patients present oxygen desaturation even when they feel relatively well.(1,2,5,6) Many models of portable wireless pulse oximeters, from different manufacturers and at various prices, are sold in Brazil.

Questions have arisen regarding the use of SpO_2 measurement in outpatient settings: What is the minimum time required to obtain a proper SpO_2 reading?; How long before the SpO_2 stabilizes?; and Is there agreement among the readings of the various oximeters used in Brazil? The objective answers to these questions have not been clearly established. Therefore, the objective of the present study was to evaluate the minimum time necessary for the appropriate measurement of SpO_2, to determine the time necessary for the SpO_2 reading to stabilize, and to evaluate the agreement among the results of four different portable wireless pulse oximeters used in Brazil.

This was a cross-sectional study, performed in a physician office and approved by the research ethics committee of the institution (CAAE No. 52677816.3.0000.5371). All the participants signed a free and informed consent form and there were no conflicts of interest.

The sample size required in order to identify good agreement (above 0.81) among the four oximeters and to measure SpO_2 was estimated with an error below 0.20, a level of significance of 5%, a confidence interval amplitude of 0.1, and the addition of 10% to compensate for losses and refusals.(7,8) Thus, we found that a minimum sample of 45 patients would be required in order to evaluate the agreement among the oximeters.

We evaluated a convenience sample comprising all volunteers ≥ 18 years of age. Patients with hypotension, hypothermia, digital clubbing, Raynaud's phenomenon, significant anemia, or fever were excluded, as were those with fake or painted nails, those in whom there were hand movement artifacts, and those who had any cognitive deficit that would prevent them from filling out the questionnaire (in the absence of information provided by family members).

The SpO_2 data were collected after the volunteers had rested for at least 5 min, during which time they were comfortably seated in a chair, with one hand resting on a table. The four portable wireless pulse oximeters used were as follows: GO_2 Achieve (Nonin Medical, Inc., Plymouth, MN, USA); ChoiceMMed (ChoiceMMed America Corp., Bristol, PA, USA); Rossmax SB100 (Rossmax, Taipei, Taiwan); and Finger Type & Oximeter (Beijing Choice Electronic Technology Co., Beijing, China). The oximeters were placed simultaneously and distributed randomly on the fingertips of the same hand. The SpO_2 was measured at three different time points (30 s, 60 s, and 120 s), determined with a stopwatch and verified photographically.

To evaluate the agreement among the oximeters, we chose the highest SpO_2 reading obtained from each device at each of the three time points and calculated the intraclass correlation coefficients (ICCs).(7,8) The results were interpreted using the criteria established by Landis and Koch,(9) in which the ICC is categorized as excellent if > 0.91, good if 0.71-0.90, moderate if 0.51-0.70, fair if 0.31-0.50, and poor if < 0.31. The level of statistical significance was set at $p \leq 0.05$. The data collected were processed with the IBM SPSS Statistics software package, version 22.0 (IBM Corporation, Armonk, NY, USA).

We evaluated 133 patients, of whom 60 (45.1%) were male and 73 (54.9%) were female. The mean age in the sample as a whole was 55.34 ± 18.90 years (95% CI: 52.09-58.88; range, 18-95 years).

The SpO_2 measurements did not differ significantly among the time points evaluated (30 s, 60 s, and 120 s), for any one device or among the four oximeters evaluated, and the SpO_2 remained stable for 120 s (Table 1). For each oximeter, the highest reading was found at the 120-s time point, and that value was used to evaluate the agreement among the devices.(9) The agreement among the four oximeters was considered excellent (ICC = 0.902; 95% CI: 0.857-0.933).

Previous studies have not clearly defined the ideal time to begin reading a portable wireless pulse oximeter or the window of time necessary for the oximeter reading to stabilize.(5,6,10) To our knowledge, there have been

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Table 1. Measurement of SpO_2 at three different time points with four different pulse oximeters.[a]

Oximeter	Time point			p*
	30 s	60 s	120 s	
ChoiceMMed	96.38 ± 1.84 (96.06-96.69)	96.38 ± 1.79 (96.07-96.68)	96.39 ± 1.88 (96.07-96.71)	0.988
GO_2 Achieve	95.75 ± 2.46 (95.33-96.17)	95.78 ± 2.11 (95.42-96.14)	95.89 ± 2.22 (95.50-96.27)	0.455
Rossmax SB100	96.06 ± 2.20 (95.68-96.44)	96.07 ± 2.32 (95.67-96.46)	96.29 ± 2.22 (95.91-96.67)	0.063
Finger Type & Oximeter	94.97 ± 2.62 (94.52-95.42)	95.14 ± 2.65 (94.69-95.60)	95.22 ± 2.47 (94.79-95.64)	0.122

[a]Values expressed as mean ± SD (95% CI). *ANOVA and Bonferroni test.

no studies evaluating the agreement among wireless oximeters in physician offices.

In the present study, we have demonstrated that, in hemodynamically stable patients, the SpO_2 can be read at 30 s and remains stable up to 120 s, with no significant differences in readings among the three time points evaluated (Table 1). With the current technical qualification of the new portable pulse oximeters, future studies will be able to evaluate SpO_2 levels with confidence in less than 30 s.

In the absence of previous studies on the objectives under discussion, our results can help health professionals (physicians, nurses, and physiotherapists) evaluate the SpO_2 objectively and safely in as little as 30 s, optimizing their outpatient consultation time and allowing a flexible choice in the acquisition of these different devices to be used in the daily practice, with a good cost-benefit ratio.

Our study has some limitations. Because of the cross-sectional study design, the durability of the wireless pulse oximetry devices was not evaluated. To evaluate the accuracy of the oximeters used, it would be necessary to compare them with the gold-standard system (arterial blood gas analysis with the determination of the SaO_2).

We concluded that, in a physician office, SpO_2 can be measured properly in as little as 30 s with any of the oximeters evaluated here. We also found that the reading remains stable for 120 s and that the agreement among the four oximeters was excellent.

AUTHOR CONTRIBUTIONS

SMDM: idealization, conception, and planning of the study; interpretation of the data; drafting and revision of the manuscript; and approval of the final version. MFOM: conception and planning of the study; interpretation of the data; and drafting and revision of the manuscript. JSSP: interpretation of the data; and revision of the manuscript.

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Impact of extracorporeal membrane oxygenation in lung transplantation

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TO THE EDITOR:

Lung transplantation is a complex procedure that requires extracorporeal mechanical cardiopulmonary support in many situations. Such support can be provided preoperatively, intraoperatively, or postoperatively, depending on the patient's severity of illness and clinical status. This occurs in approximately 30-40% of lung transplants. The situations that most commonly require such support in the intraoperative period include pulmonary arterial hypertension (PAH), right ventricular dysfunction, and intolerance to single-lung ventilation.[(1)] The optimal strategy remains a matter of debate[(2)]; however, the use of extracorporeal membrane oxygenation (ECMO) has been shown to provide numerous benefits over the use of cardiopulmonary bypass. This is because ECMO support resulted in lower rates of primary graft dysfunction (PGD), bleeding, and renal failure requiring dialysis, as well as a lower rate of tracheostomy, less intraoperative blood transfusion, shorter durations of mechanical ventilation, and shorter hospital stays.[(3)]

Between January of 2017 and December of 2018, 24 lung transplants were performed at the Porto Alegre *Hospital de Clínicas*, located in the city of Porto Alegre, Brazil. The clinical and laboratory data from those transplant recipients were statistically analyzed by using the chi-square and Mann-Whitney U tests and are shown in Table 1. Of the 24 patients included in the analysis, 12 received ECMO for cardiopulmonary support, 11 (92%) of whom underwent bilateral lung transplantation, whereas 12 did not require ECMO, 7 (58%) of whom underwent unilateral lung transplantation. Suppurative lung diseases accounted for 50% of the cases of patients transplanted with ECMO support. In patients who did not require ECMO, a diagnosis of COPD was more prevalent. The first use of ECMO at our center was as a bridge to transplantation. Three of the patients in the ECMO group, given the impossibility of establishing single-lung ventilation, received venovenous (VV) ECMO only for ventilatory support. The remaining patients received venoarterial (VA) ECMO for ventilatory and hemodynamic support. Patients with significant PAH underwent peripheral cannulation under local anesthesia and sedation prior to induction of anesthesia. Patients without PAH or with mildly elevated pulmonary pressure underwent central arterial cannulation of the thoracic aorta and peripheral venous cannulation of the right femoral vein. At the end of the procedure, VA ECMO was continued in patients with PAH or was converted to VV ECMO if the patient was hemodynamically stable and did not have PAH. To that end, a single-lumen catheter previously positioned in the right internal jugular vein allowed placement of a guidewire and local cannulation. Thus, the aortic arterial cannula was disconnected and removed after reconnection with the jugular vein cannula. Decannulation from VV ECMO was performed in the ICU after extubation and confirmation of absence of PGD. There was no difference in hospital or ICU lengths of stay between patients who received ECMO and those who did not, although the former were more severely ill, as demonstrated by the need to use a greater volume of crystalloids, the greater need for transfusion, the longer operative times, and the higher percentage of bilateral transplants. The estimated 36-month survival was 66.7% among patients who received ECMO, compared with 91.7% among those who did not. Although mortality was higher in the ECMO group, the difference was not statistically significant ($p = 0.143$).

The first reports of the use of ECMO date back to the 1970s; however, they were limited to experimental strategies with unfavorable outcomes.[(4)] The use of ECMO in the pediatric population and in patients with ARDS[(5)] has resulted in technical progress and increased experience. Although the use of ECMO during lung transplantation was first described in 2001, it has only recently been introduced in Brazil.[(6)] VV ECMO provides ventilatory support by drawing deoxygenated blood from the venous system in order to oxygenate it and return it to the same system. In contrast, VA ECMO enables cardiopulmonary bypass by returning oxygenated blood to the arterial system.[(7)] Intraoperative ECMO, in addition to ensuring greater safety during cardiac manipulation, reduces the chance of reperfusion injury by allowing better control of blood flow after the pulmonary artery clamp is released, thereby preventing the first implanted graft from receiving the entire cardiac output during implantation of the second graft. In addition, intraoperative ECMO precludes the need for aggressive ventilation to maintain gas exchange and allows continued support in the postoperative period.[(2)] In patients with PAH or considerable hemodynamic instability, it is essential to maintain VA support in the postoperative period, since cardiac output has to be reduced to enable remodeling of the right ventricle, which is chronically hypertrophic.[(8)] In other patients, there is no consensus on the type of or need for postoperative support. As for our team, in cases in which it is possible to discontinue VA support at the end of the surgery, we prefer to avoid decannulation and carry out conversion from VA to VV support, which is continued in the postoperative period. Thus, mechanical ventilation at protective settings is delivered until early extubation is achieved and spontaneous ventilation begins. The use of VV ECMO for the treatment of severe PGD is well established, increasing survival and minimizing the deleterious effects of mechanical ventilation. There

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Table 1. Data from patients undergoing pulmonary transplantation between January of 2017 and December of 2018. Porto Alegre *Hospital de Clínicas*, Porto Alegre, Brazil.[a]

Data	Groups		p
	ECMO (n = 12)	No ECMO (n = 12)	
Gender (M/F)	7 (58%)/5 (42%)	6 (50%)/6 (50%)	0.68
Age, years	48 (17-60)	55 (22-65)	0.14
Type of transplant			0.027
- Unilateral	1 (8%)	7 (58%)	
- Bilateral	11 (92%)	5 (42%)	
Diagnosis	2 (17%)	2 (17%)	0.12
- Pulmonary fibrosis	3 (25%)	0 (0%)	
- Cystic fibrosis	3 (25%)	7 (58%)	
- COPD/emphysema	3 (25%)	2 (17%)	
- Bronchiectasis	1 (8%)	0 (0%)	
- PAH	0 (0%)	1 (8%)	
- Alpha-1 antitrypsin deficiency			
PASP ≥ 35 mmHg	7 (58%)	2 (17%)	0.09
MPAP, mmHg	28 (17-79)	22 (13-32)	0.16
FEV_1, % predicted	21% (16-70%)	23% (17-42%)	0.63
FVC, % predicted	37% (13-78%)	40% (33-56%)	0.16
Operative time, h	11 (8-17)	6 (3-11)	< 0.001
Cold ischemia time of the first graft, min	432 (270-540)	400 (205-558)	0.45
Cold ischemia time of the second graft, min	632 (520-720)	635 (480-705)	0.82
Crystalloid, mL	6,500 (3,000-32,600)	2,800 (1,400-7,000)	< 0.001
Need for blood transfusion	9 (75%)	1 (8%)	0.001
ICU length of stay, days	12 (5-103)	7 (2-16)	0.17
Hospital length of stay, days	27 (20-117)	29 (17-76)	0.84
90-day mortality	3 (25%)	1 (8%)	0.27
Mean estimated 36-month survival, months	27	35	0.143*

[a]Values expressed as n, n (%), or median (minimum-maximum). ECMO: extracorporeal membrane oxygenation; M/F: male/female; PAH: pulmonary arterial hypertension; PASP: pulmonary artery systolic pressure; and MPAP: mean pulmonary artery pressure. *Log-rank test comparing the Kaplan-Meier curves of the two groups.

is also evidence that the institution of ECMO within 2 hours of the diagnosis of grade 3 PGD results in increased survival, whereas delayed institution of ECMO is associated with very high mortality.[9] Other studies have shown that cases requiring ECMO for the treatment of PGD have a significantly reduced rate of long-term graft survival, as compared with cases not requiring such management.[10] Thus, institution of VA ECMO in the intraoperative period helps hemodynamic stability and provides protection for the graft, whereas continued VV support in the postoperative period reduces the need for mechanical ventilation and provides preemptive treatment of possible reperfusion injury.

In our experience, we found that the use of ECMO to provide cardiopulmonary support in patients with suppurative lung disease with or without concomitant PAH resulted in good survival, although these patients were more severely ill than those who did not receive ECMO; however, hospital and ICU lengths of stay were similar in both groups of patients, making this strategy an important part of the therapeutic arsenal in the setting of lung transplantation.

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Effect of very vigorous physical activity on cardiac autonomic modulation in smokers and nonsmokers: an epidemiological study

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TO THE EDITOR:

Cardiac autonomic modulation (CAM) is an important component of cardiovascular health,(1) and its reduction has been associated with increased risk of death.(2) Smoking has been associated with low CAM, because nicotine has a negative effect on cardiac vagal control and, consequently, on parasympathetic modulation.(3) In contrast, engaging in physical activity (PA) is an important lifestyle habit that has been positively associated with high CAM, because PA improves vagal activity.(4) Nonetheless, it is not clear in the literature whether different intensities of PA could eliminate or at least mitigate the relationship between smoking and reduced CAM. Our hypothesis was that very vigorous PA would mitigate the effects of smoking on CAM.

This was a cross-sectional study, approved by the Research Ethics Committee of the *Universidade Estadual Paulista* (São Paulo State University) School of Science and Technology, located in the city of Presidente Prudente, Brazil (Reference no. 72191717.9.0000.5402). The sample size was calculated with the objective of achieving a correlation value of r = 0.24 between vigorous PA and heart rate variability (HRV) in an adult population,(5) a power of 80%, and an alpha error of 5%. To minimize multiple comparison biases and include adjustment for sex and age in the analysis, an additional 20 participants were included for each covariate, resulting in a minimum sample size of 207 subjects. The sample comprised residents of Santo Anastácio, a town located in the southeastern region of Brazil. Because the random sampling process was based on households and the proportionality of inhabitants in the 23 urban census tracts of Santo Anastácio was considered, all of those who were eligible in each selected household were evaluated. The detailed study protocol is available elsewhere.(6) If more than one person in a randomly selected household was eligible to participate in the study, they were also included in the study; therefore, the final sample comprised 258 adults (≥ 18 years of age), 150 of whom were women. Individuals who were on any medication to control HR or reported any pathophysiological or chronic condition were excluded from the study.

Participants were instructed not to consume stimulants or alcoholic beverages and to avoid physical exercise 12 h prior to HRV assessment.(7) The HRV indices were used in order to evaluate CAM. For this purpose, the beat-to-beat HR at rest was recorded with an HR monitor (Polar V800; Polar Electro OY, Kempele, Finland) for 30 min, with participants resting in the supine position and breathing spontaneously. For the analysis of CAM, 1,000 RR intervals (the time between two R waves) were selected, and HRV indices were obtained from the domains of time—root mean square of successive differences (RMSSD) and standard deviation of all normal-to-normal RR intervals (SDNN)—and frequency—low frequency: −0,04 Hz to 0,15 Hz; and high frequency: −0,15 Hz to 0,4 Hz in normalized units. In addition, we performed a quantitative analysis of the Poincaré plot, calculating the standard deviation perpendicular to the line of identity (SD1) and the standard deviation along the line of identity (SD2). The collection, processing, and analysis of data followed the standards described in the literature,(7) and indices were analyzed with the Kubios HRV Analysis software, version 2.0 (The Biomedical Signal and Medical Imaging Analysis Group, Department of Applied Physics, University of Kuopio, Finland).

Smoking status was assessed by the following questions: "Do you currently smoke?"; "How many days a week?"; and "How many cigarettes a day?." The intensity of PA was measured with a GT3X accelerometer (ActiGraph LLC, Pensacola, FL, USA) positioned on the right side of the participant, at waist level. Participants used the equipment for seven days (minimum of five days for at least 10 h daily in order to be included in the analysis). The cutoff point recommended by Sasaki et al.(8) was used in order to determine the intensity of PA—light intensity: < 2,690 counts/min (metabolic equivalent of task [MET] < 3.00); moderate intensity: 2,690-6,166 counts/min (MET = 3.00-5.99); vigorous intensity: 6,167-9,642 counts/min (MET = 6.00-8.99); and very vigorous intensity: > 9,642 counts/min (MET > 8.99).

The relationship between CAM and smoking was analyzed by multiple linear regression, the different intensities of PA being inserted one by one into the model (Table 1). The level of significance adopted was 5%.

The sample characteristics by smoking status revealed that the mean SDNN was lower in the smokers (n = 23) than in the nonsmokers (40.0 ± 21.6 ms vs. 50.8 ± 23.1 ms; p = 0.014), as was the mean SD1 (17.5 ± 15.9 ms vs. 26.7 ± 22.1 ms; p = 0.041) and the mean SD2 (50.1 ± 28.6 ms vs. 66.5 ± 27.6 ms; p = 0.007), whereas the mean low frequency index was higher among the smokers (68.2 ± 15.4 vs. 61.3 ± 17.6; p = 0.039), as was the mean number of minutes per day engaged in light PA (3,998.7 ± 905.2 vs. 3,645.0 ± 850.1; p = 0.047). No significant differences were found between smokers and nonsmokers regarding the mean age, RMSSD, high frequency index, moderate PA, vigorous PA, and very

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vigorous PA. Smokers reported smoking a mean of 13.4 ± 9.4 cigarettes/day, and the mean number of pack-years was 0.66.

Table 1 shows that the SDNN and SD2 both had an inverse relationship with smoking. However, that relationship was mitigated after the insertion of very

Table 1. Relationship between cardiac autonomic modulation and smoking adjusted for different intensities of physical activity (N = 258).

Variable	Group		p
	Smoker (n = 23) Mean ± SD	Nonsmoker (n = 235) Mean ± SD	
Age, years	46.65 ± 14.99	41.96 ± 17.21	0.183
Weight, kg	76.14 ± 13.69	77.20 ± 16.10	0.747
Height, cm	165.57 ± 8.04	165.59 ± 9.96	0.928
BMI, kg/m^2	27.12 ± 4.11	28.25 ± 5.35	0.348
Total counts per day	34,862.60 ± 13,274.11	41,352.77 ± 3,617.27	0.583
	ß	95% CI	p
RMSSD			
Model 1	−8.83	−20.33; 2.65	0.131
Model 2	−8.12	−19.69; 3.44	0.168
Model 3	−8.22	−19.81; 3.36	0.164
Model 4	−8.26	−19.88; 3.34	0.162
Model 5	−7.33	−18.77; 4.11	0.208
SDNN			
Model 1	−10.19	−18.96; −1.95	0.025
Model 2	−9.91	−18.83; −0.98	0.030
Model 3	−9.94	−18.89; −0.99	0.030
Model 4	−9.93	−18.89; −0.96	0.030
Model 5	−9.18	−18.00; −0.36	0.041
Low frequency			
Model 1	5.59	−1.26; 12.45	0.109
Model 2	4.93	1.95; 11.81	0.149
Model 3	5.04	−1.84; 11.92	0.151
Model 4	5.14	−1.71; 12.00	0.141
Model 5	5.06	−1.81; 11.94	0.149
High frequency			
Model 1	−4.53	−11.50; 2.43	0.201
Model 2	−3.84	−10.84; 3.11	0.280
Model 3	−3.97	−10.97; 3.01	0.264
Model 4	−4.07	−11.04; 2.88	0.250
Model 5	−3.98	−10.97; 3.00	0.263
SD1			
Model 1	−7.46	−16.17; 0.87	0.074
Model 2	−6.90	−15.46; 1.50	0.113
Model 3	−6.95	−15.53; 1.62	0.112
Model 4	−6.97	−15.57; 1.62	0.111
Model 5	−6.30	−14.78; 2.17	0.145
SD2			
Model 1	−13.49	−24.08; −2.90	0.013
Model 2	−13.72	−24.40; −3.05	0.012
Model 3	−13.73	−24.44; −3.02	0.012
Model 4	−13.70	−24.43; −2.97	0.012
Model 5	−12.86	−23.44; −2.27	0.017

RMSSD: root mean square of successive differences; SDNN: standard deviation of normal-to-normal intervals; SD1: Poincaré plot standard deviation perpendicular to the line of identity; and SD2: Poincaré plot standard deviation along the line of identity. Model 1: adjusted for sex and age; Model 2: model 1 + adjustment for light physical activity; Model 3: model 2 + adjustment for moderate physical activity; Model 4: model 3 + adjustment for vigorous physical activity; and Model 5: model 4 + adjustment for very vigorous physical activity.

vigorous PA in the statistical model (confirming our initial hypothesis).

The main finding of the present study was that smoking was inversely correlated with CAM, especially in relation to indices that reflect overall variability (SDNN and SD2). After inserting the different intensities of PA into the model (relationship between smoking and CAM), we found that very vigorous PA mitigated the effect of smoking on CAM.

Different hypotheses can explain the findings of the present study. One of the possible mechanisms is that vigorous and very vigorous PA could contribute to an increase in shear stress, promoting the release of nitric oxide and, consequently, an increase in parasympathetic activity.[9] Given the strong relationship between angiotensin and sympathetic modulation, which can be stimulated by the nicotine contained in cigarettes,[10] vigorous PA could also decrease angiotensin II levels, thus improving CAM.

Our study has some limitations. First, we did not employ other methods of assessing smoking status, such as determining the level of exhaled carbon monoxide. In addition, the cross-sectional design of the study precluded the assessment of causal relationships. However, the study has a number of strengths, including the randomized sampling process and the objective measurement of PA intensity by accelerometer. In terms of practical applications, our findings suggest that smokers who routinely engage in more vigorous PA may show improvement in CAM.

On the basis of our findings, we can conclude that very vigorous PA mitigates but does not eliminate the smoking-induced reduction in CAM in adult smokers. Smokers should be encouraged to perform vigorous PA in order to avoid a reduction in CAM.

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Reference equations for plethysmographic lung volumes in White adults in Brazil as derived by linear regression

Thamine Lessa[1], Carlos Alberto de Castro Pereira[2], Maria Raquel Soares[2]

TO THE EDITOR:

Reference values for lung function vary according to the technique used for testing, as well as according to sample selection, sample size, and the statistical model used. In a multicenter study involving 244 never smokers and published in 2019, we derived reference equations for plethysmographic lung volumes in White adults in Brazil.(1) We used quantile regression to estimate predicted values and limits of normal, as was done in a study conducted in Germany and aimed at establishing reference values for lung volumes and airway resistance.(2) To facilitate the calculation of predicted values and limits of normal, we present here the reference equations derived by linear regression analysis.

The criteria for inclusion in the study were as follows: being over 20 years of age for females and over 25 years for males; having a BMI of 18-30 kg/m^2; having no significant respiratory symptoms; having no current respiratory disease; having no history of respiratory disease; having no heart disease; having never undergone thoracic surgery; having no relevant occupational exposure history; being a never smoker; and being White (as described by the individuals themselves and as observed by the interviewer). All tests were performed by technicians or physicians certified in pulmonary function testing by the Brazilian Thoracic Association and using the same plethysmograph (Vmax Encore 22; SensorMedics, Yorba Linda, CA, USA).

In the original study,(1) quantile regression was used in order to derive reference values, whereas, in the present study, linear regression analysis was used. The same 244 White adults (122 males and 122 females) were evaluated in the two studies.

All statistical analyses were performed with the Stata statistical software package, version 12 (StataCorp LP, College Station, TX, USA) and the IBM SPSS Statistics software package, version 22.0 (IBM Corporation, Armonk, NY, USA). The median values obtained by quantile regression were compared with the mean values obtained by linear regression analysis. The mean values obtained by linear regression analysis in the present study were compared with the mean values obtained by Neder et al.(3) and those obtained by Crapo et al.(4) Paired t-tests were used for comparisons. Values of $p < 0.005$ were considered significant.

The linear equations and limits of normal are shown in Table 1. For males, median TLC as determined by quantile regression was 6.71 L and mean TLC as determined by linear regression analysis was 6.61 L, whereas, for females, they were 4.78 L and 4.88 L, respectively. For males, median RV as determined by quantile regression was 4.78 L and mean RV as determined by linear regression analysis was 4.88 L, whereas, for females, they were both 1.59 L.

The differences observed in the previous study(1) were the same as those observed in the present study. For males, the differences between the mean VC and TLC values obtained by Neder et al.(3) (linear regression analysis) and those obtained by linear regression analysis in the present study were 0.51 L and 0.58 L, respectively ($p < 0.001$ for both). For females, they were 0.35 L and 0.20 L, respectively ($p < 0.001$ for both).

The differences between the predicted values obtained in the present study and those obtained by Crapo et al.(4) were irrelevant. However, the reference ranges for TLC were more sensitive in the present study because the standard error of the estimate (SEE) was smaller. For males, the SEE for TLC was 0.79 L in the study by Crapo et al.(4) and 0.61 L in the present study. Therefore, the equation presented here is more sensitive in detecting increased or decreased TLC. For females, the SEE for TLC was 0.54 L in the study by Crapo et al.(4) and 0.50 L in the present study.

Quantile regression is widely used for data analysis in non-homogeneous populations and has become a useful tool to complement the classical linear regression analysis.(5) The use of the median rather than the mean is much more robust to outliers. Another advantage is that any percentile can be estimated. However, when quantile regression is used for multiple percentiles, the curves can intersect, resulting in invalid distributions, such as the 95th percentile being less than the 90th percentile, which is impossible. Although there are methods for correcting this problem, they are very complex. Therefore, linear regression analysis is preferable when feasible. Such is the case with our sample; linear regression makes it easier to enter the equations into the software used in pulmonary function test equipment, allowing their widespread use. Therefore, the present study shows predicted values and limits of normal as determined by linear regression analysis, including means and the SEE.

We found only small differences between the mean values obtained by quantile regression and those obtained by linear regression analysis. A comparison between the values suggested by Neder et al.(3) and those presented here showed that the latter are significantly lower. They are, however, similar to those obtained by Crapo et al.(4) Nevertheless, Crapo et al.(4) found a greater dispersion of

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Table 1. Reference equations for plethysmographic lung volumes in White adults in Brazil as derived by linear regression. We suggest that the predicted values for RV and functional residual capacity be used without including patient weight. The limits of normal are calculated by multiplying the standard error of the estimate or residual error by 1.645 (for one-tailed variables of interest) or 1.96 (for two-tailed variables of interest).

Linear equation	Height coefficient		Age coefficient		Weight coefficient		Constant		R^2		Standard error of the estimate	
Sex[a,b]	F	M	F	M	F	M	F	M	F	M	F	M
TLC (L)	0.057	0.081	–	–	–	–	−4.205	−7.404	0.38	0.48	0.50	0.61
VC (L)	0.038	0.064	−0.016	−0.02	–	–	−1.967	−5.422	0.61	0.69	0.38	0.45
RV (L)	0.021	0.014	0.017	0.018	–	–	−2.60	−1.273	0.32	0.32	0.38	0.41
RV/TLC, %	–	–	0.345	0.305	–	–	15.58	14.723	0.50	0.53	6.1	4.7
FRC including weight	0.048	0.066	0.012	0.011	−0.018	−0.025	−4.695	−6.623	0.24	0.29	0.43	0.54
FRC without including weight	0.034	0.041	0.009	0.009	–	–	−3.381	−4.123	0.17	0.18	0.45	0.58
RV including weight	0.020	0.049	−0.006	−0.007	−0.010	−0.026	−1.462	−4.775	0.30	0.32	0.31	0.50
RV without including weight	0.012	0.023	−0.007	−0.01	–	–	−0.693	−2.16	0.26	0.18	0.32	0.55
IC (L)	0.014	0.018	−0.009	−0.011	0.013	0.020	−0.223	0.986	0.44	0.48	0.32	0.42
IC/TLC, %	−0.314	−0.360	−0.220	−0.161	0.510	0.354	89.94	91.58	0.27	0.30	6.0	5.8

F: female; M: male; FRC: functional residual capacity; and IC: inspiratory capacity. [a]Females: age, 21-92 years; height, 140-174 cm; BMI = 18.4-30.4 kg/m²; White (n = 122). [b]Males: age, 25-88 years; height, 156-189 cm; BMI = 19.7-30.1 kg/m²; White (n = 122).

TLC values, the sensitivity for detecting restrictive lung disease and mild hyperinflation therefore being lower.

In summary, reference equations for plethysmographic lung volumes in White adults in Brazil were derived by linear regression analysis in the present study. Although the values presented here are similar to those estimated by quantile regression, they are easier to use and can therefore be more widely used.

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LETTER TO THE EDITOR

Migratory pulmonary infiltrates in a patient with COVID-19 and lymphoma

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TO THE EDITOR:

COVID-19 has become a pandemic and a major challenge for health professionals, the health care system, and the population itself. Most COVID-19 patients present with mild symptoms, including self-limited flu-like symptoms. However, approximately 20% present with moderate to severe disease, characterized by pneumonia. In addition, 5% can progress to severe respiratory failure, usually in the second week after symptom onset.(1) Chest CT findings include peripheral/bilateral ground-glass opacities or multifocal/rounded ground-glass opacities, with or without consolidation or crazy-paving pattern.(2) Other CT findings include the reversed halo sign and the target sign, as well as findings consistent with pulmonary embolism.(3-6) To our knowledge, this is the second reported case of a patient with COVID-19 and migratory pulmonary infiltrates consistent with organizing pneumonia (OP), the patient having responded well and rapidly to corticosteroid therapy.(7)

A 47-year-old female patient with follicular lymphoma was re-evaluated 33 days after the onset of COVID-19 symptoms. The patient was RT-PCR–positive for COVID-19 and reported progressive worsening of dyspnea, requiring supplemental oxygen at 2 L/min to reverse hypoxemia. Her laboratory test results were as follows: lymphocyte count, 1,040 cells/mm^3; D-dimer level, 6,106 ng/mL; negative serum galactomannan; negative for cytomegalovirus by real-time serum PCR; normal procalcitonin; elevated C-reactive protein (15 mg/dL); and normal lactate. The chest CT scans were reviewed, showing migratory pulmonary infiltrates without signs of pulmonary thromboembolism (Figure 1). A presumptive diagnosis of OP was made on the basis of prolonged clinical progression and CT findings, and the patient was started on methylprednisolone at 80 mg/day. At 7 days after treatment initiation, the patient showed significant improvement, with a C-reactive protein level of 1.3 mg/dL and an SpO_2 of 95% on room air, being discharged from the hospital. At 92 days after the onset of COVID-19 symptoms, a chest CT scan showed resolution of the pulmonary infiltrates and the patient had an SpO_2 of 97% on room air and a C-reactive protein level of 1.0 mg/dL. Prednisone was tapered and discontinued after three months of treatment. At five months after the onset of COVID-19 symptoms, the patient remained asymptomatic, with an SpO_2 of 97% on room air and a C-reactive protein level of 0.1 mg/dL.

The present case report adds to the literature on COVID-19. COVID-19 should be included in the differential diagnosis of migratory pulmonary infiltrates along with cryptogenic OP and secondary OP (associated with drugs such as amiodarone, bleomycin, cyclophosphamide, mesalazine, anticonvulsants, and cocaine; with diseases such as rheumatic diseases, leukemia, and lymphoma; and with radiation therapy, among other causes), as well as with eosinophilic pneumonia.(8)

It should be noted that the patient was evaluated at a time when corticosteroid use was not standard therapy for patients with COVID-19 and hypoxemia.(9,10) In addition, there was a concern that the use of corticosteroids might worsen the prognosis of COVID-19, based on the literature on Middle Eastern respiratory syndrome, SARS, and even influenza.(10) Therefore, it was a challenge to decide whether or not to use corticosteroids in the present case. Prolonged duration of symptoms, as well as late clinical worsening, together with migratory pulmonary infiltrates, raised the hypothesis of OP secondary to infection (COVID-19), which was confirmed by the exuberant response to corticosteroids in our patient. In addition, our patient had a lymphoma, which can also cause migratory pulmonary infiltrates (consistent with OP). However, she had received six cycles of chemotherapy with rituximab, cyclophosphamide, vincristine, and prednisone for grade 3A follicular lymphoma, followed by maintenance therapy with rituximab every two months. A PET-CT scan taken after 11 cycles of maintenance therapy showed that the patient had achieved complete remission. Therefore, a neoplastic cause was thought to be less likely given the temporal relationship between RT-PCR positivity for SARS-CoV-2 and clinical and laboratory findings of COVID-19, as well as the fact that the symptoms did not recur after corticosteroid discontinuation. It is of note that the first reported case of COVID-19 and migratory pulmonary infiltrates (consistent with OP) was that of a leukemia patient who responded well to treatment with corticosteroids, clinical and CT findings of OP therefore being attributed to COVID-19.(7) In addition, our patient presented with chronic myeloid leukemia after the lymphoma and responded to treatment.

In conclusion, COVID-19 should de included in the differential diagnosis of migratory pulmonary infiltrates along with OP and eosinophilic pneumonia.

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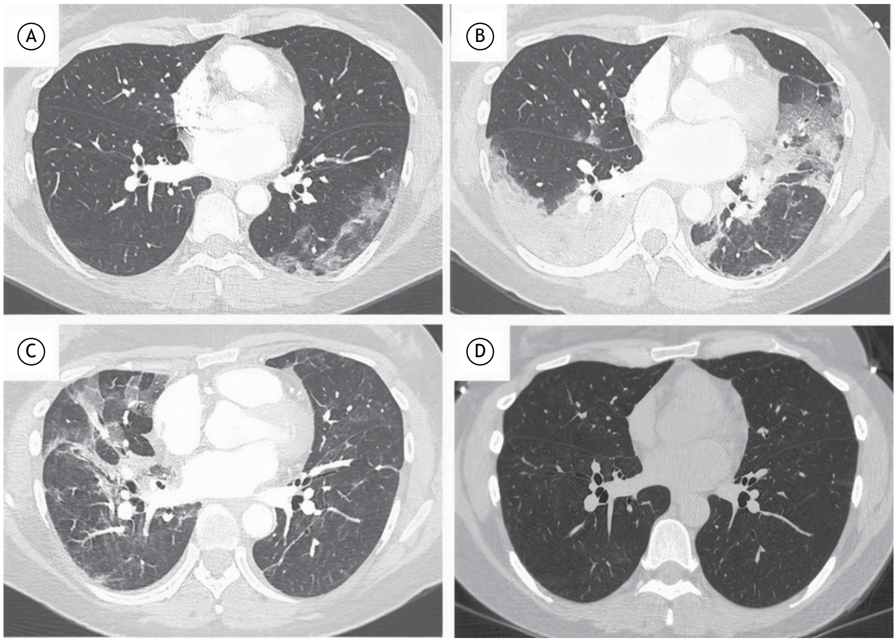

Figure 1. HRCT scans taken 14 days, 24 days, and 33 days after the onset of COVID-19 symptoms (in A, B, and C, respectively) and showing progressive migratory pulmonary infiltrates consistent with organizing pneumonia. In D, HRCT scan showing resolution of the pulmonary infiltrates 92 days after the onset of COVID-19 symptoms.

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Calcified metastases of teratoma

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A 37-year-old male patient was admitted for oncological follow-up. He had undergone right orchiectomy via the scrotal pouch two years prior for the resection of a tumor mass; the histopathological diagnosis was a combination of germ cell tumor, teratoma components, and areas of malignant degeneration. At that time, he had venous vascular invasion with metastases in the abdominal lymph nodes and the lungs (Figures 1A and 1B). The lung metastases were noncalcified. He underwent palliative treatment with chemotherapy, which resulted in stabilization of the tumor. A recent CT showed masses and nodules in both lungs, predominating in the right base, containing foci of calcification (Figures 1C and 1D). Biopsy of a pulmonary nodule was compatible with a post-pubertal metastatic teratoma with adenocarcinomatous transformation. At presentation, the patient was stable and receiving a new chemotherapy regimen.

Malignant transformation of teratomas is rare, occurring in only 3-6% of testicular germ cell tumors. The most common types of malignant transformation include sarcoma, carcinoma, and primitive neuroectodermal tumor. Teratomas with malignant transformation are usually metastatic at presentation, have a high recurrence rate, and are more aggressive than are teratomas without malignant transformation. The most common sites of metastasis are the lymph nodes, liver, and lungs. The treatment of teratomas with malignant transformation remains challenging. The standard treatment is radical orchiectomy, with or without chemotherapy and/or radiotherapy.[1,2]

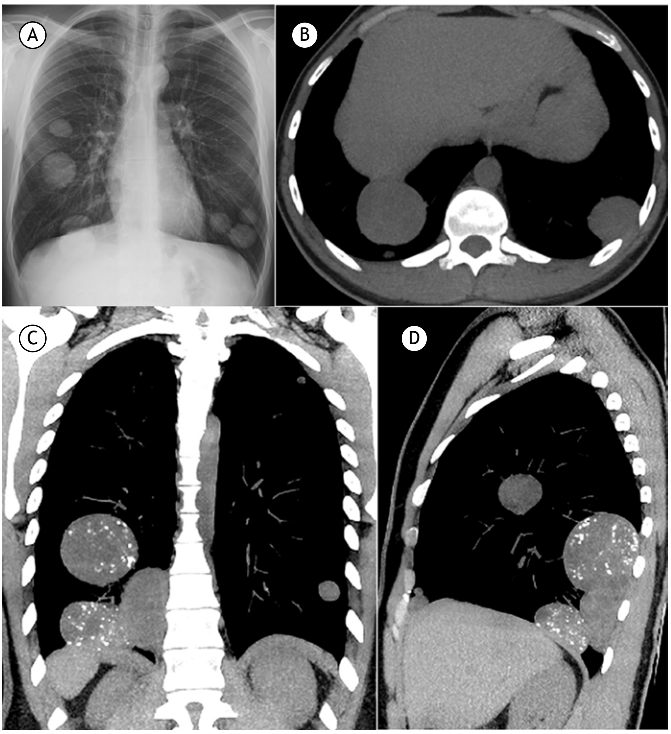

Figure 1. A chest radiograph (in A) and a chest CT scan (in B) obtained in October of 2017 showing multiple noncalcified nodules and masses in both lungs, predominantly in the lower regions. A chest CT performed two years later in the coronal (in C) and sagittal (in D) planes demonstrated growth of the nodules and masses, which contained calcification foci.

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ERRATUM

In the article "Lung transplant in patients with familial pulmonary fibrosis", DOI number http://dx.doi.org/10.36416/1806-3756/e20200032, published in the Jornal Brasileiro de Pneumologia, 46(6):e20200032, 2020, in the odd pages header:

Where it reads:

Vita E

It should be read:

De Vita E

ISSN 1806-3713

J Bras Pneumol. 2021;47(1):e20190221errata
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ERRATUM

Artigo: EBUS-TBNA versus surgical mediastinoscopy for mediastinal lymph node staging in potentially operable non-small cell lung cancer: a systematic review and meta-analysis

Publicação: J Bras Pneumol. 2020;46(6):e20190221

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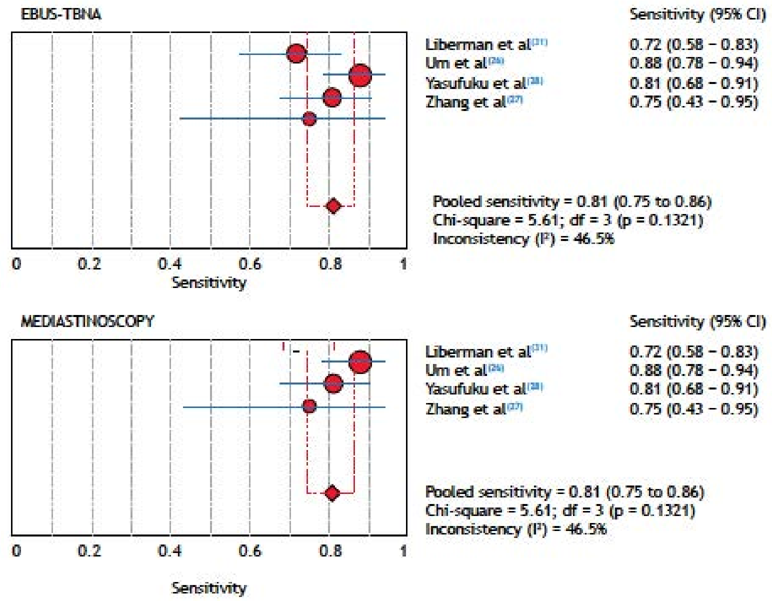
On page 6 of the original publication, in Figure 2, where is written



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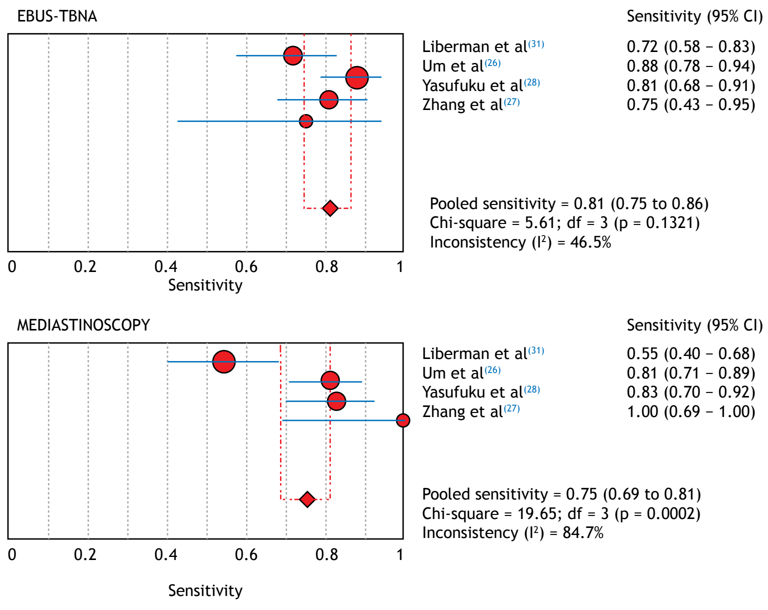

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