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PULMONOLOGY

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Volume 27. Number 3. May-June 2021

CONTENTS

Letters to the Editor

Correspondence

Pulmonology 27 (2021) 189–190

PULMONOLOGY

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EDITORIAL

Prioritizing care for severe asthma during SARS-CoV-2 pandemic

The new coronavirus (SARS-CoV-2)[1] is characterized by high contagiousness: this has forced to implement existing strategies or to conceive new approaches toward the management of chronic diseases in order to limit the spread of the virus among healthcare workers, patients and their caregivers. In this context, individuals affected by severe asthma have represented a challenge for the health care system during the lockdown phase of the SARS-CoV-2 pandemic. First, it is commonly accepted that these patients could be at greater risk for more severe disease if infected with SARS-CoV-2; therefore, as strongly encouraged by the Global Initiative for Asthma document that has issued frequently asked questions (https://ginasthma.org/about-us/faqs/) about asthma management in the context of COVID-19, all measures should be applied to limit the risk of infection. Second, an individual suffering from the most severe forms of asthma who experiences acute exacerbation may, to some extent, mimic the onset of COVID-19 disease. Indeed, early observations indicate that the clinical spectrum of COVID-19 disease can be very heterogeneous, perhaps related to the infectious dose and the viral load of SARS-CoV-2 within the first weeks of disease onset; cough and dyspnea may overlap, challenging the diagnosis at least in the first phases, and therefore delaying the appropriate therapeutic strategies. Taken together, these considerations force clinicians, and mostly those who daily cope with severe asthma and severe asthmatics, to adopt novel, and not rarely never experienced before, strategies and pathways to continue treating patients without increasing the risk of contagious. Pandemics are unanticipated, and the time has come to put together skills and experiences, and to make the best out of the clinical activities that centers of excellence for asthma around the world have proposed.

In our perspective, the current emergency situation has accelerated the application in real life contexts of techniques of home monitoring and teleconsulting, aiming to minimize the risk of exposure to positive COVID-19 patients related to in-person healthcare visits in hospital facilities.[2] Most of the outpatient visits have been transformed into ''virtual visits'' in which the patient is followed by means of electronic tools.[3] Telemedicine has proven to be particularly useful in the management of patients with chronic diseases such as asthma who need continuous monitoring. Romano et al.,[4] showed that the use of this approach in persistent asthma is associated to reduction in symptoms and improvement in quality of life. Another study comparing telemedicine with face-to-face visits showed equal disease control suggesting that telemedicine can be considered a valid alternative.[5] The question is whether severe asthmatics under biological treatment are also candidates for distance monitoring. No doubt that this is applicable when symptoms are under control, and patients can be regularly followed by phone calls of electronic diaries. In other words, in the context of severe asthma virtual patient encounters become efficient for delivering clinical services within a risk-stratified context. On the other hand, when the disease is out of control, symptoms are not crystal-clear, the suspect of drug-related side effects is concrete, or patients want to arbitrarily stop the biologic drug, face-to-face-interactions are mandatory. This scenario requires deep thinking on how to design dedicated areas in outpatient clinics at the hospitals or ambulatory services for severe asthma, since agreements on how to prioritize service shut down and patient care are scarce and mostly reflect regional epidemic and local decisions.

Prior to describing potential measures or promising decisions, it should be clear that such measures would be for emergency purposes only, such as at the present time, with the hope that the contingency planning will eventually have an end. Most of the suggestions below are appropriate for the greatest level of social distancing and quarantine, such as that during a lockdown state, but obviously may vary according to the evolving conditions. In the hope of a return to normality, some of the clinical decisions at social or institutional levels may even last, if deemed necessary and cost-effective.

We envision a condition in which patients already under biologic drugs are advised to continue the administration of medications. There is no scientific reason why severe asthmatics should stop their medications. With the aim to

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reduce contacts and to avoid any withdrawal of biological treatment, patients supported programs (PSP) should be implemented and home delivery of medications activated. The PSP often offers a nurse support and a training to patients and/or caregivers on the subcutaneous injection technique of administration. This is particularly important for older patients, since it has been demonstrated that biologics are safe and commonly used in this population.[6] The PSPs were born before the outbreak, but this is a unique opportunity to implement them, in that, they are becoming a resource for the health care system, preserving patients from visiting the hospital when the clinical conditions do not necessarily require it. A re-organization of the public health system that involves local pharmacies able to deliver the drug, community nurses qualified to administer the drug at home, health-care workers appointed to specifically train and educate patients and their care-givers to self-management, application of digital medicine services to follow stable patients is mandatory. At this stage, lung function assessment should be limited because of the potential for coughing and droplet formation.[7]

A situation that cannot be underestimated is the potentially tragic consequences of fake news on subjects affected by severe asthma. Since stress, fear and anxiety can trigger asthma attacks, patients should be advised to only rely on scientific sources about COVID-19, and provided with psychological support whenever needed. Some centers for excellence for severe asthma have already incorporated a psychologist in their multidisciplinary team.

In the case of refusal of home administration, or need for face-to-face-visits, appointments at the hospital facilities should always be assured, using a specific operational plan that includes a phone triage to explore the occurrence of respiratory symptoms suggestive of COVID-19 the day before the in-person visit and/or contact with COVID-19 positive subjects. Upon entering the facility, the patient should be instructed to follow rigid protocols to mitigate risk to both medical staff and patients during the ongoing pandemic, including separate waiting areas and pathways, administering specific questions related to health status and measuring body temperature. Proper use of medical masks is mandatory for both patients and health-care workers.[8]

Our experience and current reports[9] support the strategy that, during the COVID-19 pandemic, every effort should be made in patients affected by chronic respiratory diseases at high impact like severe asthma to minimize patient contact with the health-care system, planning specific pathways that allow patients to receive appropriate medical care and to continue the biological therapies administration, preventing the loss of disease control and exacerbations. Whether specific phenotypes of asthma will guide decisions on how to manage the disease in relation to the susceptibility to virus infection is a current object of active research.[10] Innovative tools, such as telemedicine[11] and digital medicine services, are strongly encouraged, and home-delivering and self-administration of the biological drugs will necessarily become (like it or not) an essential part of the overall clinical management of severe asthma.

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EDITORIAL

Preaface to the series: How can we do it

Reading an article is an interesting challenge. Most of us are looking for new results or new intriguing observations. Others are searching for a new therapeutic tool to apply in their clinical practice, those with the most curiosity are also attracted by the methodology used to design the study and therefore to depict strengths and limitations.

Whoever you are and whatever your ''profile'' in this context, there is often something missing after you have finished reading an article, which is how this will really fit into your daily practice.

So you are left with a sort of discrepancy between what you have read on your PC or in the journal and what you will do when you go back to your ward to take care of your patients. How many times did you feel like thinking ''*well nice paper, but how can I apply it outside a research scenario. Too many barriers, too many exclusion criteria, too many complicated analyses and set up, better if I quit considering this in my practice*''.

In this issue of the journal we start a new series entitled ''How can we do it'', that has the ambitious aim of reducing the gap between what we read in an article and our daily routine. The aim is to publish 2–3 articles every 12 months.

Some journals are already indirectly tackling this issue, but usually from the Authors side, with an approach like ''how I am used to doing it'', rather than using the words WE DO together.

Well, our goal is to start with a clinical case and bring in the readers on a journey, trying first to explain why we want to use this approach, second if we have enough scientific evidence to support us and last but not least how we set about, interpret or put into practice a specific treatment.

This holds particularly true when we need to focus our attention on some devices (i.e. ventilators), techniques (i.e. rehabilitation procedures, weaning strategies) or even on reading results of a specific assessment (i.e. Arterial Blood gases or Polysomnography).

In this issue of the journal we were targeting the use of High Flow Nasal Cannula (HFNC) to treat patients with Acute Respiratory Failure (1). The introduction is a real life case, followed by a physiological rationale and clinical evidence. So far, quite ''usual'' approach, while the new and in our view interesting part, is a suggestion of a flow chart on basic and advanced set up of the device. Last[1] are describing in an unbiased fashion, details and differences of the different HFNC devices available so far on the market.

Lastly, we are also keen to having ''on board'' in these series, not only well known Authors, but also young motivated experts, in order to get a really fresh approach to the topic. It is not by chance that we welcome in the first paper two young women, a nice pairing of Argentinian and Italian approach, a classical example on how doctors can make complicated things simple, because the authors ''explain things, because they have seen them and have the experience in managing them''.

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PULMONOLOGY

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EDITORIAL

Palliative and respiratory care: Preparing the future

What do Obstructive pulmonary disease, interstitial lung disease, neuromuscular disease, Lung cancer, Asthma, Obstructive sleep apnea and Obesity hypoventilation syndrome have in common? They all affect the respiratory system. They are chronic and progressive conditions and they are, for the most part, incurable.

Advances in Medicine in recent decades have led to increased life expectancy, including for patients with respiratory conditions. Unfortunately, curative treatment isn't always possible and it may not mean that there is any increase in quality of life. Diagnostic and therapeutic decisions may not be in line with the patients' real needs, and may inflict greater suffering.[1,2] Patients with incurable disease are frequently highly symptomatic and suffer loss of functional ability, which should justify a shift in our goals of care, regardless of prognosis, focusing on comfort, dignity and quality of life. This supports the rising importance of Palliative care, a specialized field of Medicine, with tools that could and should be learned by all doctors.

Particularly in Respiratory care, there is, without a doubt a call for greater education, which should begin with basic training in Palliative care, because so many respiratory conditions are, as previously stated, chronic and incurable.[3,4] The initial training process should begin during Respiratory specialty training, which we feel currently has a gap in knowledge to be filled.

Palliative care interventions in respiratory conditions include management of symptoms such as dyspnoea, fatigue, cough, haemoptysis and increased respiratory secretions.[5] Management of dyspnea has been object of particular interest in the past few years. Pharmacological and non pharmacological therapies are available to relieve dyspnoea, however there is still a general fear of implementing some of these measures, mainly due to lack of knowledge of their benefits and risks,[6] particularly regarding opioid use. Opioids remain first line recommendation with grade 1 level of evidence for the relief of respiratory distress in advanced lung diseases if other measures such as bronchodilators, diuretics, corticosteroids and other soothing measures are insufficient.[4]

Education in Palliative care would add value to the current respiratory training programme, both professionally and personally. Communication skills are honed, the patient is assessed globally, interpreting signs and symptoms beyond the respiratory system, with the aim of treating symptoms properly. There is a focus on multi disciplinary team work and special care taken to avoid futile measures. Medical care becomes more patient-centered with a focus on patient preference and views. The familyś role is paramount and their presence, role and views taken into account during this approach which aims to validate the person as a whole; their relationships and what matters to them becomes just as central as the disease which afflicts them.

Palliative patients often present with considerable complexity, not only because of the presence of multiple co morbidities and the severity of their main disease, but also due to the many dimensions that influence patient suffering. Frequently there is no readjustment in goals of care, so that the main purpose becomes quality above quantity of life, with the latter being something that should not be achieved at any cost.[1] This readjustment of goals is still perceived by some as ''giving up'', which adds to the stigma attached to palliative care. It should be seen as the exact opposite; investment in whatever is most suitable for the patient and their family; this is what is recommended by the World Health Organization (WHO).

Palliative care is defined by the WHO as an approach that improves quality of life for patients and their families when facing issues relating to life-threatening illness, through the prevention and relief of suffering by means of early identification and treatment of pain and other symptoms, and also issues in the physical, psychosocial spiritual fields.

This definition is a tall order; its major goal to act on global human suffering and provide comfort and dignity, both to the patient and their family.[1] After a placement in a Palliative care unit, during their respiratory training programme the author argues that education in this field is paramount for appropriate care of patients with advanced lung disease. Considering current international recommendations for doctors and their training, our present reality with increased prevalence of chronic and advanced disease and the desire to improve the patient experience,[4,5] we believe that an integrated placement in Palliative care should be part of the Respiratory specialty training.

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Conflicts of interest

The authors have no conflicts of interest to declare.

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ORIGINAL ARTICLE

Cardio-pulmonary-exercise testing, stress-induced right ventricular diastolic dysfunction and exercise capacity in non-severe chronic obstructive pulmonary disease

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Introduction

Although treatable and preventable, chronic obstructive pulmonary disease (COPD) is still associated with high morbidity and mortality.[1] Dyspnea and exercise incapacity are the cardinal symptoms of the disease.[2,3] It has traditionally been related to ventilatory or gas exchange abnormalities,[4,5] but results from clinical research studies have changed the current perception. Recent data suggest that cardiac dysfunction and pulmonary vessel impairment may be essential contributors to both symptoms even in non-severe forms of COPD.[6,7]

Right ventricular dysfunction is an independent predictor of effort intolerance in a general population of patients.[8] However, little is known about its frequency and outcomes in milder forms of COPD. COPD population studies have introduced the novel paradigm of ''cor pulmonale parvus.''[9–11] They demonstrate that COPD patients have small RV dimensions, RV hypertrophy and right ventricular diastolic dysfunction (RVDD).[12] RVDD is an early sign of pulmonary vasculopathy and precedes the clinical/echocardiographic manifestation of pulmonary hypertension.[13–15] RVDD detection is thus essential for the early diagnosis of pulmonary vasculopathy for COPD management and physical activity improvement.

The aims of the current study are: (1) to detect the frequency of exercise-induced RVDD in non-severe COPD patients without echocardiographic signs of pulmonary arterial hypertension at rest; (2) to find RV echocardiographic parameters – predictors for stress RVDD; (3) to analyze the cardio-pulmonary exercise testing abnormalities, associated with stress RVDD; (4) to determine which echocardiographic parameters are independent factors for the 6-minute walk test (6-MWT) performance.

Materials and methods

Patients and study protocol

Thae study was prospective, conducted with 224 outpatients diagnosed with COPD at the University Hospital for Respiratory Diseases ''St. Sophia'', Sofia. All of the subjects had exertional dyspnea and normal left ventricular systolic function at rest (left ventricular ejection fraction >50%) but only 163 of them demonstrated non-severe COPD – FEV1 > 50%. Only clinically stable patients participated in the study – none of which had experienced exacerbation of respiratory symptoms or other chronic comorbidity during the previous

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three months; nor had there been any change in supportive medical therapy during those three months.

The following exclusion criteria were considered: (1) LVEF < 50%; (2) over grade 1 LVDD at rest; (3) echocardiographic signs of systolic pulmonary arterial hypertension; (4) valvular heart disease; (5) documented cardiomyopathy; (6) severe uncontrolled hypertension (systolic blood pressure >180 mmHg and diastolic blood pressure >90 mmHg); (7) atrial fibrillation or malignant ventricular arrhythmia; (8) ischemic heart disease; (9) anemia; (10) diabetes mellitus; (11) cancer; (12) chronic kidney disease; (13) recent chest or abdominal surgery; (14) recent exacerbation (during the last three months); (15) recent change (during the last three months) in medical therapy; (16) non-invasive positive-pressure ventilatiton support; (17) long-term ambulatory oxygen therapy. The flowchart of the design of the study is presented as Fig. 1.

''The recruitment period was between April 2017 – April 2018, and was approved by the local Ethical Committee (protocol 5/12.03.2018). All the patients had visited the clinic because of routine annual examination. Medical history and current medication were recorded. There was no change in current therapy before or during the study. During the initial visit, inclusion and exclusion criteria were taken into account. Within 3–4 days, patients who were eligible for the study were given an appointment spirometry and body plethysmography. Computed tomography (CT) and 6-minute walk tests were done within 5–6 days of the initial visit. Cardio-pulmonary exercise testing (CPET) and stress echocardiography were executed within 7–10 days. CPET was divided ino two sessions within two consecutive days. During the first session subjects were acquainted with the protocol and were introduced to the bicycle. β2 agonists and anticholinergics were withdrawn 24 h before all physiological tests – spirometry, body plethysmography and cardio-pulmonary exercise testing.

Procedures

Pulmonary function testing

All subjects underwent preliminary clinical examination which included chest X-ray, spirometry, electrocardiogram, and echocardiography. Those eligible for the study underwent spirometry and exercise stress test. Both tests were performed on Vyntus, Carefusion, Germany following the guidelines. Spirometry was performed after bronchodilatation test – application of (400 μkg) of salbutamol. Following the ERS guidelines a post-bronchodilatation ratio of FEV1/FVC <70% was assumed for the diagnosis of COPD.[16] Only patients with mild/moderate airway obstruction (FEV1 >50%) were selected.

CT-emphysema score

Chest CT scans were obtained using Siemens multi-detector helical CT scanners. Patients were in the supine position. Scans were performed in full inspiration with the following parameters: collimation – 1 mm; 120–140 kV; 75–350 mA; 0.75–1 s scan time; 1–2 mm slice thickness. Emphysema is characterized by CT low attenuation areas (LAA) compared to normal surrounding lung parenchyma. An automated identification of the LAA, defined as an area with less than 950 Hounsfield unit (HU) density, was performed. Emphysema severity was determined using the Goddard scoring system.[17,18] Each lung was divided into three zones: the upper zone, extending from the apices to the level of the aortic arch; the mid-zone, extending to the level of tracheal bifurcation; and the lower zone, extending from the level of tracheal bifurcation to the diaphragm. Lung regions were graded as follows; no emphysema – score 0; ≤25% emphysema – 1; ≤50% – 2; ≤75% -score 3; >75% – score 4. Goddard score calculation is the calculation of the percentage of LAA per surface area, with the following cut-off values: mild emphysema – Goddard I – 1–7 scores; moderate emphysema – Goddard II – 8–15 scores; severe emphysema – Goddard III – 16–24 scores.

Six-minute walk testing (6-MWT)

Six-minute walking test was performed in accordance with ATS guidelines.[19] It was done on a separate day after the initial visit for study eligibility criteria and after the performance of the exercise stress test and stress echocardiography. Subjects were instructed and encouraged to walk a 30 m preliminary measured distance in a hospital corridor. SpO2, heart rate and arterial blood pressure were obtained before and during the recovery period.

Stress test protocol – cardio-pulmonary exercise testing (CPET)

All the patients underwent symptom limited incremental exercise stress test following the guidelines.[20] Subjects breathed through an oro-nasal mask (Hans Rudolf 7450 SeriesV2™ Mask, CareFusion). Breath-by-breath cardiopulmonary data (Vyntus, CareFusion) were measured at rest, warm up and incremental exercise testing. It was performed on a bicycle after the clinical examination and spirometry. Gas and flow sensors were calibrated before each test. Clinical monitoring of the patients included standard electrocardiography throughout the whole exercise test; manual blood pressure measurements, and heart rate recordings at the end of every stage.

A continuous ramp protocol was applied. After 2 min of unloaded pedaling (rest phase-0W), a 3 min warm-up phase (20 W) followed. The test phase included 20 W/2 min load increments. Patients were instructed to pedal at 60–65 rotations per minute. Patient effort was considered to be maximal if two of the following criteria emerged: predicted maximal HR is achieved; predicted maximal work is achieved; 'VE/'VO2 >45, RER >1.10 as recommended by the ATS/ACCP.[21]

A breath-by-breath analysis was used for expiratory gases evaluation. Oxygen uptake ('VO2 (ml/kg/min)), carbon dioxide production ('VCO2 (L/min)), minute ventilation ('VE (L/min)) and end-tidal CO2 pressure (PetCO2 (mm Hg)) were collected continuously at rest and throughout the exercise test. Peak values of oxygen consumption and carbon dioxide production were presented by the highest 30-s average value, obtained during the last stage of the exercise test. Peak respiratory exchange ratio (RER) was the highest 30 s averaged value between'VO2 and 'VCO2 during the last stage of the test. 10-s averaged 'VE and 'VCO2 data, from the initiation of exercise to peak, were used to calculate the 'VE/'VCO2 slope via least squares linear regression.[22] A dual

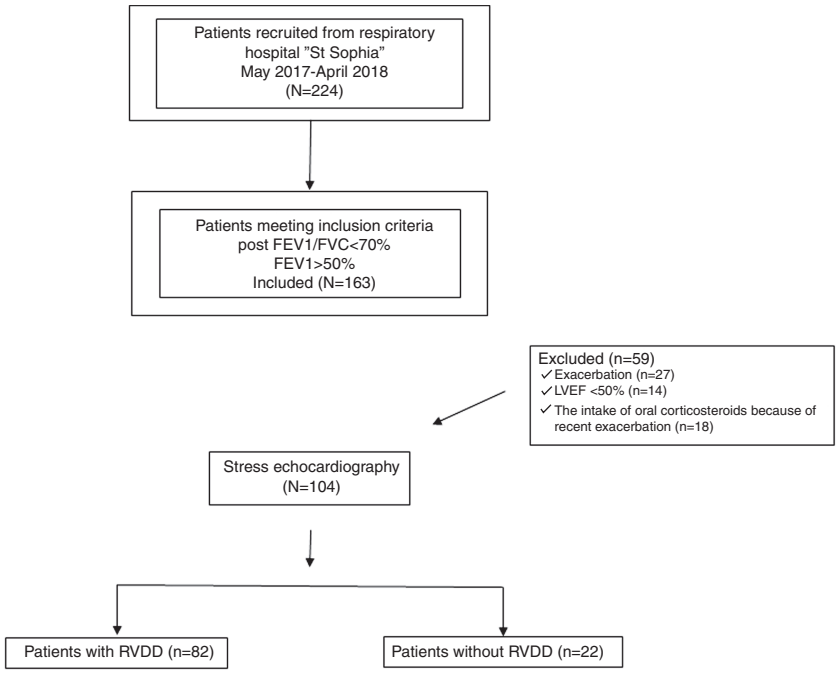

Figure 1

approach for the measurement of the anaerobic threshold (AT) was applied. Both V-slope method and the ventilatory equivalents method for ˙VO2 and ˙VCO2 were used. The modified Borg scale was applied for peak dyspnea and leg discomfort.

Breathing reserve was calculated as (MVV − peak V'E)/MVV $\times$100 where MVV is maximal voluntary ventilation estimated as FEV1 multiplied by 35.[23] Heart rate (HR) reserve − (HRR) was calculated as (peak HR-resting HR) $\times$100/((220-age) − resting HR).

Body plethysmography and dynamic hyperinflation (DH)

Body plethysmography (residual volume (RV), functional residual capacity (FRC), total lung capacity (TLC)) was performed on (Vyntus, body plethysmograph, CareFusion, Germany) using European and American Thoracic Society guidelines.[16] End-expiratory lung volume (EELV) was calculated from IC maneuvers at rest, every 2 min during exercise and at peak exercise (Vyntus). IC maneuvers were used to examine operating lung volumes and dynamic hyperinflation (DH) as previously described.[24] Data are presented as 30-s averages during rest, the last 30 s of each second minute during exercise, and at peak exercise. DH was defined as a decrease in IC from rest of more than 150 ml or 4.5% pred at any time during exercise.[25]

Echocardiography methods

Echocardiography included the generally used approaches of M-mode, two-dimensional and Doppler echocardiography. Routine structural and hemodynamic indices of both chambers were measured following the guidelines.[26,27] The systolic function of the left ventricle was defined by Simpson's modified rule. The diastolic function of both ventricles was evaluated by the E/A ratio and the average E/e' ratio at rest. As a more precise approach for diastolic dysfunction detection, tissue Doppler analysis was used. We used e' value as the average of medial and the lateral measurements for the mitral annulus. The peak of the average E/e' ratio >15 was considered as a marker for stress induced LVDD.

The dimensions of the right ventricle were assessed from the long-axis parasternal and apical four chamber view.[28] Tricuspid annular plane systolic excursion (TAPSE) and S-peak velocity were analyzed for RV systolic function evaluation. Right ventricular wall thickness (RVWT) was measured in end-diastole. Systolic pulmonary arterial pressure was calculated by Bernoulli equation and by the acceleration time (AT).[28,29] Right atrium volume index (RAVI) was measured at right ventricle end-systole by Simpson's modified rule. The peak of the average E/e' ratio >6 was considered as a marker for stress induced RVDD. Stress induced RV diastolic dysfunction was considered if stress induced E/e' ratio >6. All parameters were measured at end-expiration and in triplicate during different heart cycles.[29]

Statistical analysis

Descriptive statistics was used for demographic and clinical data presentation. The Kolmogorov–Smirnov test was used to explore the normality of distribution. Continuous variables were expressed as median and interquartile range when data was not normally distributed and with mean $\pm$ SD if normal distribution was observed. Categorical variables were presented as proportions. Data were compared between patients with and without RVDD. An unpaired Student's *t* test was performed for normally distributed continuous variables. Mann–Whithney-*U* test was used in other cases. Categorical variables were compared by the χ^2 test or the Fisher exact test. Adjustments were made for age, sex, comorbidity and medication. Receiver operating characteristic (ROC) curves were constructed. ROC analy-

sis was performed to test RV echocardiographic parameters at rest that may accurately distinguish between stress RV E/e' >6 or <6. Regression analysis was also used with the echocardiographic parameters as qualitative parameters, using their cut-off values. Univariable regression analysis was performed to assess which echocardiographic parameters are associated with stress RV E/e' > 6. Multivariable logistic regression analysis by using a forward stepwise approach detected the significant independent predictors of stress RV E/e' > 6. Predictive models were constructed. Univariable and multivariable logistic regression analyses were also used to determine the parameters significantly related with the 6MWT. Age, sex, height, weight (BMI), FEV1, Goddard score, ICdyn, stress LV diastolic dysfunction were specifically included as co-variates in both situations.

In all cases a *p* value of less than 0.05 was considered significant as determined with SPSS® 13.0 Software (SPSS, Inc, Chicago, Ill) statistics

Results

Demographic and clinical data

Subjects enrolled in the study were Caucasians with a mean age of 62.50 ± 8.5 years and a body mass index of $27.26 \pm 6.92\,kg/m^2$. They were divided into two groups – subjects with stress induced right ventricular diastolic dysfunction – 78%(82/104) (COPD-RVDD), and those without stress induced diastolic dysfunction 22%(22/104), (COPD - no RVDD). There was no statistically significant difference for the demographic and clinical parameters between the two groups (Table 1).

A trend of a higher percentage of current smokers (77% vs. 55%) in the patients w/o stress RVDD compared to those with stress RVDD may be observed. In contrast, the number of former smokers is bigger in patients with stress RVDD (23% vs. 14%). Twenty-two percent of the patients with stress RVDD are non-smokers, which is much higher than those without stress RVDD (9%). The total number of packet-years, however, predominates in patients with stress RVDD (32.11 vs. 26.52), without reaching statistical significance.

There was no substantial distinction between the patients with and without stress RVDD for incidence of GOLD stages. Mild COPD was found in 40 (49%) of the patients with stress RVDD vs. 13 (59%) in those without RVDD. Moderate COPD was encountered in 42 (51%) of the patients with stress RVDD vs. 9 (41%) in those without. Most of the patients without stress RVDD had mild COPD – 13 (59%); 9 (41%) of them had moderate COPD; in patients with stress RVDD the GOLD stages were almost evenly distributed – 40 (49%) of the patients showed mild forms of COPD vs. 42 (51%) with moderate COPD. This explains the almost identical percentage of intake of β2-agonists (79% vs. 83%) and anti-cholinergic medications (39% vs. 48%) in the subjects with/without stress RVDD respectively. Though not of clinical significance there is a trend for a larger intake of combined ICS/β2-agonists in the group with stress RVDD (71% vs. 49%).

CT of the chest and Goddard scoring were performed in a total of 68 patients. 12 of these patients were without stress-RVDD and 56 with stress-RVDD; 18 (26%) of the patients were Goddard I; 47 (69%) of the patients were Goddard II; 3 (4%) were Goddard III (Table 1). All of the patients without stress-RVDD were Goddard I (12/68–18%) 8 of them were GOLD I, 4 GOLD II. The patients with stress RVDD were more heterogeneous regarding Goddard CT data: 6 (9%) patients had Goddard I; 47 (69%) – Goddard II; 3 (4%) – Goddard III. The patients with stress-RVDD in Goddard II and Goddard III were GOLD II; only one patient from Goddard I was GOLD I; the rest were GOLD II.

Right ventricular parameters

The echocardiographic characteristics are detailed in Table 2. The median right ventricular basilar diameter was 38 mm (35–39), right ventricular systolic function – S' peak velocity 16 m/s (15–16) and TAPSE – 22 mm (21–24) were within normal limits. Median RAVI was at the upper limit of normal $19.47\,ml/m^2$ (21.38–23.61); Median RVWT – 6.5 mm (6–7) with approximately 53% of subjects demonstrating evidence of right ventricular hypertrophy. None of the subjects had evidence of right atrial and ventricular enlargement. The pulmonary artery systolic pressure was estimated in all subjects – 27 mmHg (25–30) and was not elevated at rest.

Fourteen percent (15/104) of the patients demonstrated right ventricular diastolic dysfunction at rest (E/e' > 6). Stress-induced myocardial velocities (E/e' > 6), measured 1–2 min after peak load were higher in (82/104) – 78% of the patients in comparison to the rest (22/104) – 22%. Sixty-seven percent of the patients (67%) demonstrated stress-induced elevation of the systolic pulmonary arterial pressure (baseline 26.50 ± 3.75 mmHg; after CPET 35.00 ± 4.38 mmHg). There was not a significant difference between the two groups regarding functional (systolic and diastolic) parameters of the RV at rest. In contrast, right atrial (RA) geometry was distinctive. The mean values of RAVI in the group without stress-induced RVDD were significantly lower ($16.55 \pm 1.72\,ml/m^2$) in comparison to the group with RVDD ($22.27 \pm 3.19\,ml/m^2$). The same is observed regarding right wall thickness (RWT). In subjects without stress-induced RVDD, RWT was lower (5.00 ± 0.87 mm) in comparison to those with stress-induced diastolic dysfunction (6.50 ± 1.00 mm). The functional parameters that were distinctive between the groups were the AT and sPAP, measured at peak stress (Table 2).

Left ventricular parameters

Our patients had normal LV dimensions and had preserved LV systolic function Table 2. LV wall thickness was 12 mm (11–13). 62% of the subjects demonstrated evidence of left ventricular hypertrophy. In the group with stress-RVDD 67% (55/82) had LVH; in the group without stress-RVDD 45% (10/22) had LVH. If we compare the prevalence of LVH in patients with and without stress-RVDD, no statistically significant difference (*p* – 0.408) could be established. The left atrial and ventricular dimensions were within normal limits.

Only 30% of the patients had LV diastolic dysfunction at rest (average E/e' > 8) and the remaining 70% had normal LV diastolic function at rest. In the group with stress-RVDD 33% (27/82) had LV diastolic dysfunction at rest; in the group without stress-RVDD 18% (4/22) had LV diastolic dysfunction at rest. Regarding LVDD at rest no statistically significant dif-

Table 1 Clinical and demogrphic charcteristics of the groups with and w/o stress RVDD.

	Patients w/o stress RVDD (22)	Patients with stress RVDD (82)	*p*-Value
Demographic data			
Age, year,	60.00 ± 8.00	65.00 ± 9.00	0.143*
Male:Female gender, *n*	14:8	50:32	0.298†
Current smokers, *n* (%)	17 (77%)	45 (55%)	0.341†
Former smokers, *n* (%)	3 (14%)	19 (23%)	0.235†
Non-smokers, *n* (%)	2 (9%)	18 (22%)	0.272†
Packet, years	26.52 (23.46–30.43)	32.11 (28.82–36.13)	0.176 ‡
Body mass index, kg/m^2	28.00 (25.25–30.5)	26.52 (22.72–30.61)	0.981‡
Clinical data			
Systolic blood pressure, mmHg	126.73 ± 8.41	128.87 ± 11.32	0.803‡
Diastolic blood pressure, mmHg	80.43 ± 4.14	82.31 ± 6.61	0.451‡
Current medication			
Inhaled β2 agonists, *n* (%)	18 (83%)	65 (79%)	0.321†
Inhaled anticholinergic medications, *n* (%)	11 (48%)	32 (39%)	0.068†
Inhaled corticosteroids combined with β2 agonist, *n* (%)	10 (45%)	58 (71%)	0.723†
Angiotensin converting enzyme Inhibitors, *n* (%)	17 (77%)	58 (71%)	0.108 †
в blockers, *n* (%)	6 (27%)	23 (28%)	0.317 †
Diuretics, *n* (%)	17 (77%)	60 (73%)	0.407†
GOLD stages			
GOLD I, *n* (%)	13 (59%)	40 (49%)	0.701†
GOLD II, *n* (%)	9 (41%)	42 (51%)	0.435 †
*CT data****			
Goddard I	12 (18%)	6 (9%)	0.289 †
Goddard II	–	47 (69%)	–
Goddard III	–	3 (4%)	–
Dynamic hyperinflation			
Hyperinflators	7 (32%)	57 (69%)	0.049†
Non-hyperinflators	15 (68%)	25 (31%)	0.042†
6 min walk distance			
Distance walked, m	446.05 ± 22.31	•410.76 ± 20.25	0.043‡
Heart rate at rest	112 (100–119)	117 (98–121)	0.061‡
SatO2, % after exercise	95.09 (94.1–95.3)	94.15 (93.17–95.2)	0.813†

* Unpaired *t* test.
‡ Mann–Whitney *U* test.
† Chi square test.
§ *Abbreviations*: GOLD – Global Initiative On Obstructive Lung RVDD – right ventricular diastolic dysfunction.
*** CT is performed in a total of 68 patients – 12 without stress RVDD and 56 with stress RVDD.

ference between stress-RVDD/without stress-RVDD groups was detected (p – 0.458).

A total of sixty-seven percent (67%) of all the patients had left diastolic dysfunction during exercise (E/e' > 15). No significant difference in both structural and functional parameters of the LV at rest may be discerned between the patients with and without stress induced RVDD (Table 2). Statistically significant difference is present in: LV stress E/A, LV stress E/e' (Table 2).

Ventilatory, cardiovascular and cardio-pulmonary exercise testing parameters of patients with and without stress RVDD

The ventilatory, cardiovascular and **cardio-pulmonary exercise testing parameters** during exercise in the two groups are given in Table 3. The patients with stress RVDD reached a significantly lower peak heart rate median 125 beats per minute (bpm) in comparison to those without (149 bpm).

Table 2 Echocardiographic parameters of the patients with and w/o RVDD.

	Patients w/o stress RVDD (22)	Patients with stress RVDD (82)	*p*-Value
LV structural parameters			
TDD, mm	51 (49.5–56.5)	51 (48–54)	0.536*
TSD,mm	34 (32–39)	33 (31–35)	0.473*
TDV, ml	122.5 (115–157)	121 (107.5–139)	0.616*
TSV, ml	45 (41–69)	44 (38–50)	0.481*
Septum, mm	12.00 (11–12.75)	12.00 (11–13)	0.526*
PW, mm	12.00 (11.25–12.75)	12.00 (11–13)	0.403*
LV functional parameters at rest			
LVEF, %, Simpson	65.00 (60–66)	61.00 (67–65)	0.421*
E/A ratio	0.78 (0.76–0.83)	0.84 (0.75–1.21.)	0.201*
E/e' aver ratio	6.96 (6.27–8.33)	6.66 (5.63–8.1)	0.317*
LV functional parameters after exercise stress test			
E/A ratio	1.22 (0.88–1.37)	1.71 (1.5–2.00)	0.041*
E/e' aver	8.12 (7.25–10)	17.14 (14.66–18.39)	0.036*
RV structural parameters			
RAVI, ml/m^2	16.55 (15.81–17.54)	22.27 (20.65–23.85)	0.024*
RVWT, mm	5.00 (4.12–5.00)	6.50 (6.00–7.00)	0.038*
RV diameter parasternal, mm	28 (26.5–30)	28 (26–30)	0.438*
RV basal, mm	35 (35.5–39)	38 (36–39)	0.526*
RV med, mm	23 (22–25.75)	27 (25.5–29)	0.645*
RV functional parameters at rest			
E/A ratio	0.83 (0.76–1.16)	0.71 (0.66–0.83)	0.532*
E/e' aver	5.47 (4.56–5.69)	4.54 (3.33–5.22)	0.641*
S peak velocity, cm/s	15 (15–16)	15 (15–16)	0.897*
AT, ms	170 (165–180)	170 (160–180)	0.615*
sPAP, mmHg	25.00 (23–27)	28.00 (25–30)	0.908*
RV functional parameters after exercise stress test			
E/A ratio	1.28 (1.14–1.5)	1.37 (1.22–1.52)	0.887*
E/e' aver	6.92 (5.46–8.00)	11.25 (9.00–13.33)	0.039*
S peak velocity, cm/s	15 (13–16)	14 (14–15)	0.842*
AT, msec	162.5 (155–170)	110 (95–115)	0.039*
sPAP, mmHg	32.00 (30–33.75)	38.00 (35–40)	0.043*

* Mann–Whitney *U* test.

Abbreviations: RVDD – right ventricular diastolic dysfunction; LV left ventricle; RV – right ventricle; TDD-telediastolic diameter; TSD-telesystolic diameter; TDV-telediastolic volume; TSV – telesystolic volume; PW –posterior wall; RAVI – right atrium volume index; RVWT – right ventricular wall thickness; AT – acceleration time; sPAP – systolic pulmonary arterial pressure.

The same is true for the percentage of the predicted maximum heart rate that they achieved – 77.84% vs. 86.7%. The heart rate reserve respectively is below the normal values – median 56.97 (42.18–81.94) and statistically lower than that in patients without stress RVDD – median 79.06 (70.14–88.21).

Although none of the patients in the group studied demonstrated static hyperinflation, 64 (62%) showed DH. There is a predominance of hyperinflators – 69% among the patients with stress RVDD in comparison to those without – 32% (p – 0.049). In contrast, non-hyperinflators were the majority (68%) of the subjects without stress RVDD; (31%) of the patients with stress RVDD were also non-hyperinflators (p – 0.042) (Table 1).

According to the objective ATS/ACCP criteria, exercise was considered maximal in all patients. The majority of the patients 85 (82%) stopped exercise due to dyspnea. In patients with stress RVDD, dyspnea was the predominant limiting factor in 80 (98%) of the subjects. Exhausted breathing reserve, however, was detected in only 29 (35%) of them. Only 5 (23%) of the patients without stress RVDD complained of dyspnea. Exhausted breathing reserve was the limiting factor in 1 (5%) of them. Leg fatigue was the reason for exercise cessation in 19 (18%) of the patients. In those with stress RVDD leg fatigue was encountered in 2 (2%), while 17 (77%) of the patients without stress RVDD reported leg fatigue (Table 3).

The patients with stress RVDD achieved lower load, showed lower minute ventilation at peak load, lower oxygen pulse, lower peak 'VO2 and lower' VO2 on VAT in comparison to the subjects without stress RVDD group. The patients with stress RVDD demonstrated higher VE/VCO2 slope and lower PetCO2 (Table 3).

Table 3 Cardio-pulmonary exercise testing parameters at rest and at peak exercise of the patients with and w/o stress RVDD.

	Patients w/o stress RVDD (22)	Patients with stress RVDD(82)	*p*-Value
Cardio-vascular parameters			
HR at rest, bpm	75 (63–87)	82 (68–96)	0.261†
Peak HR, bpm	149 (142–156)	125 (107–143)	0.048†
HR max, %	86.7 (82.48–93.69)	77.84 (71.24–88.72)	0.014‡
Heart rate reserve use, %	79.06 (70.14–88.21)	56.97 (42.18–81.94)	0.984‡
Ventilatory parameters at rest			
FVC, l/min	2.05 (2.11–3.73)	2.21 (1.71–2.93)	0.491†
FVC%	64.5 (67.4–90)	71 (57–80)	0.311‡
FEV 1, l/min	1.60 (1.15–2.42)	1.52 (1.14–1.75)	0.207†
FEV%	66 (41.5–82)	54.96 (40.9–63)	0.407‡
FEV1/FVC %	65.50 (54.81–68.82)	62.59 (46.57–66.79)	0.218‡‡
IC, l	3.19 (3.02–4.43)	2.87 (2.40–3.32)	0.216†
TLC, l	7.48 (6.72–8.09)	6.14 (5.59–7.28)	0.187†
FRC, l	3.69 (3.62–3.86)	3.52 (3.11–4.59)	0.232†
RV, l	2.38 (2.33–2.89)	2.81 (1.82–3.39)	0.283†
IC/TLC, %	45.62 (41.08–52.88)	41.57 (38.89–47.31)	0.179‡
RV/TLC, %	97.89 (85.67–98.98)	112.56 (104–119)	0.037‡
Acid-base balance			
Ph	7.44 (7.42–7.46	7.43 (7.41–7.45	0.093†
O2, mmHg	67.20 (63.56–71.68)	70.6 (63.2–74)	0.126†
CO2, mmHg	34.73 (31.27–39.21)	35.7 (32.5–40)	0.811†
Sat, %	94.75 (92.67–95.0)	95.00 (93.9–95.5)	0.069‡
Ventilatory parameters at peak exercise			
V_t, l	2.28 (1.79–3.34)	1.79 (1.57–2.02)	0.212†
VE, l/min	41.1 (32.12–48.17)	39.07 (31.89–48.32)	0.025†
BR, %	33.89 (21.68–39.83)	27.94 (20.87–33.38)	0.643‡
EELV/TLC, %	53 (50–59)	61 (54–70)	0.067‡
ICdyn, l	0.13 (0.07–0.16)	0.25 (0.14–0.33)	0.046†
Acid-base balance at peak exercise			
pO2, mmHg	96.87 (95.42–97.43)	93.54 (83.45–96.59)	0.061†
pCO_2, mmHg	33.03 (29.51–35.18)	38.09 (36.27–40.26)	0.041†
CPET parameters			
Peak Load, W	86.66 (78.65–94.76)	73.08 (68.93–83.16)	0.039†
Peak VE, l/min	41.1 (32.12–48.17)	39.07 (31.89–48.32)	0.025†
Peak$V'O_2$, ml/kg/min	14.30 (12.6–16.15)	13.40 (15.77–12.55)	0.121†
RER	1.05 (0.98–1.18)	1.08 (1.01–1.19)	0.503†
PeakO_2 pulse ml/kg/min	9.51 (9.02–13.1)	7.92 (6.27–9.84)	0.027†
VE/VCO_2 slope	34.11 (33.78–36.89)	36.98 (34.26–38.91)	0.016†
Borg dyspnea score	4 (3–7)	4 (3–5)	0.621†
Borg leg discomfort score	4 (4–7)	4 (3–5)	0.098†

† Mann–Whitney *U* test.
‡ Chi square test.
§ *Abbreviations*: RVDD – right ventricular diastolic dysfunction; HR – heart rate; bpm – beats per minute; FEV1 – Forced Expiratory Flow in 1 s; FVC – Forced Vital capacity; IC – inspiratory capacity; TLC – total lung capacity; FRC – functional residual capacity; RV – residual volume; V_t – tidal volume; VE – minute ventilation; EELV – end expiratory lung volume; BR – breathing reserve; V'O2 – oxygen uptake; RER – respiratory exchange ratio.

Right heart structural abnormalities and stress RVDD

ROC analysis was performed in order to assess the predictive value of the right heart structural parameters that are usually measured in clinical practice and the stress induced RVDD (stress E/e' > 6). Results are shown in (Table 4). RAVI and RVWT seem to be the parameters that have the best sensitivity and specificity. A cut- off value of 20.55 ml/m^2 for RAVI may discriminate the patients with stress RVDD with a sensitivity of 86.36% and specificity 86.11%; E/A ratio at rest (cut-off 1.05) discriminates stress RVDD patients with sensitivity 79.7%; specificity 90.5%). RVWT of 5.25 mm is discriminative with a sensitivity 100% and specificity 63%. ROC curves are presented in Figs. 2–4.

Table 4 Receiver operating characteristic curve analysis using RV echocardiographic parameters at rest to identify subjects with an stress RV E/e' > 6.

	Area under the curve	95% CI	Cut-off value	Sensitivity	Specificity
RV basil diameter, mm	0.75	0.69–0.81	35.5	63%	71%
RVWT, mm	0.66	0.66–0.77	5.25	100%	63%
RAVI, ml/m^2	0.91	0.84–0.97	20.55	86.36%	86.11%
E/A ratio at rest	0.90	0.83–0.96	1.05	79.7%	90.5%
E/e' ratio at rest	0.64	0.52–0.75	5.10	74.7%	61.9%
TAPSE, mm	0.70	0.58–0.82	21.62	68%	61%
PASP, mmHg	0.66	0.55–0.78	18.78	55%	81%
AT, ms	0.65	0.54–0.76	145	50%	75%

Abbreviations: RVDD – right ventricular diastolic dysfunction; RAVI – right atrium volume index; RVWT – right ventricle wall thickness; AT – acceleration time; PASP –pilmonary arterial systolic pressure; AT – acceleration time; TAPSE – tricuspidal annular plane systolic excursion.

Table 5 Logistic regression analysis between ventilatory and echocardiographic parameters and stress RV E/e'.

Univariable regression analysis	*p*-Value	OR	95% CI
Ventilatory parameters			
Packet-years	0.63	1.18	0.78–3.51
FEV1, l	0.78	2.01	0.86–3.87
Goddard score	0.03	1.06	0.63–3.24
ICdyn, l	0.04	5.29	2.68–9.18
RV/TLC, %	**0.301**	**0.921**	**0.689–1.223**
LV parameters			
Septum, mm	0.67	1.98	1.62–2.86
LVPWT, mm	0.81	2.17	1.93–4.49
E/A ratio at rest	0.94	0.99	0.80–1.23
E/e' ratio at rest	0.99	1.89	1.59–1.99
E/A ratio after stress	0.04	1.54	1.00–2.35
E/e' ratio after stress	0.00	4.07	1.75–12.47
RV parameters			
RV basilar diameter, mm	0.00	1.48	1.23–1.78
Rvmedian diameter, mm	0.00	1.83	1.38–2.48
RVWT, mm	0.74	0.98	0.78–1.02
RAVI, ml/m^2	0.00	3.82	2.04–7.14
E/A ratio at rest	0.00	19.73	18.52–21.01
E/e' ratio >5.1 at rest	0.03	4.79	1.73–13.24
TAPSE, mm	0.37	21.56	1.20–38.91
S peak velocity, m/s	0.33	0.73	0.55–0.97
PASP, mmHg	0.12	0.70	0.07–75.08
AT, ms	0.49	2.39	0.20–28.67
Multivariable regression analysis			
E/e' ratio >5.1 at rest	0.02	9.03	1.32–63.73
RAVI, ml/m^2	0.00	2.27	1.40–3.68

Abbreviations: FEV1 – Forced Expiratory Volume in 1 s; ICdyn – dynamic hyperinflatio; RVDD – right ventricular diastolic dysfunction; LV left ventricle; RV – right ventricle; LVPWT – left ventricular posterior wall thickness; RVWT – right ventricular wall thickness; RAVI – right atrium volume index; AT – acceleration time; PASP –pulmonary arterial systolic pressure; AT – acceleration time; TAPSE – tricuspidal annular plane systolic excursion.

To assesss the association between LV structural (septum and posterior wall thickness) and functional parameters (LV E/A, LV E/e' at rest; LV E/A, LV E/e' after stress) and stress induced RVDD, univariate regression analysis was performed (Table 5). This was also performed with the RV structural parameters and their selected cut-off values. From all the variables only the cut-off value of rest RV E/e' > 5.1 is statistically significant and clinically applicable with the odd ratio for stress-RVDD – 4.79; (95% CI – 1.73–13.24). If we apply univariate regression analysis with the echocardiographic measurements as quantitative parameters the RV basilar and median diameter, RAVI, rest RV E/e' ratio, stress

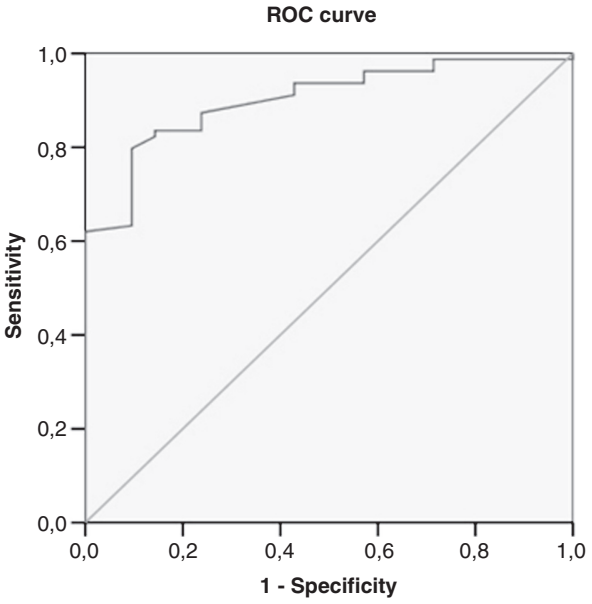

Figure 2

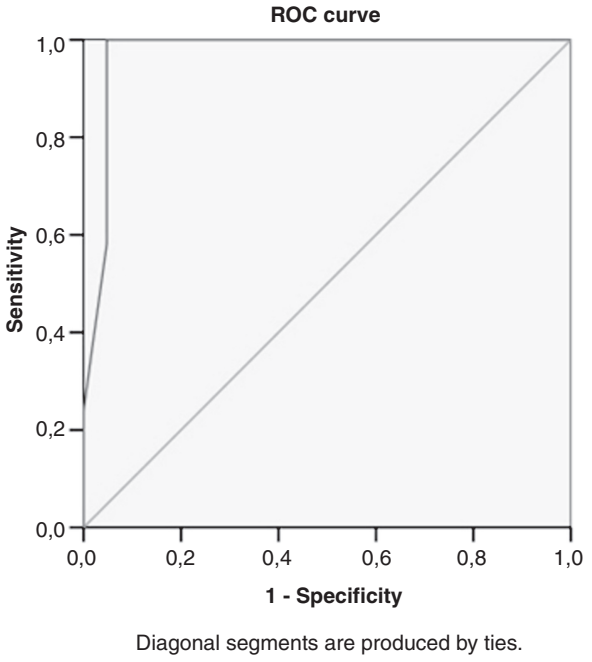

Figure 3

LV E/A, stress LV E/e', may be used as predictors (Table 5). The RV E/A ratio showed the highest odds ratio 19.73; (95% CI – 18.52–21.01); followed by RAVI – odds ratio 3.82; (95% CI – 2.04 –7.14). In multivariate regression analysis with a forward step approach RAVI and rest RV E/e' > 5.1 remained independent predictors for stress-RVDD. The combination of these two variables predicts stress-RVDD with the accuracy of 92%. This association was independent of LV diastolic dysfunction (LV E/A at rest; LV E/e' at rest; stress LV E/A; stress LV E/e'), lung function (FEV1), ICdyn, Goddard score, age, sex, and BMI, taken as covariates.

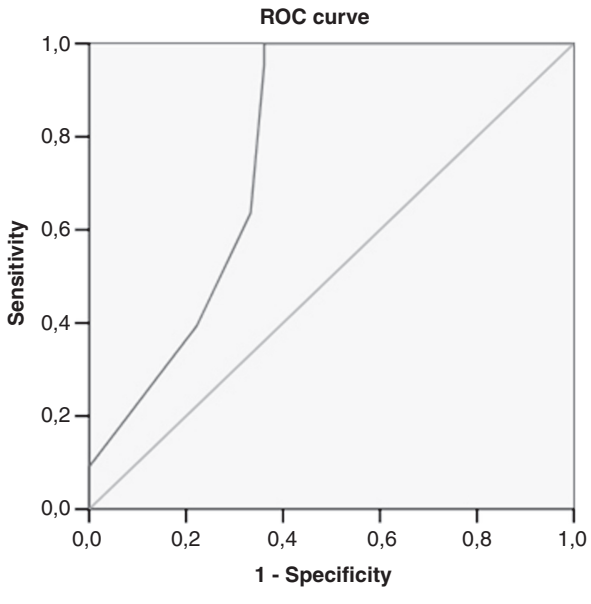

Figure 4

Correlations between 6-min walk distance and echocardiographic parameters

COPD patients with stress-RVDD achieved lower walking distance during the 6MWT. We applied univariate regression analysis between LV and RV echocardiographic parameters at rest and the 6MWT (Table 6). In univariable analysis the structural parameters of the RV were associated with the 6MWT. A 1 mm change in RVWT was associated with a 22.7 m decline in the 6MWT (b = −22.7 m; $p = 0.038$); RAVI (b = −27.9 m; $p = 0.012$). The RV functional parameters at rest (TAPSE, S-peak velocity, PASP, AT, RV E/e' ratio), LV structural and LV functional echocardiographic parameters at rest were not associated with the 6MWT. In contrast, stress induced LVDD (stress LV E/e') and stress induced RVDD (stress RV E/e') correlated to the walking distance (Table 6). A unit change in LV E/e' was associated with a 23.4 m decline in the 6MWT (b = −23.4 m; $p = 0.017$); A unit change in RV E/e' was associated with a 28.3meter decline in the 6MWT (b = −28.3m; $p = 0.031$).

In multivariate analysis with covariates LV diastolic dysfunction (LV E/A at rest; LV E/e' at rest; stress LV E/A; stress LV E/e'), lung function (FEV1), ICdyn, Goddard score, age, sex, and BMI, only RAVI, RWT, stress RV E/e', stress LV E/e' remained independent predictors of 6MWT (Table 6).

In multivariable analysis a 1 mm change of RVWT was associated with a 11.3 m decline in the 6MWT (b = −11.3 m; $p = 0.021$). This association was independent of LV diastolic dysfunction (LV E/A at rest; LV E/e' at rest; stress LV E/A; stress LV E/e'), lung function (FEV1), ICdyn, Goddard score, age, sex, and BMI, taken as covariates. The same is observed regarding RAVI (b = −12.8 m; $p = 0.017$) – a 1 ml/m^2 increase of RAVI was associated with a 12.8 m decline in the 6MWT (Table 6).

Table 6 Association between echocardiographic parameters and 6MWT.

	Univariable linear regression analysis		Multivariable linear regression analysis	
	β	*p*-Value	–	*p*-Value
RV structural parameters				
RV basilar diameter,mm	3.17	0.617		
RVWT, mm	−22.7	−0.038	−11.3	−0.021
RAVI, ml/m^2	−27.9	−0.012	12.8	0.017
RV functional parameters at rest				
E/e'	4.12	0.811		
TAPSE, mm	22.18	0.062		
S peak velocity, m/s	20.61	0.083		
PASP, mmHg	2.18	0.067		
AT, msec	1.97	0.093		
RV functional parameters after stress				
E/e' aver ratio	−28.3	0.031	−17.6	0.039
LV structural parameters				
TDV, ml	2.21	0.067		
TSV, ml	2.49	0.074		
Septum, mm	1.21	0.091		
PW, mm	1.83	0.089		
LV functional parameters at rest				
LVEF, %, Simpson	31.14	0.801		
E/e' aver ratio	5.71	0.074		
LV functional parameters after stress				
E/e'	−23.4	0.017	−16.8	0.042

Abbreviations: RVDD – right ventricular diastolic dysfunction; LV left ventricle; LVPW –left; RV – right ventricle; RVWT – right ventricular wall thickness; RAVI – right atrium volume index; PASP –pulmonary arterial systolic pressure; AT – acceleration time; TAPSE – tricuspidal annular plane systolic excursion; TSV – telesystolic volume; TDV – telediastolic volume; PW – posterior wall.

Discussion

In this study we prove that: (1) 78% of our patients showed stress induced RVDD, while 14% of them had RVDD at rest; (2) patients with stress RVDD demonstrated a higher prevalence of dynamic hyperinflation ICdyn (69%) and moderate (Goddard II) emphysema (69%); (3) patients with stress RVDD performed with worse sub-maximal exercise capacity (6-MWT), they achieved lower load, lower peak 'VO2, O2 pulse, higher VE/'VCO2 slope and lower PetCO2 during CPET; (4) in non-severe COPD patients RAVI and rest RV E/e' ratio > 5.1 are independent predictors for stress RVDD; (5) in non-severe COPD patients with stress RVDD, RAVI and RVWT are independent predictors for diminished exercise capacity (6-MWT).

COPD is a condition of augmented vessel vulnerability and arterial stiffness, which do not correspond to the smoking burden and pack-years. Arterial stiffness triggers myocardial fibrosis even without overt cardiovascular disease.[30–32] Intrathoracic pressure oscillations during breathing provoke additional wall stress to the heart of COPD patients, which may be the sole trigger for both right and left chamber diastolic remodeling.[33,34]

Although cor pulmonale is classically assumed as the major cardio-vascular manifestation of COPD, subclinical abnormalities may be found even in mild form of the disease.[35,36] MRI studies claim that even invasive PAP measurement delays the diagnosis of lung vascular pathology in the general population.[14,15,37] This is also confirmed in COPD patients.[38] Hilde et al., have investigated ninety-eight subjects by right heart catheterisation at rest and during exercise. Hemodynamic effort changes in the pulmonary circulation have revealed abnormal physiological responses in the majority of COPD patients.[38]

We support this, demonstrating that exercise exertion in non-severe COPD patients without pulmonary arterial hypertension at rest facilitates the detection of right ventricular-arterial decoupling. After symptom limited incremental stress protocol, 78% of our patients show signs of RVDD. Patients with stress RVDD have RV hypertrophy and larger RAVI, compared to those without. None of these structural parameters, correlated to the values of mPAP at rest which is routinely accepted as the clinical parameter associated with RV pathology. The data presented by Cuttica and Hilde et al.[39,40] is similar; they revealed that RV hypertrophy, dilation and systolic dysfunction, are present even with a slight increase of mPAP (18 ± 3 mm Hg).[39] Cuttica et al., detect increased RV wall thickness and right atrial area in non-severe COPD with slightly elevated sPAP (mean sPAP 44.16 ± 16.1 mmHg).[40]

In our study, RAVI is also significantly lower in COPD subjects without RVDD in comparison to COPD patients with

RVDD. Such findings have been observed in animal models and later validated in patients with respiratory diseases.[41–43] Sallach et al., have also reported that RAVI has been related more to E/A ratio, rather than to the elevated E/e' ratio.[44] In contrast, Agoston Coldea et al., have not detected an association with E/A ratio, but a weak relation between RAVI and E/e' has been established.[45] The different results are probably attributed to the different stages of COPD, where different degrees of diastolic dysfunction develop. The conditions under which RVDD is found (stress echocardiography or echocardiography at rest) could also be a possible explanation of the discrepancy.

The link between RVDD and COPD is complex and probably evolves as a result of various mechanisms – mechanical/functional (deterioration in FEV1, emphysema, hyperinflation),[10–12] biological (systemic inflammation, hypoxemia, endothelial dysfunction)[46] and neurohumoral (excess sympathetic nerve activity).[47]

The pathophysiological consequences of diastolic dysfunction are associated with abnormalities of RV diastolic compliance and relaxation. They limit the RV filling and aerobic capacity regardless of the RV function.[48] This is of special clinical importance in COPD, where stress RVDD may remain hidden under the umbrella of COPD associated exertional dyspnea. However, only 35% of our COPD patients with stress RVDD demonstrate exhausted breathing reserve. Thus, in non-severe COPD stress RVDD may itself contribute to exertional dyspnea and diminished physical activity, which is demonstrated by our results. The COPD patients with stress RVDD achieved lower load during cardio-pulmonary exercise testing; performed with lower peak VO2, lower oxygen pulse and higher VE/VCO2 slope. They demonstrated a higher PetCO2 and lower peak HR and diminished heart rate reserve in comparison to those without.

RVDD may not only limit aerobic capacity, but also correlate to COPD exacerbation rate. The frequency of exacerbations before or after the study were not in the scope of our study, however, the more common use of ICS in the stress RVDD subjects, leads us to assume that exacerbations are more likely in RVDD/COPD patients. According to the study protocol no change in therapy during or three months before the study have been undertaken, which also supports our assumption. Though no causality could be stated, it is possible to hypothesize that like pulmonary hypertension, pulmonary vasculopathy and RVDD may be independent factors for COPD exacerbation and progression.[49]

Augmented vessel vulnerability and arterial stiffness in COPD has recently been reported as independent phenomenon which does not correspond to smoking burden and pack-years.[46] We confirm this, reporting an even higher incidence of former and never smokers among the stress RVDD group. The data, regarding the link between emphysema, dynamic hyperinflation, smoking status and cor pulmonale is similar. Emphysema and DH have been correlated with diminished end-diastolic RV dimensions and RV output, independent from the smoking status (former, current or never smoker).[10–12] Emphysema and hyperinflation act synergistically, especially during exercise (dynamic hyperinflation) – predisposing to RV diastolic dysfunction – reducing the venous return, impairing RV filling and decreasing the RV dimensions – ''cor pulmonale parvus''.[10–12] In our study, however, neither emphysema (Goddard score), nor DH corresponded independently to worse RV compliance and relaxation (stress RV E/e' >6) during load. In univariate analysis they were predictors for stress RVDD, but after adjustments both parameters lost significance. Despite the statistically significant difference in RV/TLC ratio between stress/no stress RVDD subjects, it did not correlate to stress RV E/e' in univariate analysis. Moreover, under static conditions none of our patients demonstrated real hyperinflation. Thus, bodyplethysmography and static lung volumes are insufficient for the assessment of the complex lung-heart interreaction during exercise.

It is worth noting that in our modeate COPD patients no static hyperinflagion may be observed. Our statement refers to the cardio-vascular impact of moderate emphysema (Goddard II is predominant – 69% of the subjects) and DH in mild-to-moderate COPD, where these ventilatory abnormalities may not be accompanied by such significant intra-thoracic pressure changes and their direct hemodynamic and mechanistic consequences on the cardio-vascular performance may not be as profound as in moderate-to-severe COPD stages.[10–12] Moreover, not all studies have been consistent regarding the link between dynamic hyperinflation and worse cardiac performance during exercise.[50] It is suggested that the decline in cardiac output more closely parallels alterations of intra-thoracic pressure rather than the changes in lung volume.[51] Thus, it is reasonable to assume that the pathophysiological mechanisms, responsible for cardiac performance during exercise are multi-dimensional and cannot be limited to a single factor.

The subjects in our study had preserved left ventricular systolic function, so it is clear that the right heart structural changes we detected are independent of LV systolic function. As no right heart catheterization was performed, it is difficult to differentiate changes related to LV diastolic dysfunction from primary pulmonary vascular disease.

The functional impact of pulmonary vascular pathology in COPD, however, appears to be independent of the distinction between pulmonary vascular disease and pulmonary venous hypertension, related to left diastolic heart failure. The mean pulmonary artery pressure in both cases, has been associated with a lower 6-MWT, independent of the left heart filling pressures. Furthermore, both primary pulmonary vascular disease and pulmonary venous hypertension due to left diastolic heart dysfunction had negative impact on transplanted patients, compared to subjects with normal pulmonary hemodynamics.[52]

Last but not least, the detection of RVDD is of clinical importance because it may be an independent factor for limited physical activity in the general population and in COPD, in particular.[8,36] Due to the different COPD groups and diagnostic approaches, diverse results of the role of RV structural and echocardiographic parameters on physical capacity have been reported. Cuttica et al., have found a correlation between RVWT, right atrial area and diminished 6 MWT, independent from the lung function.[39] Speckle-tracking analysis assumes tricuspid regurgitation as the only predictor of exercise tolerance.[35] In contrast, Gokdenis et al., state that RVFW-S is the only marker responsible for 6 MWT.[34]

Our subjects with RVDD achieved shorter 6MWT. None of the LV structural or functional parameters at rest was associated with the 6MWT. The same is observed regarding the RV functional parameters at rest (PASP, TAPSE, S-peak velocity, AT). In contrast, RAVI, RVWT, stress RV E/e', stress LV E/e' were associated with the 6MWT.

Despite being performed under stress conditions our findings correspond to the results of Fenster et al., who performed a study in 51 moderate-to-severe COPD patients (mean FEV1 < 50%). Authors demonstrated that in more advanced stages of COPD, RVDD at rest, may be a factor for decremented physical activity, independent from LVDD at rest, age, sex, BMI or FEV1.[53] The data reported by us is also similar to the findings of Cuttica et al. They analyzed 74 non-severe COPD patients (FEV1 > 65%). Authors did not perform stress echocardiography and did not analyze RV or LV diastolic parameters at rest. They state that RV structural parameters (RVWT and RAVI), suggestive of RV diastolic dysfunction, are independent predictors for 6MWT, irrespective of age, sex, BMI and FEV1.[39]

According to our study even in the absence of PH at rest, COPD patients may perform with worse exercise capacity due to underlying pulmonary vasculopathy, which may remain undiagnosed and untreated for a long time. Hypoxia, inflammation, microvascular ischemia, and obesity may the triggers for this.[54,55] Thus, stress RVDD may develop as a consequence of COPD even in the absence of clinically manifested COPD-related pulmonary vascular disease. Non-severe COPD patients with normal PAP at rest probably experience excessive hemodynamic PAP changes during exertion. This may gradually result in RV structural changes that may be more sensitive indicators for exercise pulmonary hemodynamic abnormalities. The early identification of stress-RVDD may help with the diagnosis of a specific COPD phenotype which is associated with reduced exercise capacity. This is consistent with prior reports of PH in advanced COPD having distinct prognosis. The detection of functional abnormalities responsible for patient centered outcomes may lead to novel therapeutic targets that impact a specific disease phenotype.

Study limitations

The main limitations of this study are: (1) the relatively small sample size; (2) coronary artery disease may not be excluded as neither invasive (coronary angiography), nor sophisticated imaging modalities (exercise single photon emission computed tomography (SPECT) – myocardial perfusion imaging (MPI)) were performed; (3) COPD patients experience enhanced pressure swings during the respiratory cycle and measurements were performed at the end of expiration, which may influence the results; (4) we do not have invasive measurement of sPAP; (5) measurements were acquired in the early recovery period (approximately 2 min) after symptom-limited exercise. The timeline of changes of the pulmonary and intrathoracic pressures during the brief time interval from peak exercise to their measurement in early recovery is not well known and underestimation is possible; (6) the cross-sectional design does not establish causality.

Conclusion

In conclusion, we demonstrate that in non-severe COPD patients a high prevalence of stress induced RVDD is detected. RAVI and rest RV E/e' > 5.1 are the best predictors for stress E/e' > 6; RAVI and RVWT are associated with decrements in exercise capacity. The early diagnosis and proper management of subclinical RVDD may be a step forward in the prevention of the cardio-vascular complications in non-severe COPD patients.

Ethical approval

Ethics approval for the study protocol was received from the Ethics Committee of the Medical University, Sofia protocol 5/12.03.2018.

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The investigation was performed in Medical University, Sofia; University Hospital ''Saint Sophia'', First Therapeutic Clinic.

Authors' contributions

The design of the study was proposed by all authors. All authors have equally contributed to the recruitment and selection of patients. R. Cherneva performed the spirometry and the cardio-pulmonary exercise testing and Zh. Cherneva – echocardiography at rest and at peak stress. All authors have equally contributed to analysis of the data and writing of the manuscript. There was no funding.

Conflicts of interest

The authors have no conflicts of interest to declare.

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Appendix A. Supplementary data

Supplementary material associated with this article can be found in the online version available at doi:10.1016/j.pulmoe.2020.06.005.

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ORIGINAL ARTICLE

Small airways' function in Obstructive Sleep Apnea-Hypopnea Syndrome*

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KEYWORDS
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Abstract
Introduction and objectives: Most of the studies of the pathophysiology of Obstructive Sleep Apnea-Hypopnea Syndrome (OSAHS) focus on the collapsibility and obstruction of the upper airways. The aim of our study was the investigation of small airways' function in patients with OSAHS.
Materials and methods: We studied 23 patients (mean age, 51.6 years) diagnosed with mild to severe OSAHS, without comorbidities and 8 controls (mean age, 45.9 years). All subjects underwent full polysomnography sleep study; spirometry and maximum flow/volume curves while breathing room air and a mixture of 80%He-20%O_2. The volume of equal flows (VisoV) of the two curves and the difference of flows at 50% of FVC ($\Delta\dot{V}max_{50}$) were calculated, as indicates of small airways' function.
Results: The results showed that VisoV was significantly increased in patients with OSAHS compared with controls (18.79 ± 9.39 vs. 4.72 ± 4.68, $p = 0.004$). No statistically significantly difference was found in $\Delta\dot{V}_{max\,50\%}$ ($p = 0.551$); or the maximum Expiratory flow at 25–75% of FVC ($p = 0.067$) and the maximum expiratory flow at 50% of FVC ($p = 0.174$) breathing air.
Conclusions: We conclude that at the time of the diagnosis of OSAHS, the function of the small airways is affected. This could be due to breathing at low lung volumes and the cyclic closure/opening of the small airways and may affect the natural history of OSAHS. The findings could lead to new therapeutic implications, targeting directly the small airways.

* Preliminary results of this study have been previously reported, as an abstract, at the ERS International Congress 2017 Eur Resp J 2017 50: PA2309.

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Introduction

Sleep is a complex, active and in many ways a different condition from alertness. During sleep, the control of breathing is subject to an altered regulation. In addition, the mechanics of breathing change, the resistance of the upper airways increases and the functional residual capacity decreases. This reduction in lung volumes leads to an increased tendency towards upper airway obstruction and contributes to the reduction of flow during inhalation, although the exact mechanisms of these findings have not been described in detail.[1,2]

The most common sleep disorder-OSAHS-has been studied and reviewed extensively.[3,4] Among the important physiological traits causing OSAHS are: (1) pharyngeal anatomy/collapsibility, (2) ventilatory control system gain (loop gain), (3) the ability of the upper airway to dilate/stiffen in response to an increase in ventilator drive, and (4) arousal threshold.[4] Although, large and small airways are part of the same anatomical compartment of the lungs, the studies of the pathophysiology of OSAHS have focused primarily on the function of the upper airways.

The aim of our study is to investigate the function of small airways in patients with OSAHS, and to compare it with healthy controls.

To the best of our knowledge, this is the first investigation of the small airways in OSAHS showing that their function is affected.

Materials and methods

Subjects

23 subjects (13 males, 10 females; mean age, 51.6 years) with a diagnosis of mild to severe OSAHS, without comorbidities and 8 controls (3 males, 5 females; mean age, 45.9 years) (Table 1) were included in the study. Patients and controls were recruited at the Sleep Disorders Center of the Medical School of University of Crete from June 2013 to July 2014, complaining of sleep-related symptoms.

Subjects having any of the following were excluded from the study:

(1) Severe obesity (Body Mass Index (BMI) >40 kg/m^2), (2) Current smokers or ex-smokers >30 pys, (3) Patients with concomitant pulmonary disease (e.g. Chronic Obstructive Pulmonary Disease (COPD), asthma, interstitial lung disease, active pulmonary tuberculosis, (4) Patients previously diagnosed with sleep-related disorder, (5) Patients who have clinically significant renal, cardiovascular, neurological, endocrine, immunological, psychiatric, gastrointestinal, hepatic, or hematological abnormalities, (6) Pregnancy.

Protocol

1. Physical examination was performed and medical history was taken, including sleep disorders symptoms. The daytime somnolence was evaluated with the Epworth scale and measurements of: Weight (kg) and Height (m) were performed. The BMI (kg/m^2) was calculated, and the neck circumference (cm) was measured at the height of the cricothyroid cartilage.
2. Patients and control subjects underwent polysomnographic sleep study where the following parameters were recorded: Electroencephalography, Electrooculogram, Electromyography in submental muscle and anterior tibia muscles bilaterally, Electrocardiogram, microphone should be placed over the trachea or on the side of the neck (from AAST), the detection of air flow with oral-nasal thermistor and pressure transducer, oxyhemoglobin saturation by finger pulse oximeter, the movement of thoracic and abdominal wall with special elastic belts of thorax and abdomen for the recording of the respiratory effort and body position.

   The diagnosis of OSAHS was established when the Apnea-Hypopnea Index (AHI) $\geq$5 and its severity was distinguished as:
   - Mild: $5 \leq AHI < 15$
   - Moderate: $15 \leq AHI < 30$
   - Severe: $AHI \geq 30$
3. Patients and controls underwent spirometry, according to the ERS/ATS guidelines, in sitting and supine position.

Assessment of small airways

The small airways' function was assessed using the Helium-Oxygen flow–volume method. The subject was seated and instructed to perform maximal expiratory flow-volume curves while breathing room air or a mixture of 80% He and 20% O2. Flow-volume curves while breathing He-O2 were measured after the subject had breathed in at least three Vital Capacity (VC) inspirations of the He-O2 mixture (heliox). The two curves obtained from breathing room air and the He-O2 mixture, were superimposed visually from Total Lung Capacity (TLC). A difference of less than 5% in FVC between breathing room and the He-O2 mixture was considered acceptable (the mean of our data was <3%). When the $\dot{V} - V$ curves did not have identical FVC, they were superimposed from Residual Volume (RV)[5,6] (Fig. 1). The volume at which the flow became identical was defined as $\dot{V}isoV$. The VisoV was expressed as a percentage of the Forced Vital Capacity (FVC), according to the method of Dosman and colleagues[6] (Fig. 1). The value of $\Delta\dot{V}max50$ was calculated from the equation $\Delta\dot{V}max50 = (\dot{V}Emax50He - \dot{V}Emax50air/\dot{V}Emax50air) \times 100$, and expressed as a percentage of $\dot{V}Emax50$ while breathing room air.[6]

Statistical analysis

Descriptive analysis of the participants' characteristics was conducted. The normality assumption of the continuous variables was assessed via the One Sample Kolmogorov – Smirnov Test and through graphical inspection. Continuous variables are presented as mean $\pm$ standard deviation (SD) or as median and 25th–75th percentiles. Differences between continuous variables were assessed via the independent samples *T*-test and the independent Mann–Whitney *U* Test where appropriate. Differences between categorical variables were assessed via the Fisher's exact test. Linear regression analysis was used on the association of

Table 1 Characteristics of patients and controls subjects.

	Patients ($n=23$)	Controls ($n=8$)	p-Value
Sex			0.433
Male	13 (56.5)	3 (37.5)	
Female	10 (43.5)	5 (62.5)	
Age	51.6 ± 12.7	45.9 ± 15.5	0.310
Smoking			0.676
Ex-smokers	9 (39.1)	2 (25.0)	
Nonsmokers	14 (60.9)	6 (75.0)	
ESS	10.8 ± 5.5	5.6 ± 3.4	0.020
BMI (kg/m^2)	31.6 ± 5.7	24.6 ± 3.4	0.003
Neck circumference(cm)	40.0 ± 3.4	36.5 ± 5.0	0.036
Mild OSAHS ($5 \leq AHI < 15$)	5 (21.7)		
Moderate OSHAS ($15 \leq AHI < 30$)	10 (43.5)		
Severe OSHAS ($AHI \geq 30$)	8 (34.8)		
FEV_1 (L/min)	93.2 ± 13.7	104.8 ± 11.3	0.070
FVC (L/min)	97.9 ± 15.6	106.0 ± 14.1	0.262
FEV_1/FVC	79.7 ± 5.2	84.2 ± 3.9	0.062

AHI: Apnea-Hypopnea Index, ESS: Epworth Sleepiness Scale, BMI: Body Mass Index.

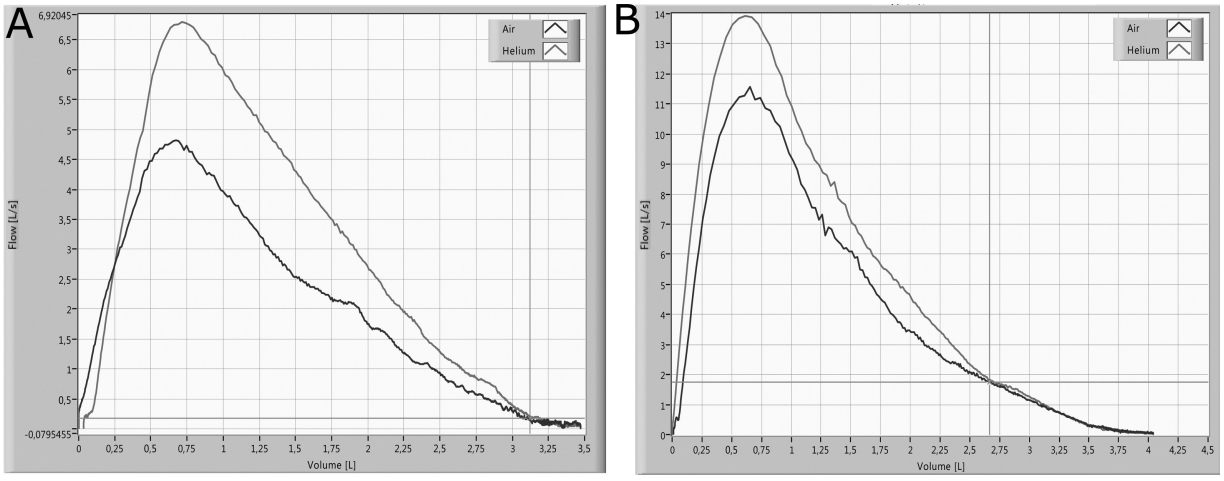

Figure 1 A. Forced expiratory flow-volume curves on breathing air (blue curve) and the mixture 80% He and 20% O2 (red curve) in a control subject. B. Same as A of a typical OSAHS patient.
Green lines show the point at where the two curves coincide (Visoٷ).

OSAHS with ٷisoV, adjusted for BMI. Wilcoxon matched-pairs signed-ranked test was used for comparison between sitting and supine posture. For all tests, a p-value < 0.05 was considered statistically significant. All statistical tests were performed using the SPSS 22.0 (IBM Corporation, Illinois, US) and Stata 13.0 (StataCorp, College Station, TX, US).

Results

Demographic data, smoking habits, pulmonary function tests (PFTs), and sleep related parameters of the patients and control subjects, are shown in Table 1.

Statistically significant differences between patient and controls, were found regarding BMI, Epworth Sleepiness Scale (ESS) and neck circumference (p-value < 0.05).

The parameters of small airways' function are shown on Table 2.

Table 2 Parameters of small airways' function in patients and control subjects in sitting position.

	Patients ($n=23$)	Controls ($n=8$)	p-Value
$MMEF_{25-75}$	77.5 ± 25.5	100.8 ± 16.3	0.067
MEF_{50}	86.3 ± 28.1	103.8 ± 21.0	0.174
Visoٷ(%)	18.8 ± 9.4	4.7 ± 4.7	0.004
[a] $\Delta\dot{V}_{max\,50}\%$	26.2 (9.1, 55.6)	37.2 (29.5, 41.8)	0.551

[a] Values are presented as Median (25th, 75th percentile).

The mean values of the basic parameters of small airways' function (Visoٷ% and DٷmaxV50% in patients and controls are shown in Fig. 2. Visoٷ was statistically significantly increased in patients with OSAHS compared to controls (18.79 ± 9.39 vs. 4.72 ± 4.68, $p = 0.004$). OSAHS was significantly associated with higher Visoٷ [beta (95%

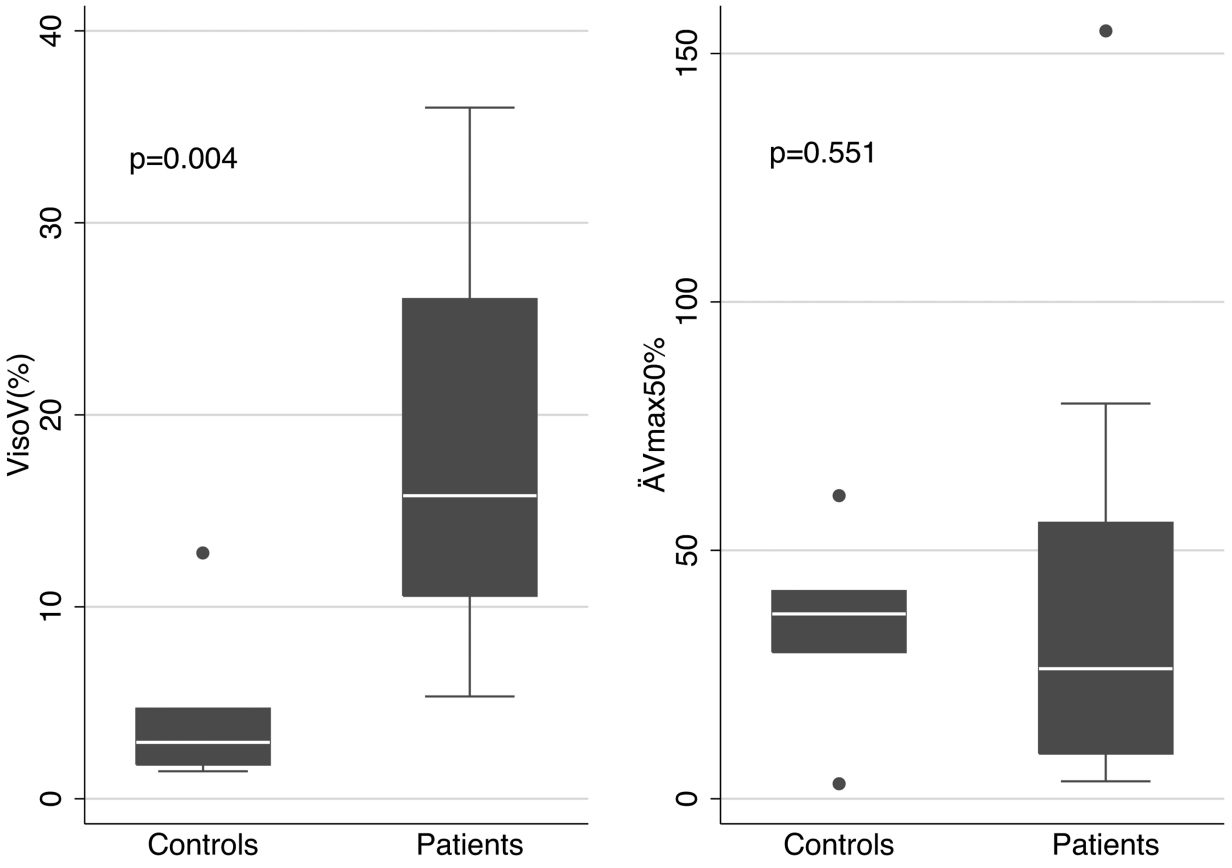

Figure 2 Mean values (±SD) of VisoṼ% and $\Delta\dot{V}$ max 50% in control subjects and in patients with OSAHS.

Table 3 Pulmonary function tests in sitting and supine position, in patients.

	Sitting position	Supine position	*p*-Value
FEV_1 (L/min)	92.5 (87.0, 101.0)	85.5 (74.0, 98.0)	0.0021
FVC (L/min)	95.0 (91.0, 109.0)	91.0 (79.0, 99.0)	0.004
FEV_1/FVC	80.0 (78.5, 81.7)	78.6 (71.7, 83.3)	0.004
$MMEF_{25-75}$	74.0 (58.0, 98.7)	63.5 (50.0, 82.0)	0.0039
MEF_{50}	86.0 (64.0, 108.0)	86.5 (58.0, 91.0)	0.0157

Wilcoxon matched-pairs signed-ranked test.

CI) = 12.118 (1.51, 22.73)], independently of BMI. No statistically significantly relationship was found between VisoṼ and ESS or neck circumference in OSAHS patients.

$\Delta\dot{V}_{max\,50}$% was not statistically significantly different {26.2 (9.1, 55.6) vs. 37.2 (29.5, 41.8), $p = 0.551$}, although a trend to decrease was seen in patients.

Non-significant differences in the mean values of FVC, Forced Expiratory Volume in 1 s (FEV_1), FEV_1/FVC, Maximal (mid-) Expiratory Flow at 25–75% of FVC ($MMEF_{25-75}$) and Maximal (mid-) Expiratory Flow at 50% of FVC ($MMEF_{50}$) were found between patients with OSAHS and the controls in sitting position (Tables 1 and 2).

In patients with OSAHS, the mean values of pulmonary function tests in supine position had significantly decreased statistically from their values in sitting position (Table 3).

Discussion

Small airways are the peripheral membranous bronchioles, 2 mm less in diameter. They make up a very large area which is difficult to approach functionally, clinically and therapeutically.[7,8]

The main finding of the present study is that small airways' function is affected in OSAHS, as the VisoṼ increases, despite normal baseline spirometric values. These findings, to the best of our knowledge, are reported for the first time.

The pathogenesis of OSAHS is multifactorial; anatomical and functional changes of the upper airway and its musculature result in partial or complete and recurrent obstructions of the upper airway during sleep. Anatomical changes contribute to the reduction of the diameter of the upper airway while the functional changes to the increased collapsibility and susceptibility to obstruction and these changes may interact, i.e., the structural changes affect the functional ones and vice versa.[9]

It is well known, that during sleep the pattern of breathing is variable and that sleep stages significantly affect this pattern.[10] In addition, in OSAHS it is reported that lung volumes may continuously vary during NREM sleep and this may contribute to passive collapse of the upper airways.[11] However, during sleep, the common finding is the reduction of FRC or the End Expiratory Lung Volume (EELV), even if it fluctuates. Breathing at low lung volumes results in reduction of the elastic restoring force of the lungs

(elastic recoil) and reduces radial traction exerted by the lung parenchyma on the airways to keep them open with reduced flow resistances.[12] This occurs even in normal sleeping subjects and may be enhanced abnormally in sleeping disorders.[1]

Additionally, in obese subjects with OSAHS, it has been shown that reduced pulmonary volumes, secondarily lead to narrowing and obstruction of the upper airways.[13] Jordan et al showed that when genioglossus muscle fails to stabilize breathing in OSAHS, this may be related to reduced lung volume.[14]

Therefore, the majority of the pathophysiological studies have focused on the collapsibility of the upper airways.

In contrast, our study found an affected function at the site of the small airways. We speculate that this could be due to opening and closure of the small airways caused by the abrupt changes in the airway pressure at low lung volumes. It is well known, that during the obstruction of the upper airways the airway pressure increases in order to reopen the collapsed site and to initiate inspiratory flow. When this has been achieved, a significant and abrupt drop in the airway pressure is seen. These changes in airway pressure are transmitted into the whole respiratory system and may cause collapsibility and flapping at the site of the membranous small airways. In support of this argument there are studies in animals showing that ventilation at low lung volumes leads to an abnormal successive opening and closure of small airways.[15] Such periodic continuous occlusion and opening, creates conditions for inflammation and oxidative stress in the regions of the final bronchioles and alveolar sacks, which means destruction of lung parenchyma.[15]

In 2002, D'Angelo E, Milic-Emili J et al, reported that small-volume ventilation causes peripheral airway injury and increases airway resistance in normal rabbits and this is probably due to cyclic opening and closing of the peripheral airways.[16]

In addition, Yalcin HC et al, in an in vitro model of airway reopening showed significant epithelial cell injury.[17] Moreover, Zerah-Lancner et al, found a significant decrease in the FEV_1/FVC ratio, in the V_{50} and V_{25}, as the severity of OSAHS increases, in 170 patients undergoing a sleep study.[18]

Baydur et al, showed expiratory flow limitation in COPD and OSAHS patients, but their results could not distinguish the two cohorts.[19]

Finally, in agreement with our results are those of Abdeyrim et al and Cai et al who used the impulse oscillation technique to show that the peripheral airway resistance increased in obese OSAS patients.[20,21] Moreover, Abdeyrim et al showed that Reactance at 5 Hz correlated with peripheral airway resistance and with the decreased FRC.[20]

In addition, Avraam et al reported that reductions in FVC while supine and with increased body weight may contribute to worsening of OSAHS.[22]

In accordance with these studies, our results show a significant decrease in patient pulmonary function values in supine position from the sitting, (Table 3) which strengthens our argument that breathing at low lung volumes may affect negatively small airways function.

Moreover, Heinzer et al showed that the increase in pulmonary volumes reduces sleep disturbances and improves sleep architecture in patients with OSAHS during non-REM sleep.[23]

Review and critique of the method

In 1974, Hutheon et al introduced the volume of isoflow as a new test for the detection of small-airway dysfunction.[24] During the terminal 10% to 15% of VC, the flow rates during helium-oxygen and air breathing are identical; this is the volume of isoflow point.[25] The isoflow phenomenon is seen because flow in the small airways is laminar and so independent of gas density.[26] Visoٷ is expressed as a percent of VC and occurs in normal nonsmoking subjects at 10% to 15% of VC from RV.[26] The reduction in radius is making the phenomenon of laminar flow to accurate at higher lung volumes (increase in Visoٷ) and this is considered as a malfunction of small airways.[27]

Despas et al reported that early manifestation of peripheral airway obstruction can be detected in patients with mild asthma using the $He\text{-}O_2$ mixture.[5] Moreover, Dosman et al showed that the use of Heliox during a maximal expiratory flow-volume maneuver was capable of detecting functional abnormalities in smokers at a stage when spirometric indices were within the normal range.[6]

This technique has been used by Siafakas et al to investigate small airways' function in acromegaly.[28] It has been also used by our department, for the investigation of small airways' function in non-respiratory diseases such as inflammatory bowel diseases, with interesting results.[29] In agreement with the present study they found alterations only in the Visoٷ index and not in the $\Delta\dot{V}_{max\,50}$ and considered that $\Delta\dot{V}_{max\,50}$ could not be a sensitive index for the early detection of small airway dysfunction.[30]

It is well known that, the small airways of the lung, the so-called ''quiet zone'',[30,31] is a difficult anatomical area to approach and therefore for studying its function. Multiple methods have been proposed to study this area of the lung, including complicated and invasive techniques. Nevertheless, there is a lack of a globally acceptable methodology to investigate small airways.[32,33]

There are some studies that criticize density-dependence tests for their variability and their validity for detecting narrowing of the small airways,[34] however the majority agree that those tests correlate well with the small airways function.[35,36]

Although, BMI was statistically different between the two groups, regression analysis showed that Visoٷ was statistically higher in OSAHS patients, independently of BMI. Similarly, Abdeyrim et al reported that FRC and Expiratory Reserve Volume reductions were independent from BMI in OSAHS patients.[20]

Limitation of our study is the quite small sample size. Only 23 patients with OSAHS were studied and 8 controls. However, the results of Visoٷ clearly separated patients from controls (Fig. 2).

Finally, preliminary results have shown a trend towards improvement in small airways parameters in OSAHS patients after therapy with CPAP. Thus, it would be worth investigating the effects of treatment of OSAHS on the function of small airways in the future.

Conclusions

The main finding of the present study is that patients with OSAHS showed a dysfunction of the small airways, since the VisoV̇ index was increased, despite their normal baseline spirometric values.

This is probably due to the reduction of the lung volumes, the cycle opening and closure of the small airways and subsequent inflammation and oxidant stress.

The function of the small airways may affect the natural history of OSAHS and these findings could lead to new therapeutic implications. However, larger studies are needed to verify our results.

Compliance with ethical standards

This study was supported by an unrestricted grant to University of Crete by Elpen Hellas, with no other involvement in the study.

Ethical approval

All procedures performed in the study were in accordance with the ethical standards of the Research Ethics and Deontology Committee of the University of Crete, and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

All subjects have signed an Informed Consent Form prior to any investigation.

Authors contributions

KG: She was involved in all parts of this work, the design of the study, the experiments, the analysis of the data, and the interpretation of the results, the drafting and writing of the manuscript.

SS: Contributed in the design of the study, in the analysis of the data and supervised the polysomnographic sleep studies.

GV: Contributed in the acquisition and the analysis of the data and in their statistical interpretation.

VL: He was involved in the design of the study, in the analysis of the data and supervised the Heliox experiments.

NT: contributed in the design of the study, organized the Heliox experiments and was involved in the analysis of the data.

NS: He is the senior investigator of the study involved in all aspects: design, analysis, interpretation of the results and supervised the writing of the manuscript.

All authors have read and approved the final manuscript.

Conflicts of interest

The authors declare that they have no conflict of interest.

The authors have no relationship with the tobacco industry or its affiliates and subsidiaries that benefited any of the manuscript authors or the tobacco industry in its promotion of tobacco products.

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BRIEF COMMUNICATION

Alterations in central hemodynamic in patients with COPD after acute high intensity exercise

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KEYWORDS
COPD;
Central aortic pressure;
Lung function

Abstract The present study investigated the relationship between central hemodynamics and lung function and the response to an acute bout of exercise in COPD.
Methods: Based on the severity of COPD, moderate group (MOD, n = 12) and more mild group (MLD, n = 12) underwent central hemodynamic assessments pre- and post-peak exercise.
Results: In the entire cohort (n = 24), central diastolic blood pressure (cDBP) was associated with pulmonary function. Post-exercise, cDBP remained elevated ($p < 0.01$), however, peripheral diastolic blood pressure (pDBP) was reduced ($p = 0.02$). Prior to exercise, the MOD showed higher cDBP and heart rate (HR) than the MLD ($p = 0.02$ and $p = 0.01$, respectively), but no difference in central aortic/arterial stiffness ($p > 0.05$). These findings remained similar post-exercise.
Conclusion: Central diastolic blood pressure is linked to pulmonary function in COPD and it is elevated after exercise-induced reductions in pDBP. Central diastolic blood pressure is higher in the MOD than the MLD, however, there was no difference in central aortic/arterial stiffness between groups.

Introduction

There is a growing prevalence of chronic obstructive pulmonary disease (COPD) globally and 15.2% of Americans suffer from this disease.[1] The lungs and cardiovascular systems are intimately linked and it is well known that

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smoke inhalation is a major risk factor for vascular disease. In addition, the lungs and heart compete for intrathoracic space and alterations in lung mechanics associated with lung disease – hyperinflation – and shifts in intrathoracic pressure due to lung disease likely also impact central hemodynamics.[2–4] Furthermore, pulmonary vascular remodeling occurs in COPD, which consequently influences pulmonary vascular pressures.[5,6] Therefore, the present study investigated the relationship between lung function and central aortic hemodynamics in COPD, and the response of central aortic hemodynamics to acute exercise.

Methods

The present study was reviewed and approved by Mayo Clinic Institutional Review Board. Twenty-five patients with COPD provided written informed consent and underwent pulmonary function testing (PFT), quality of life questionnaire assessment, as well as quantification of blood pressure (BP) and heart rate (HR). Subsequently, subjects were divided into either a more moderate disease group (MOD) or a mild group (MLD) based on scoring of COPD severity using lung function. Severity score was determined by quantifying lung diffusing capacity for carbon dioxide (DLCO), forced vital capacity (FVC), forced expiratory flow between 25 and 75% of FVC (FEF_{25-75}), forced expiatory volume-one second (FEV_1), maximum voluntary ventilation (MVV), and then ranking subjects from 1st (the most severe) to 24th (the least severe) based on percent predicted value for each parameter. The rankings for each of the 5 parameters were then averaged for each subject, and severity status determined by the average rank such that the 1st to 12th ranked subjects were defined as severe (MOD, n = 12) and the 13th to 24th ranked subjects were defined as moderate (MLD, n = 12). Table 1 demonstrates the subjects' characteristics.

Peripheral systolic blood pressure (pSBP) and diastolic blood pressure (pDBP) was measured manually, while central systolic pressure (cSBP), central diastolic pressure (cDBP), central pulse pressure (cPP), pressure of the incident wave (P1), augmentation pressure (AP), pulse wave velocity (PWV), augmentation index (AIx) were assessed via central arterial pressure waveform analysis (Sphygmocor, AtCor Medical, Australia). All subjects underwent a symptom-limited incremental exercise test on a cycle ergometer and the wattage was increased by 10—15 watts every minute to exertional exhaustion. During exercise, respiratory gas exchange, heart rate (HR), pSBP, pDBP, oxygen saturation (SaO_2), rate of perceived exertion (RPE) and dyspnea were assessed. After exercise, subjects were at rest for 20 min before a repeat central hemodynamic assessment was obtained.

To examine the relationships between central aortic hemodynamics and pulmonary function measures in all subjects (n = 24), correlation coefficient analysis was conducted. To compare group differences (MOD vs MLD) at pre-exercise, independent *t*-test and the Mann-Whitney U non-parametric *t*-test were conducted. To examine an exercise effect, a repeated-measures analysis of variance (ANOVA) was conducted to observe alterations in central hemodynamic parameters from pre- to post-exercise.

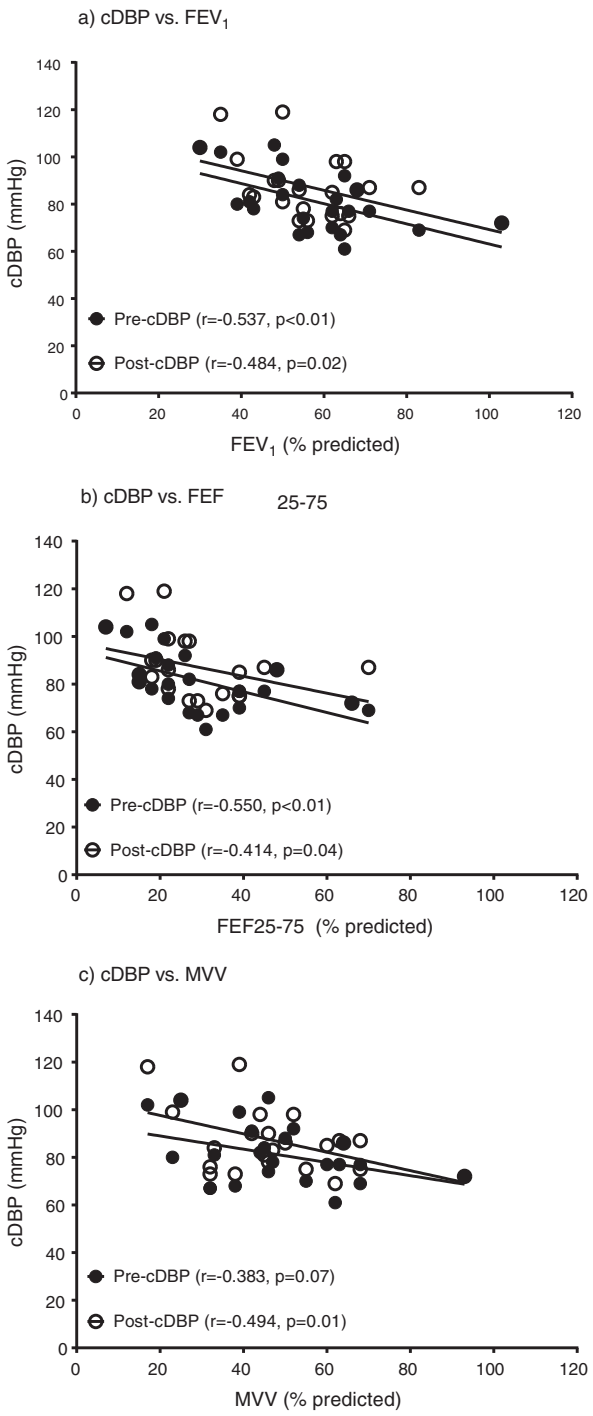

Figure 1 The relationships between central diastolic blood pressure and parameters of pulmonary function. Central diastolic blood pressure (cDBP), forced expiratory volume-one second (FEV_1), forced expiratory flow between 25% and 75% of FVC (FEF_{25-75}), maximum voluntary ventilation (MVV). a) The relationships between pre-exercise cDBP and pre-exercise FEV_1 ($r = -0.499$, $p = 0.01$) and post-exercise cDBP and pre-exercise FEV_1 ($r = -0.484$, $p = 0.02$). b) The relationships between pre-exercise cDBP and pre-exercise FEF_{25-75} ($r = -0.530$, $p = 0.01$) and post-exercise cDBP and pre-exercise FEF_{25-75} ($r = -0.414$, $p = 0.04$). c) The relationships between pre-exercise cDBP and pre-exercise MVV ($r = -0.349$, $p = 0.09$) and post-exercise cDBP and pre-exercise MVV ($r = -0.493$, $p = 0.01$).

Table 1 Subjects characteristics.

Parameters	The MOD (n = 12)	The MLD (n = 12)	*t*-test
Demographic			
Age (years)	66.5 ± 8.9	68.9 ± 9.3	p = 0.66
Sex (M/F)	8 / 4	5 / 7	
Height (cm)	170.5 ± 10.5	166.7 ± 12.9	p = 0.43
Weight (kg)	95.3 ± 21.8	82.8 ± 17.5	p = 0.14
BMI (kg/m^2)	32.6 ± 5.7	29.8 ± 5.7	p = 0.25
Current smoking status (Y/N)	3 / 9	0 / 12	
Cardiovascular			
Resting HR (bpm)	81.3 ± 9.5[a]	70.6 ± 8.8[a]	p = 0.02
pSBP (mmHg)	122.7 ± 20.0	122.3 ± 10.7	p = 0.96
pDBP (mmHg)	75.8 ± 10.6	69.0 ± 7.2	p = 0.08
cSBP (mmHg)	132.5 ± 17.9	127.5 ± 20.6	p = 0.53
cDBP (mmHg)	87.6 ± 12.8[a]	75.0 ± 8.8[a]	p = 0.01
Pulmonary			
FVC (%predicted)	70.5 ± 20.4	80.1 ± 10.2	p = 0.16
FEV_1 (%predicted)	49.8 ± 18.4[a]	65.0 ± 7.2[a]	p = 0.01
FEV_1/FVC	56.0 ± 10.4[a]	64.6 ± 8.3[a]	p = 0.04
FEF_{25-75} (%predicted)	22.0 ± 14.9[a]	37.3 ± 13.0[a]	p = 0.01
MVV (%predicted)	41.0 ± 19.5	54.3 ± 12.0	p = 0.06
Medications			
Inhaled Beta agonist (n)	12	12	
Inhaled Anticholinergic (n)	9	6	
Inhaled steroid (n)	9	7	
Oral steroid (n)	2	2	
Questionnaire			
COPD-GOLD (class I/II/II/IV)	0/3/8/4	1/11/0/0	
Quality of life	45.8 ± 25.5	40.7 ± 19.6	p = 0.39

Body mass index (BMI), peripheral systolic blood pressure (pSBP), peripheral diastolic blood pressure (pDBP), forced vital capacity (FVC), forced expiratory volume-one second (FEV_1), forced expiratory flow between 25% and 75% of FVC (FEF_{25-75}), Maximum voluntary ventilation (MVV) and GOLD disease classification for COPD.

[a] denotes significant difference at pre-exercise between groups.

Results

Entire group

From pre-exercise to post-exercise, COPD (n = 24) demonstrated significant increases in cSBP (pre vs. post, 126.9 ± 19.8 vs. 133.6 ± 15.8, p = 0.01) and cDBP (pre vs. post, 74.8 ± 8.4 vs. 81.5 ± 9.5, p < 0.01) with a significant decrease in pDBP (pre vs. post, 68.2 ± 7.6 vs. 64.9 ± 8.4, p = 0.02). However, other central hemodynamic parameters including AP, PWV and AIx were not altered (p > 0.05). In addition, pulmonary function parameters including FEV_1, FEF_{25-75} and MVV were associated with cDBP at pre- and post-exercise (Fig. 1), however, these measures of lung function were not related to cSBP, AP, PWV and AIx (p > 0.05).

MOD vs MLD groups

At pre-exercise, the MOD showed higher resting HR and cDBP than the MLD (p = 0.02 and p = 0.01, respectively, Table 1). In addition, the MOD showed a trend of higher pDBP (p = 0.08, Table 1). However, there was no significant difference between groups in cSBP, cPP, P1, AP, PWV and AIx (p > 0.05). During exercise, the MOD had lower VO_2peak (ml/kg/min, p = 0.04) and lower respiratory exchange ratio (RER, p = 0.01) than MLD. In addition, there was a trend that the MOD demonstrated a lower ratio of mixed expired CO_2 and end tidal CO_2 ($PECO_2/PETCO_2$) than the MLD, an index of ventilation distribution (p = 0.09).

Post-exercise, COPD (n = 24) showed increases in cSBP and cDBP and a decrease in pDBP, however, this phenomenon was not significantly different between the MOD and the MLD (p > 0.05). In addition, other central hemodynamic parameters including P1, AP, PWV and AIx were not significantly changed or different between groups (p > 0.05).

Discussion

Entire group

In the present study, more impaired pulmonary function was related to a higher cDBP in patients with mild to moderate COPD. This relationship was not altered post exercise. After exercise, cDBP in both patient groups remained higher than pre-exercise, however, pDBP was lower than pre-exercise. These data may suggest that obstructive lung disease is associated with higher cDBP and more hemodynamic challenges arose centrally rather than peripherally after exercise.

MOD vs MLD groups

The MOD had poorer pulmonary function, reduced exercise capacity and a trend of impaired gas exchange ($PECO_2/PETCO_2$) relative to the MLD. Additionally, the MOD had a higher cDBP, HR and pDBP than the MLD, but there was no significant difference in AP, PWV and AIx between groups. It is not clear mechanistically the cause of the isolated elevation in cDBP without changes in AP, PWV and AIx. We speculate that central/arterial stiffness might be similar between groups, however, given the higher HR and likely greater degree of obstruction and hyperinflation in the more severe group, i.e., greater mechanical constraint, the coupling of cardiac hemodynamics and cDBP maybe be differentially influenced. However, exercise did not impact differently on alterations in cSBP, cDBP and pDBP between groups.

Conclusions

Central diastolic blood pressure is elevated in COPD patients, linked to disease severity, and remains elevated after exercise-induced reductions in peripheral diastolic blood pressure. However, these observations occurred similarly between mild and more moderate disease.

Conflicts of interest

The authors have no conflicts of interest to declare.

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REVIEW

Predictive equations of maximum respiratory mouth pressures: A systematic review

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KEYWORDS
Maximal respiratory pressures;
Respiratory function tests;
Healthy adults;
Standardization;
Procedures

Abstract
Background: Maximum inspiratory (Pimax) and expiratory (Pemax) mouth pressures are commonly used to detect respiratory muscle weakness resorting to predictive equations established for healthy people. There are several predictive equations, but they are widespread in the literature. This study aimed to review the existent predictive equations of maximum inspiratory (Pimax) and expiratory (Pemax) mouth pressures for adults. Additionally, we aimed to identify which ones were generated based on international standards.
Methods: A systematic review of predictive equations of Pimax and Pemax for healthy adults was conducted. A comprehensive search was performed of Cochrane Library, EBSCO, PubMed, Scopus and Web of Science to identify studies that presented at least one equation for Pimax or Pemax developed for healthy adults. The quality of studies was assessed by two reviewers with the Quality Assessment of Diagnostic Accuracy Studies (Quadas-2).
Results: Risk of bias was high in 8 of the 20 studies included. Forty-two Pimax and 34 Pemax equations were found, mostly using the variables age ($n = 39$), weight ($n = 20$) and height ($n = 8$). These equations explained 3 to 96% of the Pimax/Pemax variance. They were developed with individuals from 11 countries (Portugal not included). Twelve Pimax and eight Pemax equations complied with international standards.
Conclusions: This review gathered the predictive equations that have been developed for both Pimax and Pemax, however most were generated from unstandardized procedures. Future studies should explore the suitability of these equations for populations for which specific ones are not available, such as the Portuguese population, and develop new equations if necessary.

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Introduction

Respiratory muscle weakness is an important clinical problem as it contributes to higher levels of dyspnoea[14] and limits exercise capacity,[15] impairing patients' daily functioning and health-related quality of life.[16] Respiratory muscle weakness is known to be diminished in 20–30% of patients with advanced chronic obstructive pulmonary disease (COPD),[17] 30–50% of patients with chronic heart failure[18] and is frequently undetected in patients with neuromuscular diseases.[19] Hence, more attention to this clinical parameter is needed and respiratory muscle strength should be routinely assessed in clinical practice.

Maximum respiratory mouth pressures are commonly used to assess respiratory muscle strength. But, despite existent international standards on measurement procedures,[20] there is no consensus on which cut-offs to use to identify respiratory muscle weakness.[13,20] Currently, absolute values of maximum inspiratory mouth pressure (Pimax) below $-60\,cmH_2O$ in men and $-40\,cmH_2O$ in women[13] are widely used for detecting inspiratory muscle weakness. However, these pressures are influenced by several personal characteristics (e.g., age, height) and therefore, a more suitable interpretation of respiratory muscle strength is commonly performed, using predictive equations of Pimax and maximum expiratory mouth pressure (Pemax).[21,22] These equations are available, but they are widespread in the literature. Although one systematic review has been conducted on this topic,[23] it is from 7 years ago, and more predictive equations have been developed since.[24,25] Furthermore, equations for Pemax have not been reviewed yet.[23] This is a serious gap in the literature. Expiratory muscle weakness is also important to detect, as it can increase residual volume,[20] and thus worsen the impaired breathing pattern in individuals with respiratory diseases, namely patients with COPD and hyperinflation.

Therefore, this study aimed to review the existent predictive equations of Pimax and Pemax for adults. Additionally, we aimed to identify which ones were generated based on international standards.

This information can be helpful to identify future suitable equations and clinically relevant respiratory muscle weakness in the Portuguese population.

Materials and methods

This is a systematic review of the literature, reported according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines.[26] The protocol was registered in the international prospective register of systematic reviews (PROSPERO) (ID: CRD42018102854).

Search strategy

After ensuring that there was no similar systematic review on PROSPERO or the Cochrane Library, a systematic search by title, abstract and keywords was conducted in the Cochrane Library, EBSCO, PubMed, Scopus and Web of Science in September 2018. Additional searches were performed in weekly automatic updates retrieved from the databases until December 2019. References of each included study were hand searched for potentially eligible studies. Appendix A (supplementary material) reports the full search strategy.

Study selection

After completion of databases search, all duplicates were removed. Then, one author screened each article for the scope of the review by their title, abstract and keywords. In parallel, an independent researcher screened 10% of all abstracts for eligibility to be included in the study. Full text of the articles was assessed, and papers excluded according to the eligibility criteria. Studies were included if: (1) included healthy adults ($\geq$18 years), (2) developed at least one predictive equation for either Pimax or Pemax (mouth pressures), and (3) were written in English, French, Portuguese or Spanish. Studies were excluded if they were qualitative studies, research protocols, thesis/dissertations, abstracts, letters to the editor, news, case studies, book chapters, guidelines, position papers and unpublished work.

In cases of uncertainty, the decision to include/exclude the article was debated between the two reviewers and a third member was consulted to reach consensus.

Data extraction

Data were extracted to a predesigned structured table with author's name, year and country, participant characteristics (sample size, number of women and men, age and body mass index (BMI)), smoking status, equipment and protocol used to assess Pimax and Pemax, established predictive equation(s), lower limits of normality (LLN), standard error of estimate (SEE) and coefficient of determination (R^2). The table was built in an excel file format to facilitate calculations when needed and then transformed and simplified to a word format.

A second table was built to aid visualization of the equations found, their explanation coefficients and which ones complied with the American Thoracic Society/European Respiratory Society standards (Pimax measured at residual volume, Pemax measured near total lung capacity, use of a flanged mouthpiece, use of noseclip not mandatory, holding pressure for $\geq$1.5 s but not much longer, avoid use of aneroid manometers, patients supports cheeks during maneuver, 3 maneuvers with less than 20% variability).[20]

The accuracy of the extracted data was verified by two reviewers and confirmed by all authors. All corresponding authors of the included studies were contacted by e-mail in case of missing data.

Quality assessment

Two reviewers independently assessed the quality of the included studies with the Quality Assessment of Diagnostic Accuracy Studies (Quadas-2).[27] This scale has two dimensions (risk of bias and applicability concerns) and four domains (patient selection, index test, reference standard and flow and timing) that are scored with unclear risk, low risk, or high risk.[27] Consistency of the quality assessment performed by the two reviewers was explored with the inter-rater agreement analysis using Cohen's kappa through SPSS statistics (IBM, version 25.0) and interpreted as <0: poor agreement; 0.00–0.20: slight agreement;

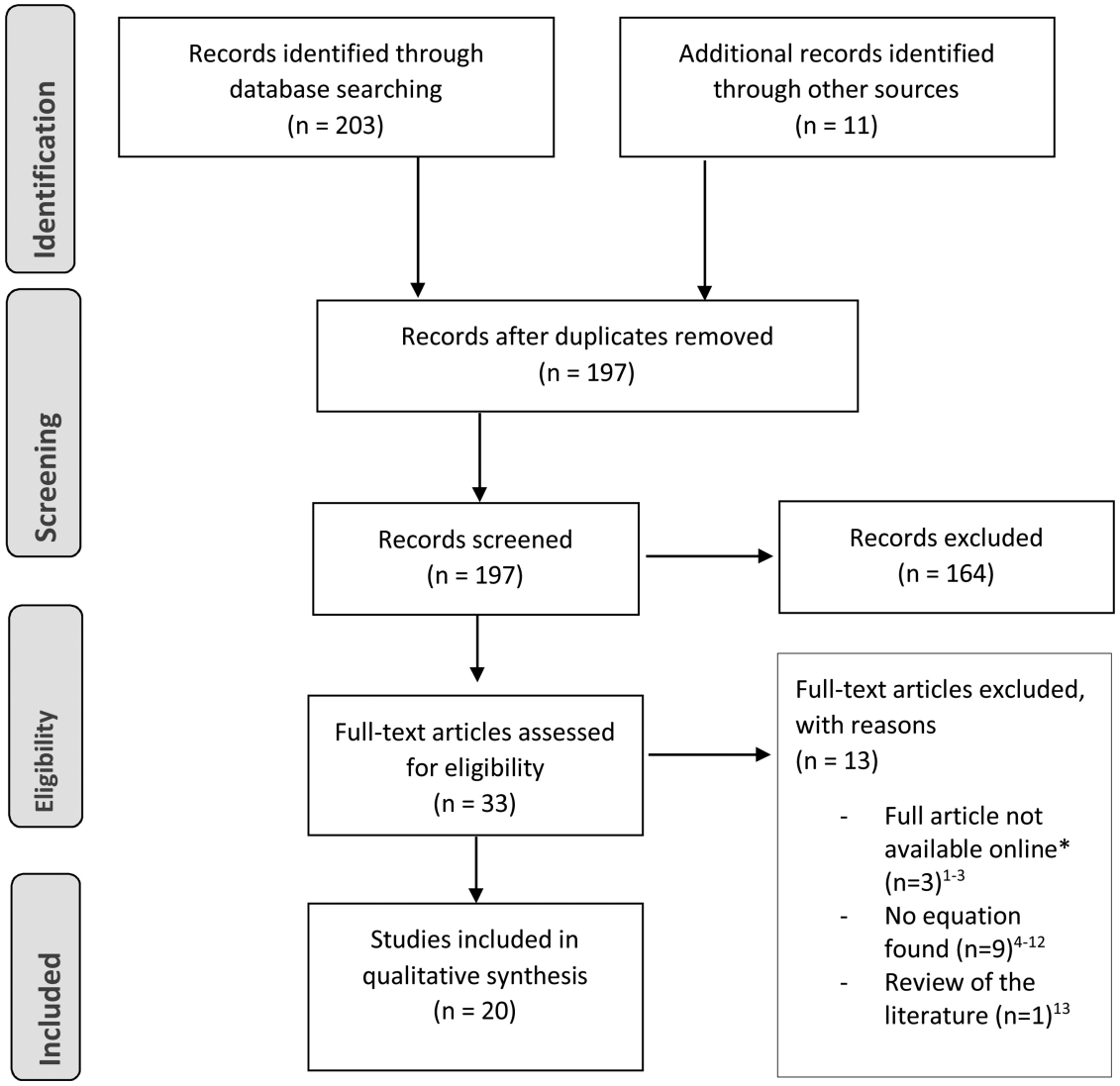

Figure 1 PRISMA flow diagram of systematic search.
*Authors were contacted and no response was obtained.

0.21–0.40: fair agreement; 0.41–0.60: moderate agreement; 0.61–0.80: substantial agreement; 0.81–1.00: almost perfect agreement.[28]

Results

Study selection

The databases search identified 203 records. Eleven additional records were identified through hand searches of references of published articles and systematic reviews on the topic. After removing duplicates, 197 studies were screened. Of these, 164 studies were excluded by title, abstract or keywords, as they did not comply with the inclusion/exclusion criteria. Of the remaining 33 studies, 13 were excluded due to: unavailability of full-text ($n = 3$),[1–3] no equations for Pimax or Pemax being developed ($n = 9$),[4–12] and being a review of the literature ($n = 1$).[13] Twenty studies were included.[24,25,29–46] A PRISMA flow diagram can be found in Fig. 1.

Quality assessment

A detailed view of the quality assessment is presented in Table B.1 (Appendix B). Overall, the quality of studies was good. Risk of bias was high in eight studies,[24,30,34,35,39,41,43,45] mainly due to inclusion of participants by convenience, and in three studies the eligibility criteria was not clear.[29,31,37] Risk of bias in the index test was high in one study.[41] Concerns with applicability were unclear for patient selection and index test in eleven studies.[24,29–31,34,36–38,41,45,46] Only three studies showed unclear risk for applicability concerns regarding the reference standard.[31,32,43] Quality assessment of the studies revealed substantial agreement between the two reviewers (kappa = 0.74, 95% CI 0.59–0.86).

Study characteristics

A detailed description of the studies can be found in Table 1. The 20 studies included a total of 9643 healthy individuals (5146 women, 4497 men). Most stud-

Table 1 Characteristics of the included studies ($n = 20$).

Author (year)	Country	*N* (sex, *n*) Age (range) BMI, mean	Smoking status	Equipment used	Protocol	Equation	LLN, cmH_2O/kPA	SEE, cmH_2O/kPA	R^2, %
Black and Hyatt (1969)[29]	United States of America	$n = 120$ n (women) = 60 n (men) = 60 20–70 y BMI: NR	Smokers included. (number NR)	Two diaphragm gauges mounted on a metal bar connected to a pressure tap in the distal end of the cylinder by rigid plastic tubing; one gauge recorded negative pressure and the other recorded positive pressure. The gauges were calibrated with a pressure transducer	Position: sitting Nose clip: yes Handling: The subject held the metal cylinder in his hand and pressed the mouthpiece tightly against his lips during the measurement; Pimax measurement: near RV Pemax measurement: near TLC Unit: cmH_2O Holding: $\geq$1 s Number of repetitions: $\geq$2 Value used: higher	Pimax = 104 − (0.51 × age) Pemax = 170 − (0.53 × age) Pimax = 143 − (0.55 × age) Pemax = 268 − (1.03 × age)	NR NR NR NR	NR NR NR NR	NR NR NR NR
Wilson et al. (1984)[30]	United Kingdom	$n = 135$ n (women) = 87 n (men) = 48 18–70 y BMI: 23.1 kg/m^2 23.3 kg/m^2	Included smokers (number NR)	Gauges manufactured for the study and with the range − 200 to +250 cmH_2O	Position: sitting Nose clip: no Handling: NR Pimax measurement: at RV Pemax measurement: at TLC Unit: cmH_2O Holding: $\geq$1 s Number of repetitions: $\geq$3 with 2 identical readings and 1 min interval Value used: NR	Pimax = − 43 + (0.71 × $Height_{cm}$) Pemax = 3.5 + (0.55 × $Height_{cm}$) Pimax = 142 − (1.03 × age) Pemax = 180 − (0.91 × age)	NR NR NR NR	NR NR NR NR	5 5 21 14

Table 1 (*Continued*)

Author (year)	Country	*N* (sex, *n*) Age (range) BMI, mean	Smoking status	Equipment used	Protocol	Equation	LLN, cmH_2O/kPA	SEE, cmH_2O/kPA	R^2, %
Bruschi et al. (1992)[31]	Italy	*n* = 749 *n* (women) = 423 *n* (men) = 326 18–70 y BMI: NR	*n* = 326 non-smokers *n* = 299 smokers/former smokers	A differential pressure transducer (Honeywell, Freeport) with a pressure range of $\pm 300\ cmH_2O$ connected to an amplifier (Gould Instruments, Ballanvilliers, France)	Position: sitting Nose clip: yes Handling: the subjects held the cheeks with their hands during the manoeuvers. Pimax measurement: near RV and FRC Pemax measurement: near TLC and FRC Unit: cmH_2O Holding: NR Number of repetitions: ≥5 Value used: highest	$Pimax_{RV} = 4.02 - (0.26 \times sex) - (0.004 \times age) + (0.47 \times BSA)$ $Pimax_{FRC} = 3.89 - (0.22 \times sex) - (0.004 \times age) + (0.52 \times BSA)$ $Pemax_{TLC} = 4.48 - (0.18 \times sex) , - (0.0004 \times age) - (0.003 \times sex \times age) + (0.25 \times BSA)$ $Pemax_{FRC} = 4.54 - (0.35 \times sex) - (0.003 \times age) + (0.24 \times BSA)$ Sex: male = 0; female = 1	NR NR NR NR	0.33 0.34 0.21 0.23	27 25 46 46
Enright et al. (1994)[32]	United States of America	*n* = 2871 Pimax = 1602 Pemax = 292 Pimax = 1269 Pemax = 244 67–78 y BMI: 26.5 kg/m^2 26.6 kg/m^2	All non-smokers	MRP-PC system (Scientific and Medical Instrument Co., Doylestown, PA). Mechanical gauge reading $\pm 150\ cmH_2O$	Position: sitting with exception of severely obese people. Nose clip: yes Handling: NR. Pimax measurement: near RV Pemax measurement: near TLC Unit: cmH_2O Holding: 2 s Number of repetitions: 3–5 Value used: highest value not exceeding the second highest value by 10%	Pimax = $(0.133\ Wt_{lbs}) - (0.805\ Age) + 96$ Pemax = $(0.344\ Wt_{lbs}) - (2.12\ Age) + 219$ Pimax = $(0.131\ Wt_{lbs}) - (1.27\ Age) + 153$ Pemax = $(0.250\ Wt_{lbs}) - (2.95\ Age) + 347$	− 32 − 52 − 41 − 71	21.50 33.30 25.40 42.50	8 18 10 15

Table 1 (*Continued*)

Author (year)	Country	*N* (sex, *n*) Age (range) BMI, mean	Smoking status	Equipment used	Protocol	Equation	LLN, cmH_2O/kPA	SEE, cmH_2O/kPA	R^2, %
Enright et al. (1995)[33]	United States of America	*n* = 288 *n* (women) = 176 *n* (men) = 112 65–85 y BMI: 26.0 kg/m^2 26.4 kg/m^2	All non-smokers	A mechanical and electronic pressure gauge (MRP1, $\pm 250\ cmH_2O$, model 83KC-37, Marshalltown, Iowa)	Position: sitting Nose clip: yes Handling: NR. Pimax measurement: near RV Pemax measurement: near TLC Unit: cmH_2O Holding: 2 s Number of repetitions: 5 Value used: highest not exceeding the second highest value by 10%	Pimax = 118 − (0.9 × age) + (0.10 × Wt_{lbs}) Pemax = 179 − (1.68 × age) + (0.36 × Wt_{lbs}) Pimax = 149 − age + (0.10 × Wt_{lbs}) Pemax = 278 − (2.27 × age + 0.28 × Wt_{lbs})	− 38 − 75 − 42 − 52	NR NR NR NR	8 23 5 12

Table 1 (*Continued*)

Author (year)	Country	*N* (sex, *n*) Age (range) BMI, mean	Smoking status	Equipment used	Protocol	Equation	LLN, cmH_2O/kPA	SEE, cmH_2O/kPA	R^2, %
Johan et al. (1997)[34]	China, Malaysia and India	China = 221 *n* = 221 *n* (women) = 90 *n* (men) = 131 Malaysia *n* = 111 *n* (women) = 42 *n* (men) = 69 India *n* = 120 *n* (women) = 43 *n* (men) = 77 20–80 y BMI: China 21.8 kg/m^2 23.0 kg/m^2 Malaysia 24.1 kg/m^2 23.9 kg/m^2 India 23.2 kg/m^2 24.3 kg/m^2	All non-smokers or smoked <400 cigarettes in their lifetime	Ashcroft pressure gauges (Ashcroft, USA) with a flanged mouthpiece.	Position: sitting Nose clip: yes Handling: NR. Pimax measurement: near RV Pemax measurement: near TLC Unit: cmH_2O Holding: $\geq$1 s Number of repetitions: $\geq$3 Value used: highest value	China: Pimax = 68.80 − (0.49 × age) − (0.05 × $Height_{cm}$) + (0.22 × Wt_{kg}) Pemax = 112.14 − (0.59 × age) − (0.11 × $Height_{cm}$) − (0.07 × Wt_{kg}) Pimax = 37.24 − (0.67 × age) + (0.15 × $Height_{cm}$) + (0.85 × Wt_{kg}) Pemax = − 106.17 − (0.52 × age) + (1.05 × $Height_{cm}$) + (1.03 × Wt_{kg}) Malaysia: Pimax = 52.48 + (0.18 × age) − (0.09 × $Height_{cm}$) + (0.12 × Wt_{kg}) Pemax = 181.87 − (0.16 × age) − (0.90 × $Height_{cm}$) − (0.43 × Wt_{kg}) Pimax = 151.32 − (0.33 × age) − (0.55 × $Height_{cm}$) + (0.38 × Wt_{kg}) Pemax = 109.82 + (0.05 × age) − (0.22 × $Height_{cm}$) + (0.30 × Wt_{kg}) India: Pimax = 54.65 − (0.48 × age) − (0.01 × $Height_{cm}$) + (0.24 × Wt_{kg}) Pemax = 130.36 − (0.49 × age) − (0.40 × $Height_{cm}$) + (0.17 × Wt_{kg}) Pimax = 112.47 − (0.31 × age) − (0.31 × $Height_{cm}$) + (0.51 × Wt_{kg}) Pemax = − 13.66 − (0.62 × age) + (0.79 × $Height_{cm}$) + (0.06 × Wt_{kg})	NR NR NR NR NR NR NR NR NR NR NR NR	NR NR NR NR NR NR NR NR NR NR NR NR	26 29 41 42 14 24 22 15 34 25 19 33

Table 1 (*Continued*)

Author (year)	Country	*N* (sex, *n*) Age (range) BMI, mean	Smoking status	Equipment used	Protocol	Equation	LLN, cmH_2O/kPA	SEE, cmH_2O/kPA	R^2, %
Morales et al. (1997)[35]	Spain	*n* = 264 *n* (women) = 135 *n* (men) = 129 18–83 y BMI: 26.3 kg/m^2 26.6 kg/m^2	All non-smokers	T tube connected to a transductor (Gouid Statham, P23 ID) connected to an amplifier (Electronics for Medicine, Simultrace Recorder VR-6, V-2203) with a 50–300 mmHg	Position: sitting Nose clip: yes Handling: Handling: the subjects held the cheeks with their hands during the manoeuvers Pimax measurement: at RV Pemax measurement: near TLC Unit: cmH_2O Holding: 2–3 s Number of repetitions: <10 Value used: highest value of 5 repetitions with 5% variability	Pimax = (− 0.64 × age) + 125.18 Pemax = (− 0.57 × age) + (0.65 × Wt_{kg}) + 116.23 Pimax = (− 1.03 × age) + (0.59 × Wt_{kg}) + 133.07 Pemax = (− 1.31 × age) + 263.12	NR NR NR NR	23.2 27.7 29.3 42.6	19 13 30 22
Harik-khan et al. (1998)[36]	United States of America	*n* = 267 *n* (women) = 128 *n* (men) = 139 20–90 y BMI: 23.9 kg/m^2 25.8 kg/m^2	23% former smokers 35% former smokers 9% occasional smokers 13% occasional smokers 7% current smokers 4% current smokers	Solid-state pressure transducer (S&M Instruments Co., Doylestown, PA) interfaced with a computer	Position: NR Nose clip: NR Handling: NR. Pimax measurement: near RV Unit: cmH_2O Holding: 2 s Number of repetitions: 3–5 Value used: one that showed a 2 s plateau of inspiratory effort with 10% variability	Pimax = 171 − (0.694 × age) + (0.861 × Wt_{kg}) − (0.743 × $Height_{cm}$) Pimax = 126 − (1.028 × age) + (0.343 × Wt_{kg})	− 32 − 37	18.5 22.4	31 42

Table 1 (*Continued*)

Author (year)	Country	*N* (sex, *n*) Age (range) BMI, mean	Smoking status	Equipment used	Protocol	Equation	LLN, cmH_2O/kPA	SEE, cmH_2O/kPA	R^2, %
Neder et al. (1999)[37]	Brazil	*n* = 100 *n* (women) = 50 *n* (men) = 50 20–80 y BMI: NR	All non-smokers	Manual shutter apparatus with the maximal pressures measured using a manometer, aneroid-type gauge (±300 cmH_2O) (Imebrás, São Paulo, SP, Brazil)	Position: sitting Nose clip: yes Handling: the subjects held the cheeks with one hand during the maneuvers Pimax measurement: at RV Pemax measurement: near TLC Unit: cmH_2O Holding: ≥1 s Number of repetitions: 3–5 repetitions with up to 10% variability and 1 min rest between repetitions Value used: highest value unless it was obtained from the last effort	Pimax = (− 0.49 × age) + 110.4 Pemax = (− 0.61 × age) + 115.6 Pimax = (− 0.80 × age) + 155.3 Pemax = (− 0.81 × age) + 165.3	NR NR NR NR	9.1 11.2 17.3 15.6	47 48 48 48
Hautmann et al. (2000)[38]	Germany	*n* = 504 *n* (women) = 256 *n* (men) = 248 18–82 y BMI: 23.9 kg/m^2 25.8 kg/m^2	87.7% never smoked Mean 17 pack-years for current/former smokers	Pressure gauge as an integral part of the pneumotachograph – piezzo-element (Type SX01, Sensym Corp, Milpitas, California, U.S.A.) was calibrated by the manufacturer	Position: sitting Nose clip: yes Handling: NR. Pimax measurement: near RV Unit: kPA Holding: 2 s Number of repetitions: ≥7 with 20–90 s of rest between repetitions Value used: highest value maintained for ≥1 s, with two consecutive measurements Failing to improve the preceding highest value.	Pimax = (− 0.024 × age) + 8.55 Pimax = (0.158 × BMI) − (0.051 × age) + 8.22	0.59 0.60	NR NR	3 9

Table 1 (*Continued*)

Author (year)	Country	*N* (sex, *n*) Age (range) BMI, mean	Smoking status	Equipment used	Protocol	Equation	LLN, cmH_2O/kPA	SEE, cmH_2O/kPA	R^2, %
Wohlgemuth et al. (2003)[39]	Netherlands	*n* = 252 *n* (women) = 126 *n* (men) = 126 18–70 y BMI: 26.2 kg/m^2 25.1 kg/m^2	*n* = 64 smokers/former smokers	Morgan manometer (type Pmax) containing a small leak (internal diameter 2 mm, 2 cm length) connected to a facemask	Position: sitting Nose clip: Yes for mouthpiece Handling: Researcher held the facemask Pimax measurement: at RV Pemax measurement: at TLC Unit: kPA Holding: 1 s Number of repetitions: ≥3 with maximum 5% variability Value used: highest	Pimax = 7.224 − (0.0406 × age) + (0.032 × Wt_{kg}) + (3.745 × sex) − (0.041 × sex × age) Pemax = 9.887 − (0.0556 × age) + (0.035 × Wt_{kg}) + (5.224 × sex) − (0.049 × sex × age) sex: males = 1 females = 0	NR NR	1.58 2.23	51 50
Windisch et al. (2004)[40]	Germany	*n* = 533 *n* (women) = 304 *n* (men) = 229 10–90 y BMI: 23.9 kg/m^2 24.2 kg/m^2	*n* = 317 current smokers *n* (women) = 84 former smokers *n* (men) = 128 never smokers	Transportable apparatus connected to a computer system (ZAN 100; ZAN1, Oberthulba, Germany)	Position: sitting Nose clip: Yes Handling: NR Pimax measurement: at RV and FRC Unit: kPA Holding: 1 s Number of repetitions: ≥7 and 30–120 s interval Value used: highest	Pimax = *y* + (− 0.08 × age) + (0.04 × Wt_{kg}) + (0.11x BMI)[a] Pimax = *y* + (− 0.04 × age) + (0.06 × Wt_{kg}) + (0.24 × BMI)[a]	0.9–5.8 0.9–5.8	NR NR	13 2

Table 1 (*Continued*)

Author (year)	Country	*N* (sex, *n*) Age (range) BMI, mean	Smoking status	Equipment used	Protocol	Equation	LLN, cmH_2O/kPA	SEE, cmH_2O/kPA	R^2, %
Lausted et al. (2006)[41]	United States of America	*n* = 48 *n* (women) = 29 *n* (men) = 19 18–34 y BMI: 22.5 kg/m^2 23.7 kg/m^2	NR	Spirometry system (Collins™, Braintree, MA)	Position: NR Nose clip: NR Handling: NR. Pimax measurement: at different volumes (10–90%VC) Pemax measurement: at different volumes (10–90%VC) Unit: cmH_2O Holding: 2 s Number of repetitions: ≥3 with ≥1 min of rest between repetitions Value used: highest	Pimax = 0.234 × Ln (100% − %VC) − 0.0828 Pemax = 0.1426 × Ln (%VC) + 0.3402	NR NR	NR NR	96 96
Sachs et al. (2009)[42]	United States of America	*n* = 1755 *n* (women) = 883 *n* (men) = 872 45–84 y BMI: 18.5–35 kg/m^2	Excluded current smokers, smoking history for the healthy subgroup NR	MRP-PC system (Scientific and Medical Instrument Co., Doylestown, PA). Calibration of the MRP transducer was checked each week against the mechanical gauge reading [−150–150 cmH_2O]	Position: sitting Nose clip: yes Handling: the researcher pressed the cheeks of the participant Pimax measurement: at RV Unit: cmH_2O Holding: ≥1 s Number of repetitions: 5 with 1 min rest between repetitions Value used: nearest 5 cm H2O value from the highest 2 within 10 cmH_2O Quality confirmed by a 5% random quality-control sample of participants	Pimax = − 388 + (1.77 × age) + (− 0.014 × age^2) + (0.41 × Wt_{lbs}) + (− 0.0041 × age × Wt_{lbs}) + (4.69 × $Height_{cm}$) + (− 0.014 × $Height^2_{cm}$) Pimax = 9.8 + (− 0.31 × age) + (1.47 × Wt_{lbs}) + (− 0.0026 × Wt^2_{lbs}) + (− 0.0059 × age × Wt_{lbs})	− 36 − 40	NR NR	27 21

Table 1 (*Continued*)

Author (year)	Country	*N* (sex, *n*) Age (range) BMI, mean	Smoking status	Equipment used	Protocol	Equation	LLN, cmH_2O/kPA	SEE, cmH_2O/kPA	R^2, %
Costa et al. (2010)[43]	Brazil	*n* = 120 *n* (women) = 60 *n* (men) = 60 20–80 y BMI: 18.0–29.5 kg/m^2	All non-smokers	Calibrated aneroid vacuum manometer (GER-AR, São Paulo, Brazil, range of ±300 cmH_2O.	Position: sitting Nose clip: yes Handling: NR. Pimax measurement: near RV Pemax measurement: near TLC Unit: cmH_2O Holding: ≥1 s Number of repetitions: ≥3 Value used: highest value not exceeding the second highest value by 10%	Pimax = (− 0.46 × age) + 74.25 Pemax = (− 0.68 × age) + 119.35 Pimax = (− 1.24 × age) + 232.37 Pemax = (− 1.26 × age) + 183.31	− 28.83 − 23.24 − 23.38 − 38.95	17.20 17.76 18.88 24.22	24.8 35.1 60.7 48.9
Simões et al. (2010)[44]	Brazil	*n* = 140 *n* (women) = 70 *n* (men) = 70 20–89 y BMI: 24.6 kg/m^2 24.7 kg/m^2	All non-smokers	Aneroid vacuum manometer (GER-AR, São Paulo, SP, Brazil) with an operational interval of ±300 cmH_2O was used	Position: sitting Nose clip: yes Handling: NR Pimax measurement: at RV Pemax measurement: at TLC Unit: cmH_2O Holding: ≥1 s Number of repetitions: ≥3 with ≤10% variability Value used: highest	Pimax = (− 0.85 × age) + 80.7 + (− 0.3 × Wt_{kg}) Pemax = (− 0.89 × age) + 125.1 + (− 0.18 × Wt_{kg}) Pimax = (− 0.76 × age) + 125 Pemax = (− 0.83 × age) + 87.69	− 69 − 19.6 − 24.6 − 24.7	41.95 11.90 14.97 15.0	84 77 72 84

Table 1 (*Continued*)

Author (year)	Country	*N* (sex, *n*) Age (range) BMI, mean	Smoking status	Equipment used	Protocol	Equation	LLN, cmH_2O/kPA	SEE, cmH_2O/kPA	R^2, %
Gopalakrishna et al. (2011)[45]	India	*n* = 250 *n* (women) = 125 *n* (men) = 125 20–70 y BMI: 23.17 kg/m^2 23.54 kg/m^2	All non-smokers	Morgan Pmax monitor [P.K Morgan Ltd. ME8 7ED]	Position: sitting with exception of severely obese people. Nose clip: yes Handling: NR. Pimax measurement: near RV Pemax measurement: near TLC Unit: cmH_2O Holding: 2 s Number of repetitions: $\geq$3 with 1 min rest between repetitions Value used: highest not exceeding the second highest value by 10%	Pimax = 45.98 + (6.47 × age) Pemax = 74.85 − (0.32 × age) Pimax = 83.36 − (0.25 × age) Pemax = 133.36 − (0.907 × age)	NR NR NR NR	NR NR NR NR	6 24 18 40
Obando et al. (2012)[46]	Colombia	*n* = 308 *n* (women) = 154 *n* (men) = 154 20–86 y BMI: 24.2 kg/m^2	All non-smokers	Pressure gauge (MICROMEDICAL RPM brand, Micro Medical Limited, PO Box 6, Rochester, Kent ME1 2AZ UK), with a range of 300 cmH_2O	Position: sitting Nose clip: yes Handling: NR. Pimax measurement: near RV during 3–4 s Unit: cmH_2O Holding: 2 s Pemax: near TLC Number of repetitions: 3 Value used: highest	Pimax = 78.237 − (− 0.446 × age) + (22.430 × sex) + (8.550 × BMI Classification) Pemax = − 97.424 + (19.788 × sex) + (0.528 × Wt_{kg}) + (0.911 × $Height_{cm}$) Values for sex not provided	NR NR	23.16 29.60	26 33

Table 1 (*Continued*)

Author (year)	Country	*N* (sex, *n*) Age (range) BMI, mean	Smoking status	Equipment used	Protocol	Equation	LLN, cmH_2O/kPA	SEE, cmH_2O/kPA	R^2, %
Pessoa et al. (2014)[24]	Brazil	*n* = 134 *n* (women) = 74 *n* (men) = 60 20–89 y BMI: 24.0 kg/m^2 25.0 kg/m^2	Non-current smokers. Previous smoking history NR	A digital manometer (NEPEB-LabCare/UFMG) with pressure transducers with an operating range of 500 cmH_2O	Position: sitting Nose clip: yes Handling: the researcher pressed the cheeks of the participant Pimax measurement: at RV Pemax measurement: near TLC Unit: cmH_2O Holding: $\geq$1.5 s Number of repetitions: $\geq$5 with 1 min rest between repetitions Value used: highest value with three reproducible repetitions (one with variation less than or equal to 10% and the other with a variation of no more than 20% of higher value)	Pimax = 63.27 − (0.55 × age) + (17.96 × sex) + (0.58 × Wt_{kg}) Pemax = − 61.41 + (2.29 × age) −(0.03 × age^2) + (33.72 × sex) + (1.40 × $waist_{cm}$) Sex: males = 1; females = 0	− 43 − 54	26.3 32.8	34 49

Table 1 (*Continued*)

Author (year)	Country	*N* (sex, *n*) Age (range) BMI, mean	Smoking status	Equipment used	Protocol	Equation	LLN, cmH_2O/kPA	SEE, cmH_2O/kPA	R^2, %
Sanchez et al. (2018)[25]	Brazil	*n* = 353 *n* (women) = 229 *n* (men) = 124 18–89 y BMI: 31.4 ± 10.3 kg/m^2	All non-smokers	Analogical manometer ''Wika'', calibrated and graduated to 6300 cmH_2O	Position: sitting Nose clip: yes Handling: NR Pimax measurement: at RV Pemax measurement: near TLC Unit: cmH_2O Holding: ≥1 s Number of repetitions: 4 with 1 min rest between repetitions Value used: highest value with two reproducible repetitions and a variation of no more than 10% of higher value	Model 2: Pimax = −94.75 + (0.816 × age) − (1.822 × BMI) Pemax = 91.58 − (0.556 × age) + (0.798 × BMI) Pimax = −108.16 + (1.307 × age) − (2.904 × BMI) Pemax = 98.36 − (0.672 × age) + (1.759 × BMI) Model 3: Pimax = −95.54 + (0.748 × age) − (0.688 × Wt_{kg}) Pemax = 87.20 − (0.506 × age) + (0.350 × Wt_{kg}) Pimax = −110.07 + (1.208 × age) − (0.942 × Wt_{kg}) Pemax = 98.84 − (0.610 × age) + (0.576 × Wt_{kg})	NR NR NR NR NR NR NR NR	63.9 36.5 63.9 36.5 63.8 36.1 63.8 36.1	21.3 28.4 21.3 28.4 21.7 29.9 21.7 29.9

Legend: BMI: body mass index; BSA: body surface area; FRC: functional residual capacity; LLN: lower limit of normality; Ln: natural logarithm; Pemax: maximum expiratory pressure; Pimax: maximum inspiratory pressure; NR: not reported; R^2: coefficient of determination; RV: residual volume; SEE: standard error of estimation; TLC: total lung capacity; VC: vital capacity; Wt: weight.

[a] Authors were contacted for constant in the model. No response was obtained.

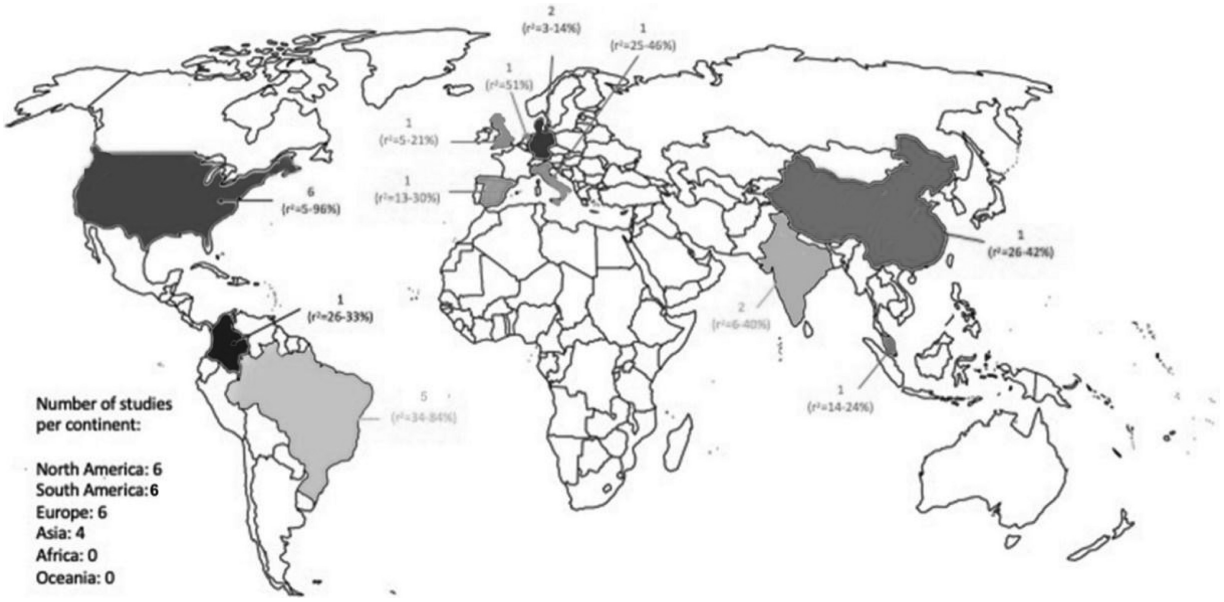

Figure 2 World map of studies with predictive equations for respiratory muscle strength and range of coefficients of determination. Numbers above range of coefficients represent the number of studies.

ies included young and older adults with ages between 10 and 90 years old ($n = 16$),[24,25,29–31,34–40,43–47] one study had only young adults (18–34 years old)[41] and three studies had only middle-aged and older adults (45–85 years old).[32,33,42] Seventeen studies reported the BMI, which ranged from 18 to 41.7 kg/m^2.[24,25,30,32–36,38–46] Twelve studies excluded smokers.[24,25,32–35,37,42–46] Seven included smokers and reported no differences in maximum respiratory pressures between smokers and non-smokers,[29–31,36,38–40] and one study did not report this characteristic.[41]

Of the 20 studies, ten used digital manometers,[24,36,37,39,40,42–46] eight used mechanical gauges,[25,29–35] one used a gauge associated with a pneumotachograph,[38] whilst in another the gauge was associated with a spirometry system.[41] Assessment protocol varied across studies. The vast majority of studies performed measurements with the participants in a sitting position ($n = 18$)[24,25,29–35,37–40,42–46] and using a nose clip.[24,25,29,31–35,37–40,42–46] Two studies did not report either the position or use of a nose clip.[36,41] Only one study performed the measurement at different volumes for both Pimax and Pemax (percentage of vital capacity),[41] whilst 19 studies measured Pimax at residual volume[24,25,29–40,42–46] and 16 measured Pemax at total lung capacity.[24,25,29,31–37,39,41,43–46,48] Half of the studies reported holding pressures for $\geq$1 s,[25,29,30,34,37,39,40,42–44] eight for 2 s,[32,33,35,36,38,41,45,46] one for $\geq$1.5 s,[24] and one study did not report the holding time[31]. Number of repetitions of the procedure varied between 2 and 10, with most studies ($n = 18$) reporting at least 3 repetitions.[24,30–46]

A total of 76 predictive equations were found, 42 for Pimax and 34 for Pemax. Variables most frequently used in the equations were: age (Pimax $n = 22$; Pemax $n = 17$),[24,25,29–40,42–46] weight ($n = 11$; $n = 9$),[24,25,32–36,39,40,42,44,46] height ($n = 5$; $n = 3$)[30,34,36,42,46] and sex ($n = 4$; $n = 4$).[24,31,39,46] Most studies produced distinct equations for each sex ($n = 15$),[25,29,30,32–38,40,42–45] with only five studies reporting a single equation for both.[24,31,39,41,46] BMI was used in five Pimax equations[25,38,46] and in two Pemax equations,[25] and waist circumference in one Pemax equation.[24] Body surface area was also used in 2 Pimax and 2 Pemax equations.[31] Only 9 studies reported LLN values,[24,33,36,38,40,42–44] 12 reported the SEE[24,25,31,32,35–37,39,40,43,44,46] and almost all ($n = 19$) the R^2.[24,25,30–46]

Overall the proposed equations explained between 3 and 96% of the variance of Pimax/Pemax, with most studies ($n = 14$) explaining less than 50%. Equations were developed with individuals from 11 countries, with the most representative continents being North America ($n = 6$), Europe ($n = 6$), South America ($n = 5$) and Asia ($n = 4$). No developed equations were found in Northern Asia, Africa or Oceania. A world map of the distribution of the existent predicted equations and respective range of R^2 can be found in Fig. 2. Of the 42 Pimax and 34 Pemax equations, 12 and 8 respectively, were generated using procedures that globally complied with the international standards. Of the remaining 56 equations using procedures that have not followed the ATS/ERS guidelines, only 36 were developed before publication of the guidelines. Table 2 summarizes the predictive equations found for respiratory muscle strength.

Discussion

This study has shown that there are 42 Pimax and 34 Pemax predictive equations developed for eleven countries. From these equations, only 12 for Pimax and 8 for Pemax derived from procedures that complied globally with the international standards.

Although a previous systematic review on respiratory muscle strength was published in 2014,[23] it only reviewed Pimax predictive equations. Therefore, the present systematic review brings novelty to the body of literature as it is not

Table 2 List of available predictive equations for maximum inspiratory (Pimax) and expiratory (Pemax) pressures for healthy adults.

Author (year)	Equation Pimax women	Equation Pimax men	Equation Pemax women	Equation Pemax men	R^2
Black and Hyatt (1969)[29]	104 − (0.51 × age)	143 − (0.55 × age)	170 − (0.53 × age)	268 − (1.03 × age)	NR
Wilson et al. (1984)[30]	− 43 + (0.71 × $Height_{cm}$)	142 −(1.03 × age)	3.5 + (0.55 × $Height_{cm}$)	180 − (0.91 × age)	5–21
Bruschi et al. (1992)[31]	4.02 − 0.26 − (0.004 × age) + (0.47 × BSA) (from RV) 3.89 − 0.22 − (0.004 × age) + (0.52 × BSA) (from FRC)	RV = 4.02 − (0.004 × age) + (0.47 × BSA) (from RV) 3.89 − (0.004 × age) + (0.52 × BSA) (from FRC)	4.48 − 0.18 − (0.0004 × age) − (0.003 × age) + (0.25 × BSA) (from TLC) 4.54 − 0.35 − (0.003 × age) + (0.24 × BSA) (from FRC)	4.48 − (0.0004 × age) − (0.25 × BSA) (from TLC) 4.54 − (0.003 × age) + (0.24 × BSA) (from FRC)	25–46
Enright et al. (1994)[32] [a]	(0.133 Wt_{lbs}) − (0.805 Age) + 96	(0.131 Wt_{lbs}) − (1.27 Age) + 153	(0.344 Wt_{lbs}) − (2.12 Age) + 219	(0.250 Wt_{lbs}) − (2.95 Age) + 347	8–18
Enright et al. (1995)[33] [a]	118 − (0.9 × age) + (0.10 × Wt_{lbs})	149 − age + (0.10 × Wt_{lbs})	179 − (1.68 × age) + (0.36 × Wt_{lbs})	278 − (2.27 × age + 0.28 × Wt_{lbs})	5–23
Johan et al. (1997)[34]	China: 68.80 − (0.49 × age) − (0.05 × $Height_{cm}$) + (0.22 × Wt_{kg}) Malaysia: 52.48 + (0.18 × age) − (0.09 × $Height_{cm}$) + (0.12 × Wt_{kg}) India: 54.65 − (0.48 × age) − (0.01 × $Height_{cm}$) + (0.24 × Wt_{kg})	China: 37.24 − (0.67 × age) + (0.15 × $Height_{cm}$) + (0.85 × Wt_{kg}) Malaysia: 151.32 − (0.33 × age) − (0.55 × $Height_{cm}$) + (0.38 × Wt_{kg}) India: 112.47 − (0.31 × age) − (0.31 × $Height_{cm}$) + (0.51 × Wt_{kg})	China: 112.14 − (0.59 × age) − (0.11 × $Height_{cm}$) − (0.07 × Wt_{kg}) Malaysia: 181.87 − (0.16 × age) − (0.90 × $Height_{cm}$) − (0.43 × Wt_{kg}) India: 130.36 − (0.49 × age) − (0.40 × $Height_{cm}$) + (0.17 × Wt_{kg})	China: − 106.17 − (0.52 × age) + (1.05 × $Height_{cm}$) + (1.03 × Wt_{kg}) Malaysia: 109.82 + (0.05 × age) − (0.22 × $Height_{cm}$) + (0.30 × Wt_{kg}) India: − 13.66 − (0.62 × age) + (0.79 × $Height_{cm}$) + (0.06 × Wt_{kg})	14–42
Morales et al. (1997)[35]	(− 0.64 × age) + 125.18	(− 1.03 × age) + (0.59 × Wt_{kg}) + 133.07	(− 0.57 × age) + (0.65 × Wt_{kg}) + 116.23	(− 1.31 × age) + 263.12	13–30
Harik-khan et al. (1998)[36]	171 − (0.694 × age) + (0.861 × Wt_{kg}) − (0.743 × $Height_{cm}$)	126 − (1.028 × age) + (0.343 × Wt_{kg})			31–42

Table 2 (*Continued*)

Author (year)	Equation Pimax women	Equation Pimax men	Equation Pemax women	Equation Pemax men	R^2
Neder et al. (1999)[37]	(− 0.49 × age) + 110.4	(− 0.80 × age) + 155.3	(− 0.61 × age) + 115.6	(− 0.81 × age) + 165.3	47–48
Hautmann et al. (2000)[38] [a]	(− 0.024 × age) + 8.55	(0.158 × BMI) − (0.051 × age) + 8.22			3–9
Wohlgemuth et al. (2003)[39]	7.224 − (0.0406 × age) + (0.032 × Wt_{kg}) + 3.745	7.224 − (0.0406 × age) + (0.032 × Wt_{kg}) − (0.041 × age)	9.887 − (0.0556 × age) + (0.035 × Wt_{kg}) + 5.224	9.887 − (0.0556 × age) + (0.035 × Wt_{kg}) − (0.049 × age)	50–51
Windisch et al. (2004)[40] [b]	y + (− 0.08 × age) + (0.04 × Wt_{kg}) + (0.11x BMI)[a]	y + (− 0.04 × age) + (0.06 × Wt_{kg}) + (0.24 × BMI)[a]			2–13
Lausted et al. (2006)[41]	0.234 × Ln (100% − %VC) − 0.0828	0.234 × Ln (100% − %VC) − 0.0828	0.1426 × Ln (%VC) + 0.3402	0.1426 × Ln (%VC) + 0.3402	96
Sachs et al. (2009)[42] [a]	− 388 + (1.77 × age) + (− 0.014 × age^2) + (0.41 × Wt_{lbs}) + (− 0.0041 × age × Wt_{lbs}) + (4.69 × $Height_{cm}$) + (− 0.014 × $Height^2_{cm}$)	9.8 + (− 0.31 × age) + (1.47 × Wt_{lbs}) + (− 0.0026 × Wt^2_{lbs}) + (− 0.0059 × age × Wt_{lbs})			21–27
Costa et al. (2010)[43]	(− 0.46 × age) + 74.25	(− 1.24 × age) + 232.37	(− 0.68 × age) + 119.35	(− 1.26 × age) + 183.31	24.8–60.7
Simões et al. (2010)[44]	(− 0.85 × age) + 80.7 + (− 0.3 × Wt_{kg})	(− 0.76 × age) + 125	(− 0.89 × age) + 125.1 + (− 0.18 × Wt_{kg})	(− 0.83 × age) + 87.69	72–84
Gopalakrishna et al. (2011)[45] [a]	45.98 + (6.47 × age)	83.36 − (0.25 × age)	74.85 − (0.32 × age)	133.36 − (0.907 × age)	6–40
Obando et al. (2012)[46]	78.237 − (− 0.446 × age) + (22.430 × sex) + (8.550 × BMI Classification) Values for sex not provided	78.237 − (− 0.446 × age) + (22.430 × sex) + (8.550 × BMI Classification) Values for sex not provided	− 97.424 + (19.788 × sex) + (0.528 × Wt_{kg}) + (0.911 × $Height_{cm}$) Values for sex not provided	− 97.424 + (19.788 × sex) + (0.528 × Wt_{kg}) + (0.911 × $Height_{cm}$) Values for sex not provided	26–33
Pessoa et al. (2014)[24] [a]	63.27 − (0.55 × age) + (0.58 × Wt_{kg})	63.27 − (0.55 × age) + (17.96) + (0.58 × Wt_{kg})	− 61.41 + (2.29 × age) − (0.03 × age^2) + (1.40 × $waist_{cm}$)	− 61.41 + (2.29 × age) − (0.03 × age^2) + 33.72 + (1.40 × $waist_{cm}$)	34–49
Sanchez et al. (2018)[25]	Model 2: −94.75 + (0.816 × age) − (1.822 × BMI) Model 3: −95.54 + (0.748 × age) − (0.688 × Wt_{kg})	Model 2: − 108.16 + (1.307 × age) − (2.904 × BMI) Model 3: − 110.07 + (1.208 × age) − (0.942 × Wt_{kg})	Model 2: 91.58 − (0.556 × age) + (0.798 × BMI) Model 3: 87.20 − (0.506 × age) + (0.350 × Wt_{kg})	Model 2: 98.36 − (0.672 × age) + (1.759 × BMI) Model 3: 98.84 − (0.610 × age) + (0.576 × Wt_{kg})	21.3–29.9

Legend:
Pimax: maximum inspiratory pressure; Pemax: maximum expiratory pressure; BSC: body surface area; %VC: percentage of vital capacity; Wt_{lb}: weight in pounds; Wt_{kg} weight in kilograms; BMI: body mass index; RV: residual volume; TLC: Total lung capacity; FRC: Functional residual capacity; $Height_{cm}$: Height in centimeters; NR: Not reported.

[a] Studies that globally complied with the ATS/ERS standards.

[b] Authors were contacted for constant in the model. No response was obtained.

limited to updating the previous systematic review, but also reviews the Pemax equations and identifies which equations were generated following the ATS/ERS guidelines.

A substantial number of equations across distinct continents were found for respiratory muscle strength, however, there is no equation available for Northern Asia, Africa or Oceania. As reference values and predictive equations are population-specific, the suitability of the existent equations needs to be tested in populations for which specific ones are not available, such as the Portuguese population. This analysis may stress the need to develop specific equations for some populations. These are important steps to interpret with confidence the values of Pimax/Pemax and guide further assessments or interventions.

Most equations integrate easy to collect variables, with the most weighted variables in the models being age, weight and height. These variables are also frequently present in predictive equations for quadriceps muscle strength[47] and exercise capacity tests,[49] which makes them highly accepted variables to enter prediction models. Predictive equations showed a high variability of explanation, and most studies explained less than 50% of the variance in respiratory muscle strength. Only four studies,[39,41,43,44] explained between 50% and 96% although the study presenting 96% of explanation had a difficult equation to apply in clinical practice, as it included vital capacity which is a more complex variable to obtain in many clinical settings.[41] Poor explanation of the variance will affect the accuracy of the interpretation of results, implying that the equation might not be suitable. Although no recommendations exist for the use of specific predictive equations, studies developing new equations should balance the quality of the predictive equations, i.e., taking the explanation of the variability into account, with their utility in clinical practice, i.e., including variables that are easy-to-use. Thus, novel variables, also easy to collect with high weight in equations may produce more powerful equations with better explanation coefficients.

Furthermore, this systematic review has shown that almost half of the equations were developed through measurements with non-digital equipment and variable protocols, which impair comparisons across studies and interpretation of the predictive values. Indeed, many studies showed lack of compliance with the ATS/ERS standards,[20] by using different number of repetitions, not using a nose clip, and holding breath during data collection with different durations. This heterogeneity in the methodological procedures was expected for older studies, but not for the ones published after the guidelines (2002). Although, the impact of choosing an equation based on the ATS/ERS standards instead of unstandardized ones to identify respiratory muscle weakness needs further investigation, the fact is that continuing to use different procedures limits the advance of knowledge in the field and should therefore be considered carefully and be well-justified.

This study has some limitations that need to be acknowledged. Although all predictive equations have been revised, the analysis of the articles did not consider the size and characteristics of the included samples. In fact, a considerable amount of studies ($n = 8$) had a high level of bias, which might have affected the validity and reliability of the equations proposed. Moreover, most equations were not validated with an independent sample. All these aspects have hindered our ability to make recommendations about which equation(s) should be used in clinical practice.

This review gathered the current predictive equations available in the literature for Pimax and Pemax and identifies which ones have followed the ATS/ERS standards. Future work could explore the suitability of the different available equations for populations to whom specific ones are not available, such as the Portuguese population, and only develop new equations for both Pimax and Pemax, if necessary.

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Appendix A. Supplementary data

Supplementary material associated with this article can be found in the online version available at http://dx.doi.org/10.1016/j.pulmoe.2020.03.003.

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Nasal high flow oxygen in acute respiratory failure

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High flow nasal cannula;
HFNC;
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ARF

Abstract Thermo-humidified nasal high flow (NHF) oxygen therapy is increasingly used in the management of respiratory failure. This therapy has recently gained attention as an alternative non-invasive respiratory support in several clinical scenarios, including acute and chronic settings. NHF enhances the patient's comfort and tolerance when compared with standard oxygen by supplying a heated and humidified mixture of air and oxygen at flows up to 60 L/min. It can be delivered through different devices. Although few studies have compared the clinical effects of different NHF systems, the purpose of this paper is to describe the major benefits of NHF and to provide a quick guide on how to implement this therapy in daily practice. We have also included a brief description of the most frequently used NHF systems.

Clinical case

A 56-year-old man with SARS-COV2 infection was admitted to our hospital on November 1st, after 7 days of fever. Comorbidities comprised hypertension and obesity. On the third day after admission, he was transferred to our Respiratory Intensive Care Unit due to worsening of his respiratory condition, including notable shortness of breath with minimal exertion. On arrival, the patient was alert, haemodynamically stable. His respiratory rate was 25/min with a reservoir oxygen mask at 15 L/min. Blood gas analysis (ABG) revealed a severe hypoxemia and alkalosis respiratory (pH 7.51, $PaCO_2$ 35 mmHg, PaO_2 118 mmHg, HCO_3^- 27 mmol/L, PaO_2/FiO_2 148). Due to patient's gas exchange impairment and clinical progression, NHF therapy trial was attempted.

Initial temperature, inspired oxygen fraction (FiO_2) and flow rate were 34 °C, 60 L/min and 60% respectively.

In order to reduce bio-aerosol dispersion, a surgical mask was placed over the patient's mouth and nose.[1] Fig. 1 shows bilateral consolidations with ground-glass areas, mainly in the posterior dependent zones on CT-scan. Based on this radiological picture, we continued NHF in awake prone positioning. Fig. 2 illustrates oxygen pulse saturation/FiO_2 (SpO_2/FiO_2), oxygen blood pressure/FiO_2 (PaO_2/FiO_2) ratios and ROX index trends within the first four days of treatment. ROX index is defined as the ratio of pulse oximetry/fraction of inspired oxygen to respiratory rate (RR). This index,

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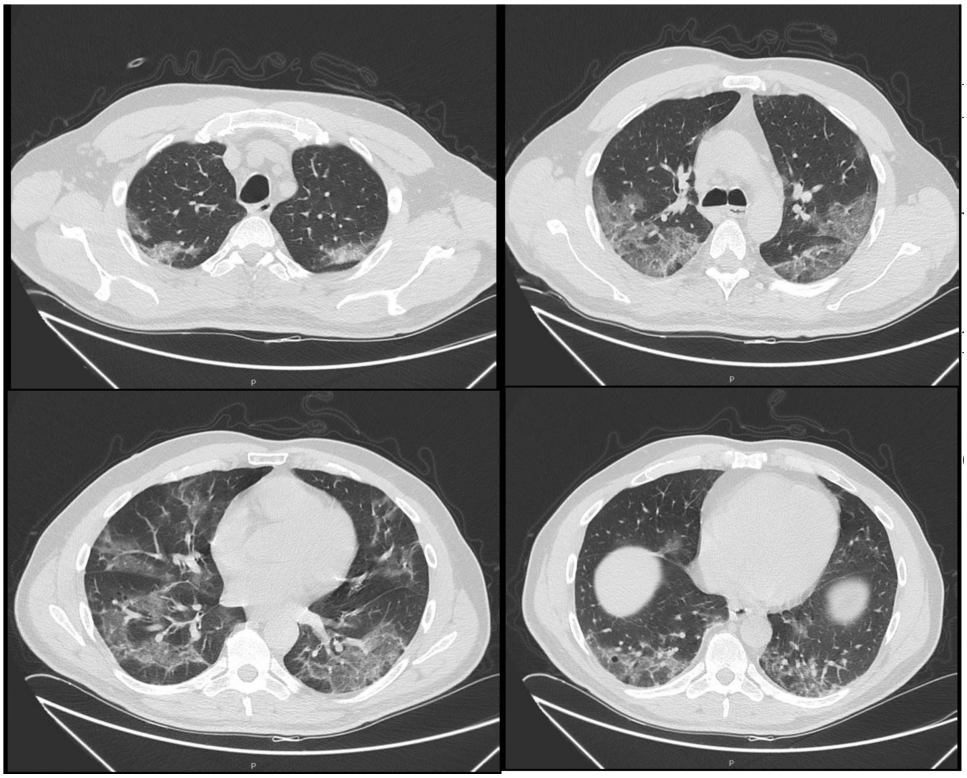


Figure 1 CT-scan. Bilateral consolidations with ground-glass areas, mainly in the posterior dependent zones.

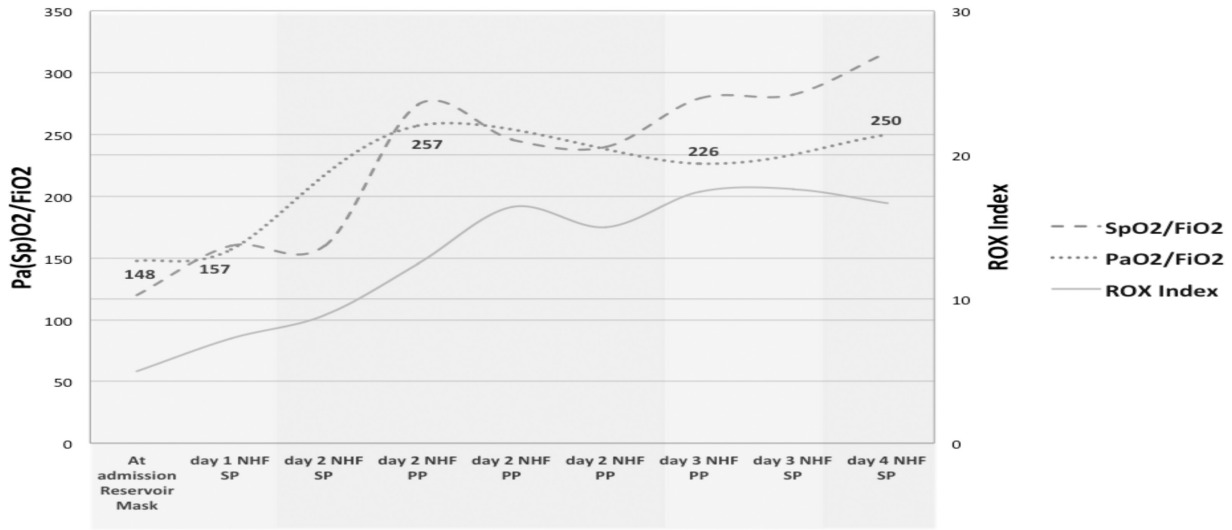


Figure 2 SpO_2/FiO_2, PaO_2/FiO_2 and ROX index trends within the first four days of treatment. Patient's SpO_2/FiO_2, PaO_2/FiO_2 and ROX index improve since NHF and prone position were implemented. (NHF: nasal high flow oxygen. SP: supine position, PP: prone position).

described by Roca et al.,[2] identifies patients at risk of NHF failure. In particular, a ROX index of 4,88 is associated with a high risk of intubation. In conclusion, NHF setting was adjusted according to the maximum patient's comfort and the best effects in terms of distending pressure and FiO_2 stability. FiO_2 was also targeted to achieve oxygen saturation between 94–96%. Prone positioning was implemented because we felt that the mild distension pressure generated by NHF could be enhanced by placing the ventilated areas in a dependent position, leading to increased V/Q mismatch.[3]

Thermo-humidified nasal high flow (NHF) oxygen therapy is increasingly used in the management of respiratory failure. This therapy has recently gained attention as an alternative non-invasive respiratory support in several clinical scenarios, acute and chronic,[4] in order to enhance patient comfort and tolerance compared with standard oxy-

gen by supplying heat and humidified mixture of air and oxygen at flows up to 60 L/minutes.[5]

NHF can be delivered through different devices. Although few studies have compared the clinical effects of different NHF systems, the purpose of this paper is to describe the major benefits of NHF and to provide a quick guide on how to implement this therapy in daily practice. We have also included a brief description of the most frequently used NHF systems: BioRespira® (IBD), Airvo 2® and OptiFlow® (Fisher and Paykel), TNI softFlow 50® (Masimo) and Precision Flow® (Vapotherm).

Physiological benefits of NHF

High flows air/oxygen mixture can be beneficial for both chronic and acute patients, who need additional oxygen supply:

- Matches patient's inspiratory flow (stable FiO_2). Conventional oxygen therapy devices such as Venturi masks or reservoir masks have holes to prevent carbon dioxide rebreathing. The patient inspires the delivered oxygen, but part of the air can be rebreathed. In addition, if the patient's ventilatory demand exceeds the flows provided by the device, the patient will breathe part of atmospheric air. For this reason, because of the relationship with the patient-breathing pattern, FiO_2 can be much lower than predicted. Pisani et al.[4] observed that calculated FiO_2 approached the prescribed FiO_2 when the delivered gas flow rates were greater than the patient's peak inspiratory flow rate. This means that, with low-flow systems, as the peak inspiratory demand increase, we cannot accurately estimate the FiO_2 that the patient is breathing. NHF delivers a flow that is much higher than the patient's spontaneous inspiratory flow in any condition, so actual FiO_2 is close to the predicted FiO_2.
- Improves lung mucociliary clearance. In normal conditions, inhaled air is conditioned in the nasal airways. The air is warmed and humidified by the nasal mucosa because of its highly vascular sinusoid tissue. Humidification is always recommended for flow rates above 4 L/min, because the humidification function of the nasal mucosa could be insufficient. In addition, unwarmed and dry gas leads to a poor tolerance of oxygen therapy.
- Washes out anatomical dead space and carbon dioxide (CO_2), allowing a higher fraction of minute ventilation to participate in gas exchange. Additionally, the nasal cannula, used for NHF, is the only respiratory interface that does not increase the instrumental dead space. With an oxygen mask, especially at low flow, carbon dioxide is rebreathed. NIV interfaces also increase the dead space. As a consequence, to maintain $PaCO_2$ (and alveolar ventilation), the minute volume has to increase, either through respiratory rate or through tidal volume (VT), or even both. For these reasons, although NHF does not provide an active inspiratory support, it may improve the alveolar ventilation and decrease respiratory rate (RR).[6] Fraser et al.[7] found that NHF leads to a reduction in respiratory rate of 10%, and in some patients, this reduction was associated with a reduction in hypercapnia.
- Provides a mild distending pressure. Although NHF is an open system, high flow from the nasal cannula increases the airway pressure usually around 3 cmH_2O,[8] depending on the flow level and the nasal prong size in relation to the nostrils. Richie et al.[6] conclude that NHF could deliver a clinically relevant mean positive airway pressure directly proportional to delivered gas flow rates. In addition, high flows could act as a resistance to exhalation when the mouth is closed.[9,10] However, it remains unclear whether NHF is sufficient to increase lung volume or recruit the collapsed alveoli. Evaluating end-expiratory lung volume (EELV), Corley et al.[11] reported increased end-expiratory lung impedance, suggesting increasing volumes and functional residual capacity with NHF compared with low-flow oxygen therapy. Also using electrical lung impedance tomography on healthy subjects in supine and prone position, Riera et al.[12] found that NHF increased global EELV, suggesting an increase in functional residual capacity, regardless of the body position. This effect could be important in patients with a higher body mass index.
- Attenuates inspiratory resistance and increases expiratory resistance. The attenuation of inspiratory resistance takes place essentially by providing an adequate warmed and humidified flow. It is known that in normal subjects,[13] inhalation of cold air causes the activation of specific receptors or osmoreceptors in the nasal mucosa, which may induce bronchoconstriction through a mechanism mediated by the activation of muscarinic receptors.[14] Besides, NHF is able to increase the expiratory resistance depending on the size of the nasal cannula and the patient's expiratory flow.[15]

A typical NHF system consists of a flow generator, active heated humidifier, single-limb heated circuit, and nasal cannula (or tracheostomy interface). There are three types of flow generators: air-oxygen blender devices, built-in flow generators (turbines), and entrainment systems (Venturi Systems). The humidifier can be a traditional ''pass-over heated humidifying system'' or a ''filter-type humidifying system'' in which humidification is generated by passing gas through a bundle of narrow tubes, or which requires an evaporative surface in contact with the gas. A heated-wire inspiratory circuit is preferred to ensure delivery of adequately humidified medical gas as well as to avoid circuit vapour loss and condensation. The lower the ambient temperature, the more likely there is to be condensation. One major reason for the patient's discomfort or intolerance is the interface. Beyond the circuit, condensation may also accumulate in the nasal prongs, which results in water droplet spray into the nostrils. NHF interfaces are specifically for this purpose. They can vary from a slender nasal cannula similar in appearance to a regular nasal oxygen cannula in which both the internal diameter and nasal prong bore are narrow, to a large bore nasal prong. Using slender nasal cannulas results in high flow out of the nasal prongs. The volumetric flow is the volume of gas that passes in a certain unit of time. The speed at which the volume moves is the velocity. The speed, at a constant volumetric flow, varies inversely proportional to the cross-sectional area of the tube. This is the reason why the smaller the cross-

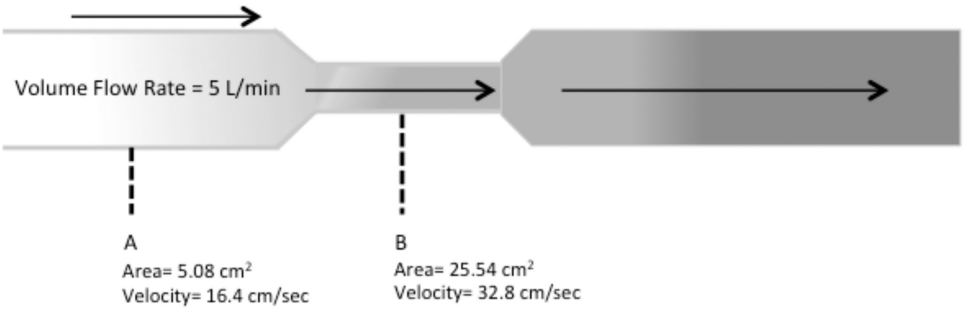


Figure 3 Fluid velocity, at a constant flow, varies inversely with the cross-sectional area of the tube.

sectional area of the nasal cannula, the greater the speed (Fig. 3).[16]

Implementation technique

a) **General considerations** (regardless of the NHF device used)
- Gas connection to the device (O_2, and compressed air if required).
- Place distilled water in the humidifier.
- Connect the circuit, appropriate to the system used.
- Switch on and heat up the water until the temperature reaches 31—37 °C.
- Select the size of the nasal cannula properly. When using a large bore nasal prong, it must not occlude more than 50% of the nostril.
- Position the cannula correctly in the patient's nostrils, to avoid lateral leakage.
- Program the parameters, according to the equipment used (temperature, flow, and FiO_2 if the setting is available).
- Switch on the device (some devices allow parameters to be programmed once the machine is on).

b) **General monitoring**
- Patients must be spontaneously breathing, alert and must be able to protect the airway.
- Check that there is no accumulation of condensed water in the tube, ensuring its inclination towards the heater.
- Aspiration of patient's secretions, if needed.
- Check that the cannula is not occluded by a mucus plug or against the patient's nose.
- Make sure the patient is in a semi-seated position at 45°. NHF can be implemented in ''awake prone position'', if needed.
- Check that the device is not disconnected from the electrical source when using high-flow devices, because not many have an internal battery.

c) **General set up**
- Temperature: it must be targeted according to the patient's comfort. The temperature needs to be set at higher values at cold weathers or high flows.
- Flow: the maximum benefit of this treatment is achieved at higher flows, although the flow should also be titrated according to the patient's comfort. It is suggested starting with flows close to 50 L/m, according to the patient's tolerance, in order to increase or decrease the flow.
- FiO_2: depending on the NHF device used, FiO_2 can be a parameter to be programmed or a parameter that depends on the flow. By using an air-oxygen blender device, oxygen concentrations are stable. On the other hand, by using turbine devices, oxygen is supplied via a low-pressure system, while the device just monitors the oxygen concentration (FiO_2). Any rise in the flow, will decrease the FiO_2, and vice versa. Venturi high flow systems use a flow generator to create a high flow by Venturi. It is composed of a flow meter and an oxygen concentration monitor. Regardless of the system used, in all cases, FiO_2 titration should depend on the SpO_2 target, recommending an SpO_2 range between 94% and 96%, or between 88%–92% in hypercapnic COPD patients.

NHF devices

Table 1 summarizes the main characteristics associated with the currently available devices.

BioRespira® (IBD)

This innovative system is a ''built-in high flow generator'' with a turbine capable of generating high flows starting from the ambient air, mixed with medical oxygen that can be supplied via a hospital cylinder or medical gas plant. Despite being a turbine device, it guarantees a fixed FiO_2 even when the flow changes. This control is based on an internal oxygen sensor and a valve that guarantees by opening and closing, the desired FiO_2. It is the only turbine system that allows setting a precise FiO_2, with a maximum achieved by 100%, independent of the variations of the flow setting. Originally, this device was invented for CPAP therapy, for this reason the flow range goes from 5 to 120 L/m and at the same time, the device allows an accurate monitoring of the airway pressure. This wide range of flow enables the patient to perform a combined therapy with CPAP requirement (flows >60 L/m) and NHF (flows <60 L/m) during resting periods. Both the nasal cannula and the tubing and humidification system are generic, recommending the use of a pass over system with a heated wire circuit, to avoid condensation and heat loss from the inspired air. Other parameters that can be monitored, apart from the airway pressure, are respiratory rate, SpO_2, heart rate and ROX index.

Table 1 Main characteristics of most frequent used NHF devices.

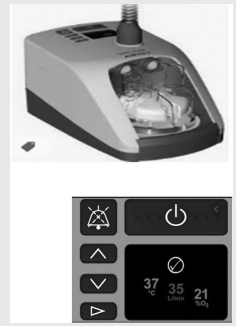
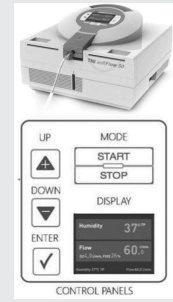
	BioRespira® IBD	Airvo2 (F&P®)	Optiflow (F&P®)	TNI softFlow 50 Masimo	Precision Flow Vapotherm®
					
FLOW (L/M)	**5—120 (NHF AND CPAP USE)**	10—60 (5 L/M STEPS)	30- 60	1060 (0,5 STEPS)	5—40 (1 L/M STEPS)
FLOW GENERATION	BLOWER	BLOWER	BLENDER	BLOWER	ELECTRONIC BLENDER
FIO_2 INDEPENDENT OF SETUP FLOW	YES	NO	YES	NO	YES
POSSIBILITY OF FIO_2 100%	YES	NO	YES	NO	YES
TYPE OF CONNECTION O_2	HIGH PRESSURE SYSTEM O_2 LOW PRESSURE SYSTEM O_2	LOW PRESSURE O_2 (UP TO 30 L/M)	HIGH PRESSURE SYSTEM AIR AND O_2	LOW PRESSURE SYSTEM O_2 (UP TO 60 L/M)	HIGH PRESSURE SYSTEM AIR AND O_2
NEED FOR COMPRESSED AIR FROM THE WALL	NO	NO	YES	NO	YES
BUILT-IN HUMMIDIFIER	EXTERNAL GENERIC	INCORPOATED F&P	EXTERNAL F&P	INCORPOATED INTERSURGICAL®	INCORPORATED
	PASS OVER SYSTEM	PASS OVER SYSTEM	PASS OVER SYSTEM	PASS OVER SYSTEM	FILTER-TYPE HUMIDIFYING SYSTEM
TUBES (INSPIRATORY CIRCUIT)	GENERIC (HEATED WIRED SYSTEM RECCOMENDED)	SPECIFIC (HEATED WIRED SYSTEM)	GENERIC	SPECIFIC (HEATED WIRED SYSTEM)	SPECIFIC TRIPLE LUMEN PATIENT CIRCUIT HEATED BY WATER RESERVOIR

Table 1 (*Continued*)

	BioRespira® IBD	Airvo2 (F&P®)	Optiflow (F&P®)	TNI softFlow 50 Masimo	Precision Flow Vapotherm®
INTERFASE	GENERIC	OPTIFLOW INTERFASE (SILICONE) NASAL: 3 SIZES, REGARDLES THE FLOW SET TRAQUEAL INTERFASE	OPTIFLOW INTERFASE. (SILICONE) NASAL: 3 SIZES, REGARDLES THE FLOW SET TRAQUEAL INTERFASE	SPECIFIC: (SLENDER SILICONE HEATED WIRED NASAL CANNULA) Standard-Plus: Flows up to 35 L/m Large: Flows up to 60 L/m Tracheal: Flows up to 50 L/m	Hi-VNI, Vapotherm: (SLENDER SILICONE CANNULA) TRACH MASK ADAPTER
ON-SCREEN MONITORING	SET FIO_2 SET FLOW **CONTINUOUS MONITORING OF PATIENT'S PARAMETERS:** AIRWAY PRESSURE SPO_2 BPM RR ROX INDEX	MEASURED FIO_2 SET FLOW SET GAS TEMPERATURE **CONTINUOUS MONITORING OF PATIENT'S PARAMETERS:** NO	MEASURED FIO_2 SET FLOW SET GAS TEMPERATURE **CONTINUOUS MONITORING OF PATIENT''S PARAMETERS:** NO	MEASURED FIO_2 SET FLOW SET GAS TEMPERATURE **CONTINUOUS MONITORING OF PATIENT'S PARAMETERS:** NO	SET FIO_2 SET FLOW SET GAS TEMPERATURE **CONTINUOUS MONITORING OF PATIENT'S PARAMETERS:** NO

NHF: nasal high flow. FiO_2: graction of inspired oxygen. O_2: oxygen. SpO_2: pulse oxygen saturation. BPM: beats per minute. RR: respiratory rate. ROX index: ratio of pulse oximetry/fraction of inspired oxygen to respiratory rate ($SpO_2/FiO_2/RR$).

Airvo 2® (Fisher and Paykel)

Fisher and Paykel defines this device as a ''pass-over humidifier with integrated flow generator''. Its internal blower delivers high flow warmed and humidified gases to patients through a heated-wired circuit and a nasal cannula or a tracheotomy interface. Temperature can be set to three target dew-point settings in 31, 34 or 37 °C and flows can be set between 10—60 L/m. A flow meter up to 60 L/m of supplementary oxygen can be connected to achieve FiO_2 around 90%. It contains an oxygen analyser to determine the oxygen fraction delivered to the patient, affected by changes to the flow setting or supplemental oxygen setting. The nasal prongs and tubing between the nasal prong and heated-wired inspiratory circuit are both large bore, and the flow to the prongs is delivered from only one side.

Optiflow® (Fisher and Pykel)

This is a fixed-performance delivery device, also known as an ''air-oxygen blender device''. With a blending system, separate pressurized air and O_2 sources are input, and the gases are mixed with a precision valve (blender). This system allows a precise control over both FiO_2 and total flow output. This blending system can provide flow rates from 30 L/m to 60 L/min and adjustable FiO_2 from 21 to 100%. Humidification is achieved by a ''pass over humidifier'' connected to a heated wire circuit and a bore Nasal Cannula (Optiflow nasal cannula) or Trach Connection.

TNI softFlow 50® (Masimo)

This device is a ''built in flow generator'' which generates the flow through an internal turbine. The applicator plug (circuit) is a silicone heated-wired circuit that enables a nasal application through a slender nasal cannula (also heated-wired and made of silicone) as well as a specific tracheal application. The TNI softFlow can be operated with two different humidifier types, but it always consists of a ''pass-over system'' chamber (Intersurgical®), with 1 °C steps, within the range from 30 to 37 °C. It can be used with the ''Humidifier Clinic'' for patients in clinics or in care facilities, or with the ''Humidifier Homecare'' for patients at home. When supplemental oxygen is required, an external, medically approved oxygen source can be connected to the TNI softFlow using the lateral oxygen inlet port. If no oxygen supply is needed, the oxygen inlet port must be kept sealed by the protective cap. The minimal operational flow is 10 L/m, with 0,5 L/m steps, to a maximum value of60 L/m for a nasal application or 50 L/m for tracheal application.

Precision Flow Vapotherm®

The Precision Flow has an electronic gas mixer (proportional solenoid/flow valve) similar to that found in mechanical ventilators. For this reason, it requires a supply of high-pressure air and oxygen. This allows the device to use FiO_2 between 21 and 100% regardless of the flow. It uses a different humidification system from the conventional pass-over humidifiers, which consists of a cartridge of steam transfer that allows no direct contact between the gas and water phases. Thus, gas and water are separated by a micro-porous membrane (0.005 μm), which could represent a protective barrier for the gas flow to the patient. The circuit consists of a triple lumen supply tube: a central one, through which the gas flow circulates, surrounded by two external lumens through which hot water circulates to maintain the gas temperature (at the set temperature). This guarantees temperature uniformity (33 °C–39 °C range) throughout the circuit, reducing the possibility of condensation. The interface (Hi-VNI, Vapotherm) is a slender nasal cannula similar in appearance to a regular nasal oxygen cannula. Both the internal diameter and nasal prong bore are narrow, and this results in high flow out of the nasal prongs. The Precision Flow has a specially designed circuit to combine NHF with nitric oxide as well as helium-oxygen (Heliox) conditioned gas mixtures. This device has an internal battery. The battery takes 2 h to fully charge for one hour of use.

In summary, NHF has recently gained attention as an alternative non-invasive respiratory support in several clinical scenarios. It is important to know the implementation technique of this treatment, as well as how to perform NHF with the different devices available in the market, because they each have different characteristics.

Conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Tuberculosis, COVID-19 and hospital admission: Consensus on pros and cons based on a review of the evidence

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KEYWORDS
TB;
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Abstract The scientific debate on the criteria guiding hospitalization of tuberculosis (TB) and COVID-19 patients is ongoing.

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Hospital admission;
Discharge;
Hospitalization criteria;
Infection control and prevention;
Length of stay;
Costs

The aim of this review is to present the available evidence on admission for TB and TB/COVID-19 patients and discuss the criteria guiding hospitalization. Furthermore, recommendations are made as derived from recently published World Health Organization documents, based on Global Tuberculosis Network (GTN) expert opinion.

The core published documents and guidelines on the topic have been reviewed.

The proportion of new TB cases admitted to hospital ranges between 50% and 100% while for multidrug-resistant (MDR) TB patients it ranges between 85 and 100% globally. For TB patients with COVID-19 the proportion of cases admitted is 58%, probably reflecting different scenarios related to the diagnosis of COVID-19 before, after or at the same time of the active TB episode. The hospital length of stay for drug-susceptible TB ranges from 20 to 60 days in most of countries, ranging from a mean of 10 days (USA) to around 90 days in the Russian Federation. Hospitalization is longer for MDR-TB (50–180 days).

The most frequently stated reasons for recommending hospital admission include: severe TB, infection control concerns, co-morbidities and drug adverse events which cannot be managed at out-patient level. The review also provides suggestions on hospital requirements for safe admissions as well as patient discharge criteria, while underlining the relevance of patient-centred care through community/home-based care.

Introduction

Tuberculosis (TB) and COVID-19 show similarities and differences, as recently discussed in the scientific literature.[1–7]

Both diseases have similar signs and symptoms,[6–10] rendering their differential diagnosis difficult as they may also present concomitantly. They might require hospital admission, although justified by different reasons.

Indications of hospital admission for COVID-19 patients have been changing during the evolution of the ongoing pandemic. The occurrence of clinical deterioration[11,12] with progressive dyspnoea and desaturation requiring medical therapy (e.g., dexamethasone) and non-invasive or invasive ventilatory support represents the most important recommendation for an immediate hospitalization as in other respiratory conditions.[12–14] Nevertheless, no previously used criteria or scores have been validated for COVID-19 patients to decide in favour of hospitalization or not[15] and new specific criteria are being explored.[16]

Indications of hospital admission for TB patients are more complex, and in different countries can go far beyond the occurrence of a life-threatening condition. Moreover, they evolved over time. At the time of sanatoria and during the pre-antibiotic era[17,18] admission was used as an 'isolation' intervention to reduce *Mycobacterium tuberculosis* transmission within the community and as support measure to ensure rest, optimal nutrition and eventually to perform pneumothorax after Carlo Forlanini's discovery in 1907.[19] In addition, in children severe extra-pulmonary TB and social circumstances likely contributed to hospitalization.[20]

Over time, hospital admission was considered ideal to better monitor the initial phase of anti-TB treatment and eventually drug adverse events, and, in some countries, to ensure adequate adherence to the prescribed regimen.[21,22] Furthermore, in several countries hospital admission is still considered an administrative measure of infection control, as patients cannot be discharged until they achieve sputum smear and/or culture conversion[21,22] Although the World Health Organization (WHO) recommends limiting unnecessary hospitalization, this is often complicated by a' per occupied bed' refund mechanism prevailing in some countries[22–24] and a sub-optimal Directly Observed Treatment (DOT)/patient's support practices at outpatient settings.

The present review evaluates the available evidence on hospital admission for TB and TB/COVID-19 and discusses the criteria guiding hospitalization.

Finally, recommendations are made following a recently published WHO (Regional Office for Europe) document on how to reduce *Mycobacterium tuberculosis* transmission in Europe.[21,22]

Methods

A non-systematic search of the scientific literature in English was carried out on PubMed without time restrictions using the following key-words: 'hospital admission' 'COVID-19', 'tuberculosis', 'length of stay', 'ambulatory care', 'prevention', 'infection control', and 'workplace'.

As hospital admission implies programmatic costs, we report available information on this obtained from the literature review.

Data on TB admissions were retrieved from countries of the WHO European Region (WHO workshop: Lessons learned from finance reforms on TB control, Copenhagen, Denmark, April 26th 2016; unpublished data reporting 2014 data) and from relevant existing cohorts allowing analysis of hospital admission-related information.

They include a secondary analysis of a large GTN cohort (global bedaquiline study)[25] and, for the duration of the hospital stay for TB in patients with COVID-19, from the ongoing global study on TB/COVID-19[26] (interim analysis, November 27th, 2020, see references for details on the two studies).

WHO definitions of multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB were adopted.[27] Although not approved by WHO (but largely used by clinicians), pre-XDR TB was defined as a form of TB caused by an MDR-TB strain with additional resistance to either a fluoroquinolone or a second line-injectable agent (amikacin, capreomycin or kanamycin).[25,28]

A writing committee of international experts including members of the Global Tuberculosis Network (GTN) developed the document after multiple rounds of revision. The document was then proposed for endorsement to the GTN.[11,29] The number of invited GTN members and those endorsing the document is reported under acknowledgements.

Evidence on TB hospital admission

European data (2016, unpublished and WHO/ECDC tuberculosis surveillance and monitoring 2020)[30]

The available data (average length of stay [ALOS] and proportion of hospital admissions for drug-susceptible and MDR-TB) are presented in Figs. 1–3, while implications for hospital admission and discharge are discussed in the following sections.

The Netherlands, Norway, Portugal and Sweden reported the shortest length of stay (LOS) (<20 days), whereas Hungary the highest (>80 days) (Fig. 1 shows the newly diagnosed 2014 cases reported in 2016).

Several Eastern Europe and Central Asia (EECA) countries reported LOS $\geq$ 60 days, with only Estonia and Georgia showing a LOS < 40 days. The Netherlands, Portugal and Sweden admitted <40% of the diagnosed patients, whereas Norway the vast majority. Other countries admitted from 80% to 100%.

MDR- and XDR-TB patients had a LOS < 50 days in Norway (Fig. 2); Estonia, Georgia, Portugal, Romania, Sweden and Uzbekistan reported <100 days. Kyrgyzstan had the lowest proportion of hospitalized patients (<40%).

In 2018 the Netherlands and Portugal reported the lowest proportion of admitted drug-susceptible TB cases (30%), Ireland and Sweden ~50%, Estonia and Hungary 60%, and the remaining countries a proportion higher than 80% (Fig. 3).[27,30]

The indicator 'percentage of hospitalization for new TB patients'(1.C.1, Fig. 3) has been added to allow a comprehensive evaluation of the different aspects of TB management in the Region.

An important note is that the information included in Figs. 1–3 refers to countries with different epidemiological characteristics and different rules/practices governing admission and discharge of TB patients.

Global bedaquiline study (2017)[25]

Although the bedaquiline study was not specifically designed to describe hospital admission (its main focus was the programmatic evaluation of safety and effectiveness of bedaquiline-containing regimens), it included detailed information on this, which is useful to report and discuss.

A total of 364/428 (85%) TB cases from 16 countries (Argentina, Australia, Belarus, Belgium, Greece, India, Italy, the Netherlands, Peru, Portugal, South Africa, Russian Federation, Spain, Sweden, and the United Kingdom) were admitted to hospital: the final anti-TB treatment outcome was reported for 224/368, with 144/368 still on treatment, while no information on hospitalization was available for 60 (14%). The proportion of patients admitted to hospital with a final outcome was: 5/224 (11%) for MDR-TB, 68/224 (65%) for pre XDR-TB, and 111/224 (24%) for XDR-TB. The proportions of admission for those still on treatment were: 31/144 (21.5%) for MDR-TB, 44/144 (30.5%) for pre XDR-TB and 69/144 (47.9%) for XDR-TB.

The median (IQR) LOS was 178.5 (93.5–302.5) days for patients who completed their treatment and 180 (91–217) days for those still on therapy.

In this study, countries from different settings had different rules/practices on TB patients' admission and discharge. Furthermore, as the study described the early phase of bedaquilne use, a possible bias related to increased hospital admissions due to uncomplete understanding on adverse events severity cannot be excluded.

Global TB and COVID-19 project (2020, interim analysis)[26]

At an interim analysis (preliminary data, unpublished) on the first 381 patients, 222 (58%) were hospitalized for TB (46/222 with final anti-TB treatment outcome and 176/222 still on treatment), 118 (31%) were not hospitalized, and 41 (11%) with unavailable data.

Importantly, 141 (37%) patients were admitted for concomitant TB and COVID-19. More information on hospital admissions will be possible when the global dataset, in its final format, will be analyzed.

The median (IQR) LOS for TB patients with a final treatment outcome was 29 (10.8–36.5) days, lower than that for patients still on treatment (47, 13.5–106.5 days).

Relevant experiences from the literature in Africa, America and Europe

Africa

A cost analysis performed in South Africa[31] clearly demonstrated that significant savings can be obtained by reducing the LOS of MDR-TB cases. A decentralised model of TB care improves case detection and treatment initiation rates, ensuring treatment outcomes comparable to those seen in centralised specialist centre.[32] Adoption of decentralised treatment in South Africa may reduce the overall costs for the national TB programme by 15–18%.[31,33]

Hospital admission could be limited to patients facing treatment-related issues (such as life-threatening conditions, drug adverse events, failure, need to use injectable medicines or other treatment measures not manageable outside the hospital), which might more frequently occur in patients with XDR- than with MDR-TB (although XDR-TB does not *per se* contraindicate the possibility of home management).[31] Adequate referral system from primary

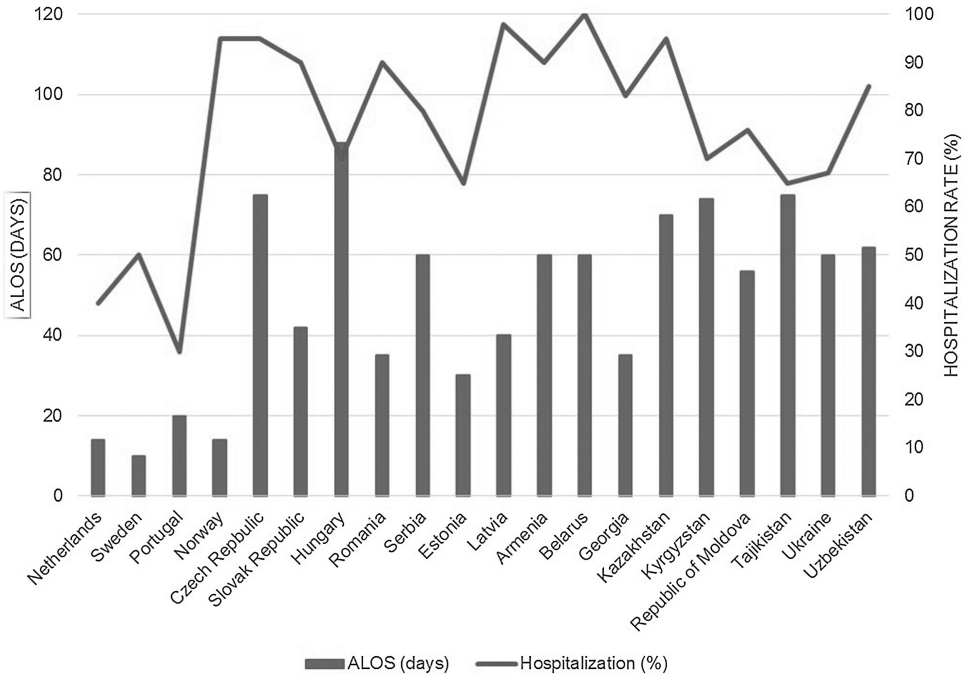

Figure 1 Hospitalization patterns (Average Length of Stay in days and proportion of admitted out of those treated) for newly diagnosed tuberculosis patients in Europe.
ALOS: average length of stay.

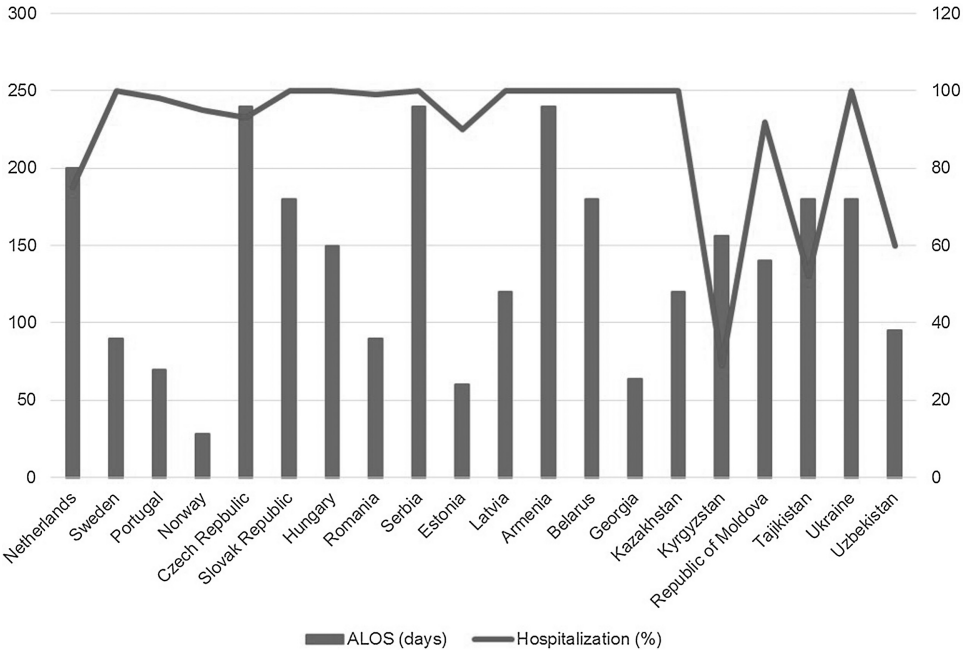

Figure 2 Hospitalization patterns (Average Length of Stay in days and proportion of admitted out of those treated) for patients undergoing treatment of multidrug-resistant tuberculosis in Europe.
ALOS: average length of stay.

healthcare to specialised services is needed to maintain a continuum of care.

Children are often admitted to hospital for diagnostic reasons, but long-term admission is mainly because of disease severity, including TB meningitis, TB/HIV co-infection and drug-resistant TB, social circumstances or a combination of disease severity and social circumstances.[34]

TB meningitis, the most devastating form of TB in children, is often treated in hospital. A study in Cape Town, South Africa showed huge cost savings and improved family interaction with effective home-based treatment with good

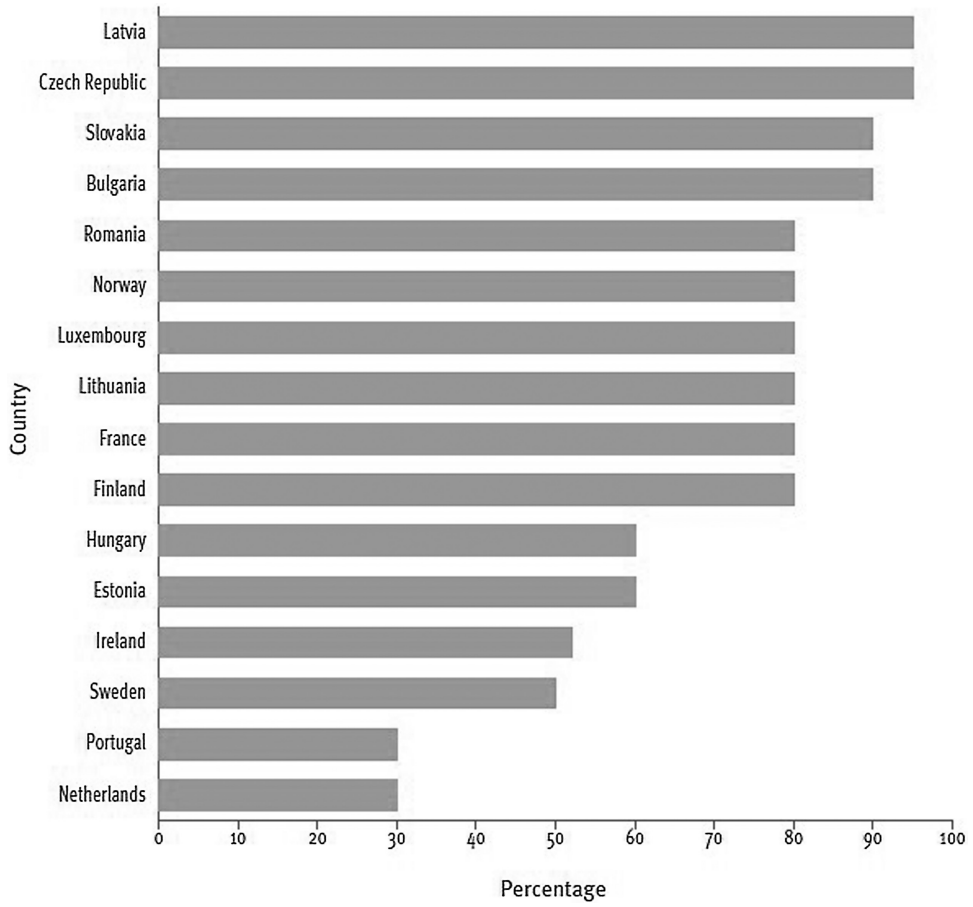

Figure 3 Tuberculosis surveillance and monitoring 2020, and ECDC.[30]
WHO EURO: World Health Organization Regional Office for Europe; ECDC: European Centre for Disease Prevention and Control.

follow-up in children deemed clinically and socially suitable for home-based TB meningitis treatment.[35]

America

In Montreal, Canada, a study evaluated LOS temporal trends for patients with pulmonary TB between 1993 and 2007.[36] The median LOS was 17.0 days, with positive sputum-smear cases showing a longer hospital stay (≥14 days) in comparison with those without (OR = 1.90; 95% CI: 1.34–2.70). Furthermore, older age (≥50 VS. 18–49 years) was associated with longer LOS (OR = 1.66; 95% CI: 1.15–2.40). A LOS ≥ 14 days was consistent with the minimum length recommended by national guidelines but further evidence was needed to evaluate the impact of hospital admission in reducing the community risk of *Mycobacterium tuberculosis* transmission.

Another experience from Montreal (January 1997- May 2007) reported on 0.65 hospitalizations per TB case, with 17.8 hospital days per TB patient, and a mean LOS of 27.2 days.[37]

In the USA[38] the overall mean annual number of hospitalization events per individual TB patient increased over time from 0.49 (1997–2000) to 0.57 (2013–2016). Moreover, the mean LOS increased from 7.3 to 11.3 days, equal to a change from 3.6 to 6.5 hospital-days per patient.

The mean (standard deviation [SD]) LOS in three Brazilian hospitals in 2013 was 28.2 (32.6) days, without statistically significant differences between HIV-positive and -negative TB patients.[24]

Of a cohort of 3991 TB/HIV co-infected patients in Rio de Janeiro, Brazil,[39] evaluated between 2007 and 2013, 46.6% were hospital admitted (10.44 per 100 person-years). An annual decrease was recorded for both the hospitalization rate (incidence rate ratio 0.92) and LOS (median of 15 days in 2007 VS. 11 days in 2013; p-value for trend <0.001).

Europe

A survey conducted in 1999 in an Italian sample recruiting 203 pulmonology centres showed a median LOS of 34 days for sputum smear-positive, 20 days for sputum smear-negative, and 21.5 days for extra-pulmonary TB cases. Sputum smear conversion to negative was considered the key criterion for discharge in 61% of the centres.[40] A switch from hospital- to home-based treatment (limiting hospital admission to severe cases) was recommended based on cost-effectiveness.[41] In the study no information of the patients' drug resistance profile was available.

In a Portuguese sample of 15,296 TB cases (4,415, 28.9% admitted) enrolled between 2008 and 2013, hospital admission did not influence treatment outcomes, with 13.8%

unfavourable outcomes among hospitalized patients compared with 7.6% among non-hospitalized ones.[42,43]

In the Russian Federation, as published in 2007, the LOS was rather longer both before (86 days) and after (90 days) the implementation of the WHO Directly observed treatment, short-course (DOTS) Strategy.[44] This LOS refers to patients with drug-susceptible TB.

In Spain 41% of cases were managed in 2014–2015 as outpatients,[45] with a mean LOS of 11.3 (±7) days. Out of 319 patients included in the study, only 14 (4.5%) were TB drug-resistant. The authors concluded that an important proportion of the overall management cost of TB patients was related to hospital admission, and recommended to reduce the hospital stay. This prospective study involved 19 hospitals belonging to SEPAR (Sociedad Española de Aparato Respiratorio) network.

A recent study from Switzerland[46] estimated a TB hospitalization rate of 81% between 2002 and 2015, with a median (IQR) LOS of 14 days (6–22). LOS increased in case of miliary TB, older age, and for some hospital locations. The most prevalent comorbidities were HIV infection, liver disease, anaemia, malnutrition, and genito-urinary tract disease. LOS was specifically evaluated in the following subgroups: 1) malnutrition, cachexia and anaemia (median, IQR: 20, 13–31, days); 2) alcoholic liver disease and hepatitis (median, IQR: 23, 14–37.5, days) and 3) adverse drug events (median, IQR: 20, 13–30, days).

Summary of the findings

1) The proportion of *newly diagnosed* admitted TB cases ranges between 50% and 100% (47% in Brazil, 57% in USA, 65% in Canada, >80% in the WHO European Region where the proportion of patients hospitalized is higher than in the other settings evaluated;
2) The proportion of *MDR-TB* admitted patients is ∼100% in Europe and 85% in the bedaquiline study;
3) The proportion of *TB and COVID-19* admitted patients is around 58% according to the limited evidence available, which included about 80% of drug-susceptible TB patients.[26] Different reasons are likely behind this figure, including the need to admit patients after simultaneous diagnosis of both diseases, or to re-hospitalize TB cases already discharged after initial anti-TB treatment and worsened because of COVID-19 (or COVID-19 appearing in already hospitalized TB patients).
4) LOS of *newly diagnosed cases* ranges from 20 to 60 days in Europe, similarly to Canada (mean 17 and median 27 days), Brazil (median 15 days), and Italy (not included in the European dataset: 31 days for sputum smear-positive patients and 20 days for other cases). Studies from USA report the lowest LOS (mean 10 days) and the Russian Federation the highest (∼90 days).
5) LOS of *MDR-TB patients* was 50–100 days in most of European countries, ∼180 days in the bedaquiline study (which reported severe cases with high proportion of XDR-TB) and 29–47 days for *TB and COVID patients*.

The duration of hospital stay depends on bacteriological conversion in several countries.

TB/COVID-19 admissions

Global TB/COVID-19 project (2020, interim analysis)

An interim analysis was conducted on 381 patients from 40 countries: 263/381 (69%) were hospitalized for COVID-19, 31/263 (12%) were still hospitalized, 201/263 (76%) were discharged and 31/263 (12%) died, whereas 113/381 (30%) were not hospitalized. Information on hospital admission was missing in 5 (1%) patients. As reported under 'TB admissions', a total of 141/381 (37%) patients underwent hospital admission for concomitant TB and COVID-19.

The median (IQR) LOS attributed to COVID-19 was 16 (10–22) days.

Hospital admission data for COVID-19 is not yet comprehensively and systematically reported by Member States to WHO. Following different sources of already existing data inputs, however, hospital stay duration can differ widely depending on numerous factors, including age and co-morbidities among others.

A study conducted in 25 European countries by the members of the Paediatric Tuberculosis Network European Trials Group on COVID-19, hospital admissions in children and adolescents identified 582 individuals during April 2020 with polymerase chain reaction (PCR) test confirmed of SARS-CoV-2 infection with a median (IQR) age of 5·0 years (0·5–12·0): TB was not documented as comorbidity in any of these individuals.[47]

Recommendations on hospital admission

Several documents consistently reported recommendations for TB-related hospital admission in Europe[21,22,48] summarised as follows:

a) TB-related conditions requiring hospital treatment (i.e., respiratory failure and surgical emergencies e.g - haemorrhage, pneumothorax, and pleural effusion);
b) Severe forms of TB and/or pre-existing co-morbidities exacerbated by TB which cannot be managed in outpatient settings (e.g., coma, liver or renal disease, uncontrolled diabetes, etc.)[49];
c) Life-threatening or severe adverse effects associated to anti-TB drugs (e.g., arrhythmias, psychosis, renal failure, hearing loss), particularly in fragile/non-self-sufficient patients.

Additional considerations on hospitalization include:

1) Patients where effective and safe treatment cannot be ensured in outpatient, community, and home settings (e.g., homelessness, overcrowding, exposure of children aged <5 years and pregnant women in households, children with severe TB and unreliable caregivers) or difficult geographical accessibility (e.g., long distance to outpatient facilities or problematic travel conditions);
2) Involuntary isolation of non-adherent patients once all other healthcare options have been unsuccessfully tried.

It was recommended to care for admitted patients in single rooms. In hospital settings, people with presumed infectious TB or confirmed pulmonary TB should be assessed rapidly for MDR-TB, using existing rapid diagnostic methods to allow adequate management and reducing the risk of transmission, especially to those patients with immune-compromised conditions/status.

Importantly, several pre-conditions have been proposed to allow safe in-hospital management:

a) Appropriate infection control and prevention measures should be in place and continuously assessed[50];
b) Respiratory isolation rooms should be available for TB patients until they are smear/culture-negative;
c) Staff should be trained and adequately supervised, and adhere to administrative measures included in the facility's infection control and prevention plan;
d) Trained staff should be available to ensure quality patient-centred care;
e) Open and safe space should be available for patients to socialize according to infectiousness status and resistance patterns (ideally not mixing infectious with non-infectious patients or drug-susceptible and drug-resistant patients);
f) ''Friendly'' but effective administrative procedures should be in place to facilitate regular access of visitors;
g) Protocols should be in place for effective communication and coordination, detailing terms of reference for involved staff including accountability and responsibility, for laboratories providing services during treatment and for peripheral units receiving patients after hospital discharge;
h) Reference clinical centres located in low TB incidence countries should ensure quality services based on a minimum number of patients necessary to maintain proficiency.

Specific recommendations on hospitalization of TB/COVID-19 patients are not yet available. As of today, we need to consider the existing criteria for the most severe prevalent condition. If TB is the most relevant condition, the criteria defined above can be used to guide decisions. COVID-19 hospitalization will be needed when the disease is clinically severe, i.e. in presence of respiratory failure (desaturations, and need for oxygen supplementation or mechanical ventilation) or, in the future, when the patient will meet specific clinical-radiological scores that are under study.[12]

Criteria guiding hospital discharge

Criteria for hospital discharge of co-infected (SARS-COV-2 and TB) patients should be based mainly on the TB clinical course given that COVID-19 is a disease with a fast clinical evolution and it can stop requiring hospitalization more rapidly than TB.

The criteria for hospital discharge are:

a) Clinical improvement of TB (e.g. improvement of signs and symptoms, radiological improvement, weight gain);
b) Clinical improvement of the co-morbidities and/or of the adverse events precipitating the hospital admission;
c) Effective treatment and continuity of care ensured with a patient-centred model of care as per WHO and national guidelines.

Bacteriological conversion *per se* is not a mandatory criterion for hospital discharge, given that precautions are recommended to educate family members on basic infection control and prevention requirements and to monitor the continuation of treatment at home. Adequate treatment can render patients rapidly non-infectious, although sputum smear positivity can be present for a longer period (dead bacilli).[21,22] Nevertheless, transmission can occur if an ineffective regimen is prescribed – for example, when a first-line or sub-optimal regimen is used in MDR-TB patients. Thus, MDR- and XDR-TB regimens need to be guided by rapid drug susceptibility testing.[21,22,29,51,52]

Typically, patients have already infected their household members prior to diagnosis.[21,22] Therefore, contact-tracing of household members and other close contacts is essential to rapidly diagnose and treat them and reduce transmission of *Mycobacterium tuberculosis* within the community.

In summary, ambulatory treatment of TB (regardless of smear and drug-susceptibility patterns) is possible from the beginning to reduce the risk of hospital transmission and improve treatment adherence. Importantly, outpatient care should be organised following strict infection control and prevention measures.

Conclusions

Existing evidence from WHO guidance and the literature review indicate that a high proportion of TB cases continue to be admitted in hospitals, and for relatively long length of stay. This is particularly evident in Europe.

Among the different reasons behind this finding, existing legislation on infection control (e.g. patients cannot be discharged until bacteriological conversion has been achieved) and funding mechanisms (focus on per bed occupancy) play a role, slowing down the 'reduction of unnecessary hospital admission' recommended by WHO.

A collaboration of all stakeholders involved in TB prevention, diagnosis and treatment is necessary to support the WHO recommendations in order to reduce patient suffering, TB transmission and lower costs within a patient-centred vision.

Declarations of interest

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LETTERS TO THE EDITOR

Never Give Up: Lesson learned from a severe COVID-19 patient

To the Editor,

COVID-19 pandemic is causing major health consequences in affected persons needing hospital admission. Since the first epidemic outbreak in China we have learned that several factors including older age, comorbidities and individual immunological responses to infection may differently address the risk of disease progression and outcome.[1] Moreover, there is now quite a unanimous consensus that mortality rate of critically ill patients with SARS-CoV2 pneumonia admitted to Intensive Care Unit (ICU) is really considerable[2] and even a slightly higher than that recorded in patients with moderate to severe Acute Respiratory Distress Syndrome (ARDS).[3]

Different attempts using experimental anti-viral[4] and/or systemic anti-inflammatory drugs[5,6] have been made to counteract both disease progression and fatal prognosis. Meanwhile, an expert opinion-based document was launched in order to address the early management-related actions for the individual patient, including the choice of an appropriate setting of care and the timing for non-invasive (NIV) or invasive mechanical ventilation (MV).[7]

In light of this, we here report the clinical course of a 72-year old Caucasian male (M.A.) admitted for SARS-CoV2 pneumonia at our University Hospital in Modena on last March 5th. A multidisciplinary medical staff composed of different specialists (infectious diseases, pulmonology, intensive care) was in charge of care and assuming shared clinical decisions.

Past medical history was characterized by limited atherosclerosis, systemic arterial hypertension, and stable chronic B-cell lymphocytic leukemia (LLC) only requiring periodic follow-up. Onset of symptoms was reported 6 days before admission and infection by SARS-CoV-2 was confirmed by RT-PCR swab nasal/throat samples on the day of admission. Patient presented with fever (38 °C), dry cough, tachypnea (respiratory rate-RR = 24 bpm) and mild respiratory failure (PaO2/FiO2 242 breathing room air). Fig. 1 shows the chest-X-ray and the lung ultrasound pattern on admission (day 1). Given the neurological and hemodynamic stability (Subsequent Organ Failure Assessment-SOFA score was 1) he was admitted to the Infectious Disease Unit where oxygen supply through nasal cannula at the flow of 2 L/min and antiviral therapy with darunavir/cobicistat was started in addition to hydroxychloroquine and azithromycin according to our local recommendations. Blood C-reactive Protein (CRP 7.8 mg/dl) was high whereas white blood cell-WBC count ($62.510\,ml^{-1}$) was abnormally increased also due to his LLC condition.

On day 4, patient experienced a major respiratory worsening (PaO2/FiO2 105), with RR > 40 bpm) despite oxygen supply at FiO2 60%). A multidisciplinary staff evaluation was conducted to balance the need for immediate endotracheal intubation (ETI) and MV with the potential risks derived from his hematological co-morbidity. Decision was taken for a non-ICU care approach thus NIV in pressure support mode was started with the aim to target a pulse oximetry level >90% and a RR <30 bpm. At the same time, other anti-

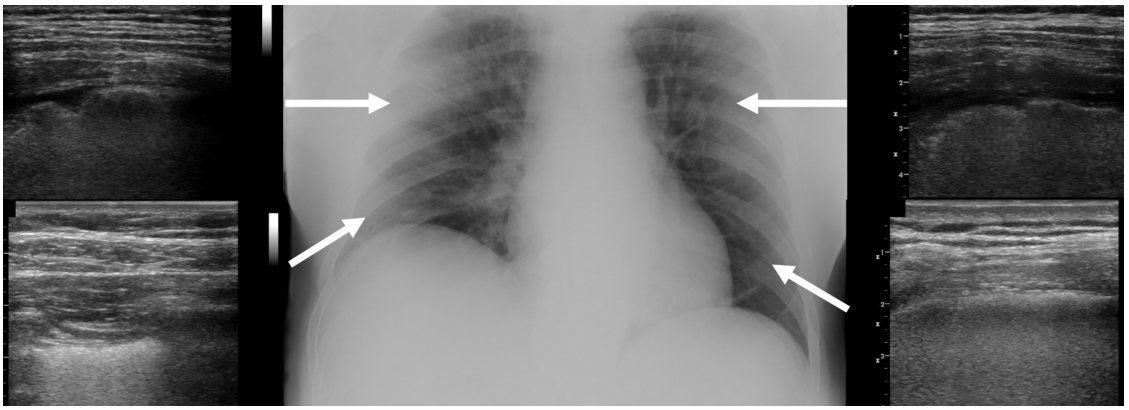

Figure 1 Chest X-ray on admission shows diffuse interstitial abnormalities alongside scattered bilateral infiltrates. Arrows indicate the local ultrasound patterns, in particular: irregular vertical artifacts (B-lines) with impaired pleural sliding next to subpleural small consolidations in the upper anterior sites and thick and confluent B lines in the low posterior site.

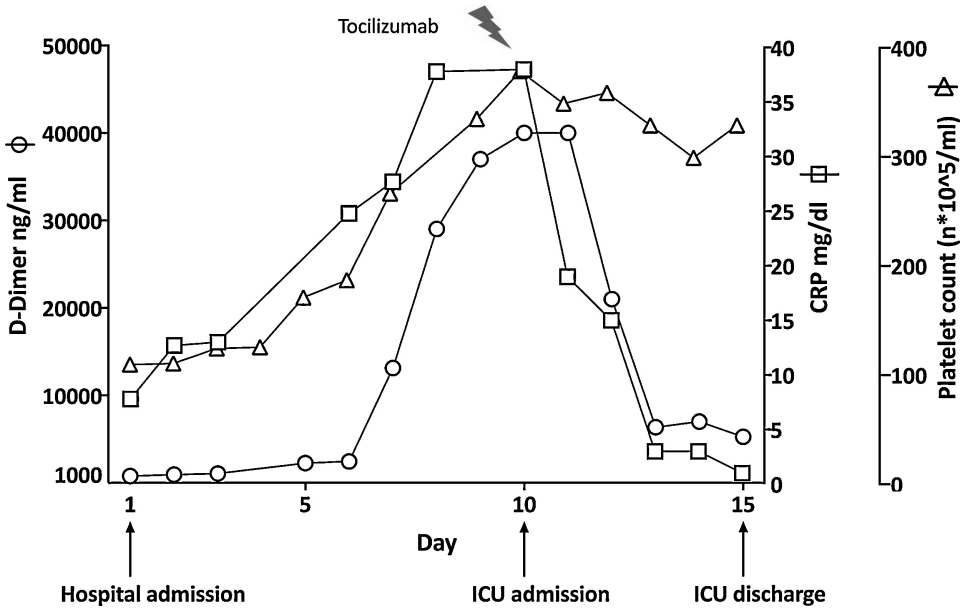

Figure 2 Time course of the inflammatory serum biomarkers D-dimer (*circle*), CRP (*square*), and Platelets (*triangle*), during admission in the COVID-19 area at the University Hospital of Modena.

inflammatory drugs for off-label therapeutic indication were not available in the hospital pharmacy.

From day 5 to 9, patient continued on supported breathing. Finally, he presented uncontrollable respiratory distress despite NIV and maximal oxygen supply (PaO2/FiO2 < 100) on day 10. There was a further multidisciplinary evaluation and, having become available, off-label i.v. Tocilizumab (8 mg/kg of body weight with 2 infusions 12-hour apart)[6] and admission to ICU for endo-tracheal intubation and mechanical ventilation were adopted as rescue therapies. On day 13 patient's condition and gas exchange improved (PaO2/FiO2 121) and tracheostomy was performed, while patient progressively returned to an assisted breathing modality. The time course of the main inflammatory serum markers over the admission period is shown in Fig. 2.

On March 18th (day 15), M.A. was transferred to a different hospital in our provincial area (Ospedale di Sassuolo) for weaning purpose. Respiratory condition progressively improved reaching spontaneous breathing on day 23, while a supervised physiotherapy protocol was started due to the consequences of prolonged immobility. Tests to assess the vocal cord and swallow integrity were then performed, according to the recommended procedures, leading on April 6th (day 31) to removal of both the naso-gastric tube and the tracheal cannula. Oxygen supplementation was also withdrawn on the same day. Two consecutive nasal/throat RT-PCR swab samples were confirmed negative for RNA virus and specific immunoglobulin-G were dosed in serum, so patient was discharge as cured and transferred to a rehabilitation unit to complete his recovery (day 33).

The story of M.A. confirms the heavy risk and the long and difficult clinical process behind any severe pneumonia due to SARS-CoV2 infection and prompts several considerations.

First, it is quite clear that the clinical course in patients hospitalized due to pneumonia and worsening respiratory failure is unforeseeable, thus requiring great attention and prompt action. The complexity, comorbid status and age of the patient only partially explain this variability. Indeed, it has been recently hypothesized that least 3 different grades of increasing severity may be recognized, which correspond to, distinct clinical findings, response to therapy and clinical outcome, and are likely to depend on the balance between the viral phase and the host inflammatory response.[8]

Second, the history of M.A. at least partially proposes the unprecedented decisions to be taken, whether by hospital, physicians and/or nurses, i.e. withhold a ventilator and/or access to ICU when faced with an anticipated shortage of ventilators and ICU-beds during an uncontrolled epidemic outbreak[9] or with a clinical discussion on a proportionate treatment. This might in turn overexpose clinicians to the risk of civil or criminal liability in the absence of clear Government assurance when facing extraordinary events.[10] Given the particular condition to which M.A. rushed after admission, the decision taken to proportion intensity of respiratory support by NIV could have led to an unwanted liability.

Third, it should be noted that, as tocilizumab was not available to prompt a potentially anti-inflammatory drug effect, even in a later stage as was the case of our patient (see Fig. 2), the choice to use NIV was indeed the only means to ''buy time'' before any upgraded decision of care could be taken. This highlights the role that noninvasive respiratory support may have during COVID-19 epidemic, which is not only to manage the advanced hypoxic respiratory failure,[7] but also to help clinicians to assist a very severely ill patient even if at high risk. Ongoing data on this epidemic are showing that the decision to prevent endotracheal intubation by NIV might be a safe option for patients. While we are waiting for more convincing data on the role of anti-inflammatory agents to early brake systemic inflammation and progression of the disease,[6,11] it has been

discussed whether or not early ETI and MV would be the best option for the COVID-19 patient's outcome.[12] One of the hypotheses behind this is that COVID-19 is not a typical ARDS, so MV in many cases is not the right treatment. COVID-19 patients show significant vasoconstriction of small blood vessels compared to the healthy and ARDS patients. It is known that ventilation reduces the small blood vessel size, meaning it is probably making things worse for most COVID-19 patients. Notably, a very recent audit in UK in over 6000 patients shows that death rate in COVID-19 patients using advanced respiratory support (ETI, MV, ECMO) is significantly higher as compared with patients on basic support (oxygen with inspiratory fraction >50%, CPAP/BIPAP) (66.3 vs. 51.6%, respectively). This in turn expresses a much higher risk rate when compared to that (22%) occurring in a retrospective series of hospitalized non-COVID viral pneumonia.[13]

Finally, present experience has led clinicians to the evidence that such a very severe situation with difficult and risky decisions unavoidably lead the patient to a long clinical course with associated disability.[14] Since beating the virus is just the beginning, any lack of access to early physiotherapy and to a long-term strategy for survivors of severe COVID-19 is a problem to be overcome urgently.[15]

From our personal experience during COVID-19 epidemic we encourage colleagues not to give up in all circumstances due to this happily ending story.

(At the time of submission, the smiling photo of M.A. received 1.641 like and 79.712 visualizations on LinkedIn at https://www.linkedin.com/feed/update/urn:li:activity:6653733697633812481/)

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Consent to publish data

Informed consent to publish data was obtained from the patient.

Conflicts of interest

The authors have no conflicts of interest to declare.

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Prevention measures for COVID-19 in retail food stores in Braga, Portugal

COVID-19 is the designation of the World Health Organization for the infectious disease caused by the new coronavirus, which can cause severe respiratory infection, such as pneumonia.[1] The main modes of transmission of COVID-19 are: 1) close contact with people infected by the virus or 2) contact with contaminated surfaces or objects. Transmission takes place through droplets that are expelled when a person with COVID-19 coughs, sneezes or speaks, or through contact with contaminated hands that touch the eyes, nose or mouth of a person (hands are easily contaminated by contact with objects or surfaces where droplets from an infected person have landed).[2] Knowing that close contacts can contribute to increasing the spread of the infection, breaking these transmission chains is essential.

In this context, the Portuguese Directorate-General of Health (DGS) has been issuing guidelines on the public health measures to be adopted by public service establishments to prevent the spread of the virus.[3] Briefly, the best practices recommended by DGS include the following: guarantee that checkout counters maintain physical distance of 1 m; post signage on the floor to help customers maintain adequate social distancing; create physical barriers between employees and customers, in order to avoid ''excessive approximation between individuals''. As measures for cleaning and sanitizing, DGS recommends disinfecting the whole store area at least once a day; and frequently cleaning (at all hours) the high-touch surfaces, such as ticket dispenser machines or ATMs. Moreover, alcohol-based solutions should be provided in strategic locations.[3] This observational study aims to describe the measures adopted to prevent the transmission of COVID-19 by retail food stores in the municipality of Braga, Portugal.

To this end, a researcher from the Institute of Education of the University of Minho designed and implemented a descriptive observational study, carried out between 5th and 8th April 2020, with a convenience sample of eight retail food stores in the municipality of Braga (Portugal). Observations and registries were made by three researchers in different types of stores (mini markets, supermarkets, and hypermarkets). Each store was observed once. Researchers were, on average, 10 min in each outlet. Data was collected by filling out a previously prepared form, which included the following variables: I. Measures adopted outside the store (signs of disinfection of the floors; disinfection of shopping carts/baskets; measures to prevent overcrowding; existence of signage that encourages employees and customers to practice health safety procedures such as social distancing and wearing face mask); II. Measures adopted inside the store (indication of the necessary physical distance between people; provision of hand sanitizer, gloves, or other personal protective equipment); III. Employees (cashier: use of a visor or a mask/glasses, use of gloves, existence of acrylic separator walls at counters; store operators: use of a visor or a mask, use of gloves); IV. Customers (gender; age group; use of a surgical or handmade face mask, or a scarf; use of a visor/other; use of gloves).

Six of the eight establishments observed showed signs of disinfection of the floors. Four of them disinfected shopping carts/baskets; almost all employed measures to prevent overcrowding ($n = 7$) and all of them displayed signage and warnings about COVID-19. As to measures adopted inside the store, most had indications of the necessary physical

distance between people ($n = 7$); three provided hand sanitizers, only one provided gloves. Regarding employees, in four of the eight stores observed the cashiers wore a visor or mask/glasses and gloves; in seven stores there was an acrylic separator wall between them and the customers. Store operators wore gloves in three out of eight outlets, but in only two cases they used a visor or a mask. Of the 78 customers observed, 47 (60.3%) were women and the majority were between 18 and 65 years old ($n = 60$; 76.9%). In the total sample, 26.9% ($n = 21$) used a surgical mask and 0.05% ($n = 4$) used a handmade mask or scarf. No customer wore a visor. Gloves were the most commonly used equipment by customers ($n = 25$; 32.1%).

To sum up, compliance with prevention measures recommended to avoid COVID-19 contamination in retail food stores in Braga varied widely between outlets in April 2020. There were examples of excellent practice, but also of poor practice. Only one store met all recommended standards. The situation is more worrying in mini markets, where none of the recommendations were being followed. The main shortcomings, in general, were the absence of protective equipment for the employees, and lack of hand sanitizer for customers. According to recent information from the European Centre for Disease Prevention and Control,[4] one of the best preventive practices to reduce the transmission of COVID-19 is the generalized use of face masks as a complementary measure to safety distance, proper education being fundamental for their safe use.

Ethical disclosures

Protection of human and animal subjects

The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data

The authors declare that the procedures followed were in accordance with the regulations established by the Commission for Clinical and Ethical Research and in accordance with the Helsinki Declaration of the World Medical Association.

Right to privacy and informed consent

The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

Conflict of interest

The authors have no conflicts of interest to declare.

Authors' contributions

Precioso conceived this study, collected the data, designed, and carried out statistical analysis. Samorinha and Precioso wrote the first draft of the manuscript. Samorinha carried out statistical analysis and revised the manuscript critically. All authors contributed substantially to the interpretation of data, critical discussion, and revision of the manuscript, and approved its final version.

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Pulmonary artery thrombosis in COVID-19 patients

Dear Editor,

Arising in China in the winter of 2019, COVID-19 (caused by the SARS-CoV-2 virus) has caused a global pandemic and severely stressed medical systems across the world.

Although knowledge about this novel coronavirus is still emerging, the most common reason for hospitalization of COVID-19 patients is severe respiratory distress.[1]

COVID-19 has been accurately described as the cause for a proinflammatory and hypercoagulable state with marked elevations seen in Lactate Dehydrogenase, Ferritin, C-reactive protein, D-Dimer, and Interleukin levels.[2]

The inflammatory response, including production of inflammatory cells and cytokines, induces a procoagulant effect and diffuse endothelial damage that predisposes thrombotic vascular lesions and Disseminated Intravascular Coagulation (DIC).[3]

D-Dimer is related to the severity of the disease and an increased value is associated with the worst. prognosis. Retrospective studies demonstrated that patients admitted to

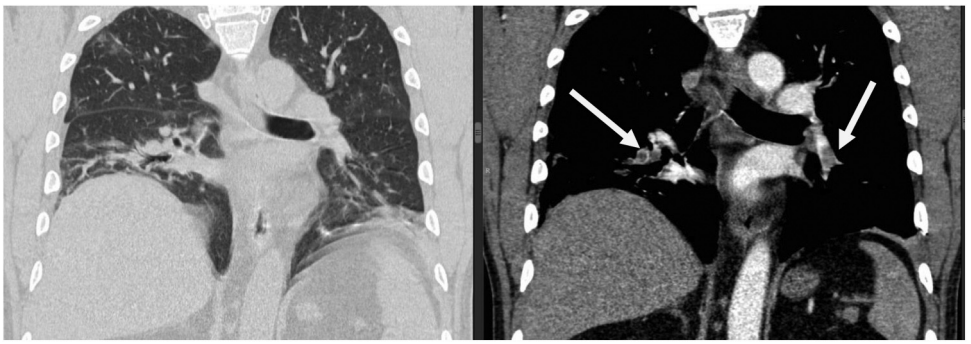

Figure 1 Computed Tomography Pulmonary Angiography (CTPA) described signs of Pulmonary Artery Thrombosis (PAT) involved the lower pulmonary branches (yellow arrows).

Table 1 Laboratory parameters in patients with Pulmonary Artery Thrombosis (PAT) and the patients without PAT.

	All Pts admission	PAT pts admission	All pts 5 days	PAT pts 5 days	All Pts 10 days	PAT pts 10 days
C-Reactive Proteine (mg/l)	54,6 ± 58,1	54,6 ± 58,1	44,9 ± 65,1	54,6 ± 58,1	27,0 ± 25,5	49,5 ± 27,6
Lymphocite (mmc)	1294 ± 761,3	1260 ± 414,5	1465 ± 657,6	1075 ± 219,2*	1762 ± 858,6	1290 ± 336,7*
Platelets (mmc)	250,000 ± 84,000	263,000 ± 147,000	300,000 ± 114,000	252,800 ± 52,900	352,300 ± 102,900	289,000 ± 113,000
Fibrinogen (mg/dl)	432,3 ± 114,1	530 ± 121,6	428,5 ± 138,2	426,0 ± 14,1	379,6 ± 100,4	466,1 ± 142,1
LDH (U/l)	264,4 ± 101,3	326,2 ± 121,9	295,2 ± 120,6	314,5 ± 37,5	264,0 ± 73,5	309 ± 63,7
INR	1,2 ± 0,1	1,1 ± 0,01	1,2 ± 0,15	1,05 ± 0,1	1,2 ± 0,1	1,1 ± 0,1
D-Dimer Ug/l	465,1 ± 121,7	627,4 ± 178,6	538,3 ± 102,8	2143,6 ± 327,5*	576,9 ± 169,1	1764,9 ± 227,5*

* $P < 0,05$.

Intensive Care Unit (ICU) had an elevated D Dimer value and, in this setting, some Authors recommended a therapeutic heparin doses for the patients with higher values.[4]

A recent ICU observation reported an increased risk of Pulmonary Embolism (PE) in COVID-19 compared to the historical control group even in patients that had undergone the Low Molecular Weight Heparin (LMWH) prophylaxis.[5]

We evaluated 138 patients with COVID 19 admitted to our Institution between March 2020 and May 2020. All patients were COVID 19 positive according to clinical diagnostic criteria reverse-transcription–polymerase chain-reaction (RT-PCR) and Chest Thoracic tomography. On admission, most of them were haemodynamically stable (78%) and febrile (87%). During hospitalization, some developed progressive respiratory failure and received oxygen supplementation (41%). Four of them were started on Continuous Positive Airways Pressure (CPAP) but two died because of worsening Respiratory Failure.

All patients were treated with hydroxycloroquine (400 mg/day), darunavir/ritonavir (800/100 mg/day) and enoxaparin (4000 UI/day). Some patients (26 pts) received additional therapy with IL-6 and IL-1 antagonist (20%). Every three days after their hospitalization, laboratory exams with inflammatory and coagulation parameters (INR, activated partial thromboplastin time, platelets count, fibrinogen, D-Dimer) were repeated.

In patients with progressive elevation of D-Dimer of over three times the normal value (from 1822 to 5911 μg/mL), we performed a Computed Tomography Pulmonary Angiography (CTPA) and a Doppler Ultrasound (DU) of the lower limbs. The tests were done during the second week of their hospitalization (12,3 ± 3,2 days).

We identified eleven patients with high D-Dimer value, nine of them (6,7%) had signs of Pulmonary Artery Thrombosis (PAT) without Deep Venous Thrombosis (DVT). The lesions were distributed bilaterally at the lower arterial branches (Figure 1). None of the nine patients experienced an objective respiratory worsening and those in oxygen therapy (5 patients) maintained a constant flow. Therapeutic anticoagulation was started with subcutaneous enoxaparin (1 mg/kg) twice daily, followed by warfarin. All patients were discharged home: length of hospital stay (LOS) 21,1 ± 3, 7 days.

In Table 1 the laboratory parameters were compared between patients with and without PAT: five days after admission, only D-Dimer value and lymphocyte count were significatively different between the two groups.

Parameters are expressed as mean ± SD and statistically evaluated by Student T test. $P < 0,05$ was considered statistically significant.

Coagulopathic disorders are significantly increased in COVID-19 patients, especially among those with severe dis-

ease. Several mechanisms combine systemic inflammation with alterations of coagulation in COVID 19 patients.[6]

In severe or critically ill patients, the endothelial cells are damaged and release a large amount of inflammatory mediators that may predispose vascular thrombosis. A study performed in ICU setting reported an increased risk of Pulmonary Embolism (PE) in COVID-19 patients treated with Low Molecular Weight Heparin (LMWH) prophylaxis compared to the historical COVID 19 negative control group.[7] Another Study reported that the prevalence of Venous Thromboembolism Events (VTE) was higher in ICU compared to general wards patients: 47% vs 3%.[8]

High blood values of the procoagulant factor levels including fibrinogen and D-dimers have been associated with the worst prognosis and higher mortality.

Kaminetzky and coworkers compared the results of a cohort of 62 patients who underwent CTPA for suspected PE prior to the first case of COVID 19, with 62 patients COVID 19 positive.[9] CTPA was positive for PE in 37% of COVID 19 patients (14,5% in pre COVID patients), D-Dimer was associated with a higher prevalence of thromboembolic events and correlated with the degree of PE severity.

In a group of patients admitted to non-ICU wards, DU failed to detect DVT independently of the severity of their condition and length of in-hospital bed rest. The Authors observed that this is apparently in contrast with the relatively frequent reports of PE in hospitalized COVID-19 patients It is possible that local thrombi in the lungs may be the cause of pulmonary arterial manifestations.[10, 11]

In this paper we reported COVID-19 patients with interstitial pneumonia admitted in our non-ICU Ward.

During the course of hospitalization, in eleven of them, we observed a progressive increase of D-Dimer over three times the normal value, associated with low or normal values of other coagulation or inflammatory blood parameters (CRP, LDH, Ferritin, fibrinogen, INR, aPTT).

Nine CTPA demonstrated a distal thrombosis of the lower pulmonary arterial branches. The mainly basal localization where the pulmonary inflammation is most diffuse and the loss of signs of DVT may suggest a pulmonary thrombosis rather than an embolism.

It is noteworthy that no patients had any signs of respiratory worsening and some of them did not receive oxygen therapy and they were breathing room air.

In conclusion, we described patients with moderate disease who developed a pulmonary vascular injury strictly correlated with an elevation of D-Dimer values. This parameter may help clinicians in identifying COVID-19 stable patients at risk of concurrent pulmonary artery thrombosis.

Further studies will need to better define the meaning of these preliminary observations.

Conflicts of interest

The authors have no conflicts of interest to declare.

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Are patients with autoimmune disorders eligible for immunotherapy?

Dear Editor,

Positive results from recent clinical trials led to the approval of immunotherapy based on checkpoint inhibitors (ICI) for a variety of cancers.[1] The ICI-class drugs include anti-PD-1 (nivolumab, pembrolizumab), anti-PD-L1 (atezolizumab, durvalumab, avelumab), and anti-cytotoxic T lymphocyte-associated antigen (CTLA-4) agents (ipilimumab, tremelimumab).[2] It is important to mention that all trials leading to the approval of CTLA-4 or PD-1/PD-L1 blocking agents excluded patients with pre-existing active autoimmune disorders (AD) from enrolment,[1] because of the potential for increased severe toxicity, such as fulminant myocarditis. Having an overactive immune system is the main reason why many patients with cancer and AD have not been included in hundreds of clinical trials of immunotherapy drugs.

Up to 80% of patients under ICI experience inflammatory and immunorelated adverse events (irAEs) in various organs that can be detrimental to patient outcomes.[3] The actual mechanism of ICI-induced toxicities remains poorly defined, as does the exact mechanism of several AD.

AD represent a spectrum of conditions with a common denominator: the (auto) immune attack and damage of normal tissues, either localized in individual organs, systems, or widespread (systemic). More than 80 distinct AD have been identified, including some diseases with moderately high prevalence such as rheumatoid arthritis, and inflammatory bowel disease.[1] As the use of ICI expands to more types of cancer, the need to determine the risk-benefit ratio in patients with cancer and pre-existing AD is increasing. The number of studies and clinical cases reported is growing. Khan et al. conducted a study in the University of Texas in order to calculate the incidence of AD in the population of lung cancer patients older than 65. Approximately 14% to 25% of the enrolled patients had an AD. The most common AD diseases in the patients studied were rheumatoid arthritis (5.9%), psoriasis (2.8%), and polymyalgia rheumatic (1.8%).[4] A more recent paper by Khozin et al.,[5] also presents a high value of prevalence of AD in lung cancer patients (22%). Potential explanations included in these articles, for the relatively high rate of AD among patients with lung cancer include advanced age at diagnosis and smoking history, which has been linked to higher risk of certain AD.[4]

In this context, the authors describe two clinical cases of patients with AD, who were treated with immunotherapy, without adverse effects.

Case 1

The authors present the case of a 68-year-old male with a diagnosis of squamous cell carcinoma, initially in stage IIIC (T4N3M0). He had a history of asymptomatic systemic lupus erythematosus, diagnosed at the age of 48. At the time of the lung cancer diagnosis, he was being treated with hydroxychloroquine and corticosteroids for dyslipidaemia, COPD and high blood pressure. The patient was treated with first-line platinum and gemcitabine doublet, after decision in a multidisciplinary meeting, because of the large size of the tumour. Docetaxel was used as second line therapy, after evidence of imagiological progression, and because of the PD-L1 negative expression on tumour cells, Nivolumab was started after disease progression. After four months of immunotherapy, without adverse effects or flare of lupus, imagological confirmation of the progression led to the suspension of therapy.

Case 2

A 63-year-old male with a diagnosis of squamous cell carcinoma, initially tumour stage IVA (T2bN3M1a), due to pleural, pulmonary and ganglionic contralateral mediastinal metastasis is described. The patient had history of psoriasis since he was 50 years old, and smoking habits. At the time of the lung cancer diagnosis, his AD was stable only on topical corticotherapy. The patient was treated with first-line platinum and gemcitabine doublet and, after disease progression, because of the PD-L1 negative expression on tumour cells, Nivolumab was started as second line therapy. The patient is currently in the 6th month of immunotherapy, with stability of the imagological findings. During the entire course of treatment with nivolumab, his psoriasis remained stable without the need for systemic immunosuppression.

Several published articles have described the use of ICI in patients with AD, similar to the cases reported in this article. (Table 1) In a group of 52 patients with pre-existing AD and advanced melanoma, treated with PD-1 antibodies (either pembrolizumab or nivolumab), twenty (38%) patients flared after a median of 1.3 months after the initiation of PD-1 antibody treatment, including 7/13 with rheumatoid arthritis, 3/3 with polymyalgia rheumatica, 2/2 with Sjogren's syndrome, 1/2 with scleroderma, 2/2 with immune thrombocytopenic purpura, 3/8 with psoriasis, and 1/4 with Graves' disease.[1] Khunger et al., reported two cases of patients with Psoriasis, who were treated with Nivolumab for up to 6 months, without worsening of the underlying condition.

Leonardi et al.[6] also conducted a study in 56 patients with NSCLC and AD who received a PD-L1 inhibitor. A total of 55% of patients developed an AD flare and/or an irAE. Exacerbation of the AD occurred in 13 patients. Immune-related adverse events occurred in 21 patients (38%). PD-L1 therapy was permanently discontinued in eight patients because of irAEs.

Kennedy et al. summarized the 8 largest retrospective case series that specifically evaluated patients with pre-existing autoimmunity who underwent treatment with ICIs. The patients in these case series had a wide variety of well-controlled AD, making it difficult to draw conclusions about safety regarding a specific disorder. irAEs and autoimmune exacerbations occurred in a minority of patients.[2]

Based on the limited safety data from the published case series, recommendations regarding which patients may be appropriate for considering ICI therapy in the setting of

Table 1 Some retrospective case series evaluating patients with AD and ICI use. Adapted from Laura et al.

Study	Number[a]	Tumour	ICI	AD flare	irAE rates[b]	Discontinuation
Tison et al[1]	112	Melanoma (59%) NSCLC (35%) Other (6)	PD-1/PD-L1 85% of patients	42%	38%Gr 3–5 16%	Not stated
Leonardi et al[2]	56	NSCLC	PD-1/PD-L1	23%	38%Gr 3/4 10%	14%
Menzies et al[3]	52	Melanoma	PD-1	38%	29%Gr 3/4 10%	12%
Danlos et al[4]	45	Melanoma (80%) NSCLC (13%) Other 7%	PD-1	24%	22%	9%
Johnson et al[5]	29	Melanoma	PD-1	24%	31%Gr 3–5 31%	Not stated
Gutzmer et al[6]	19	Melanoma	PD-1	42%	16%	0%
Richter et al[7]	16	Melanoma NSCLC NHL	PD-1 (69%) Ipilimumab 31%	6%	38%Gr 3/4 25%	31%
Lee et al[8]	8	Melanoma	Ipilimumab	75%	50%Gr 3/4 50%	62.5%

[a] Includes patients study with preexisting autoimmune disease.
[b] Excludes immunotherapy-related events that were felt to be an exacerbation of the patient's underlying autoimmune disorder.
1 – Tison A, Quere G, Misery L, et al. OP0196 safety and efficacy of imune checkpoint inhibitors in patients with cancer and preexisting autoimmune diseases: a nationwide multicenter retrospective study [abstract]. Ann Rheum Dis 2018;77:Abstract 147.
2 – Leonardi GC, Gainor JF, Altan M, et al. Safety of programmed death-1 pathway inhibitors among patients with non-small-cell lung cancer and preexisting autoimmune disorders. J Clin Oncol 2018;36:1905–1912.
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pre-existing AD were made.[7] Patients with neurologic AD, such as myasthenia gravis, or life-threatening AD should not be considered candidates for ICI therapy. Patients receiving high levels of immunosuppression should also be approached with caution. Patients with pre-existing AD who could be considered for ICI treatment include those with a non-life-threatening AD, who have good control on either no immunosuppression or relatively low levels of immunosuppressive therapy.

It is recommended that a multidisciplinary team should be involved in the decision to initiate ICI therapy, with close monitoring and clear consideration of the severity of the underlying autoimmunity, prognosis of cancer, alternative therapeutic options, and a clear understanding of patients' preferences with respect to the risks and benefits of the various options. Finally, it is important to continue to expand understanding of the pathogenesis of irAEs and improve the ability to predict and manage irAEs.

Conflicts of interest

The authors have no conflicts of interest to declare.

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Drug reaction with eosinophilia and systemic symptoms syndrome associated with osimertinib

To the Editor,

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a rare and severe adverse drug reaction, occurring generally about two to eight weeks after the introduction of a causative drug.[1] Cutaneous involvement usually begins with a morbilliform eruption, with cutaneous edema, mainly involving the face, upper trunk, and extremities, spreading from the face to the entire body, with edema of the face being a characteristic finding. Other cutaneous manifestations include vesicles, pustules, erythroderma, and purpuric lesions.[2] DRESS syndrome can be accompanied by different systemic symptoms including fever, lymphadenopathy, hematological abnormalities, or visceral involvement (kidney, liver, heart, lung, muscle, and even brain). Blood test abnormalities typically persist for several days. DRESS syndrome can be life-threatening and is associated with organ failure, with a described mortality up to 10%, although analysis of prospective data shows a lower mortality rate, around 2%.[3] Besides causative drug discontinuation, supportive therapy is generally sufficient and may include antipyretic drugs, systemic antihistamines, and topic corticosteroids. However, in severe cases, with visceral involvement, systemic corticosteroids (0.5–2.0 mg/kg) are usually needed. Aromatic anticonvulsants (e.g. phenytoin, carbamazepine, phenobarbital) and sulfonamides are the most frequent drugs associated with DRESS syndrome.[3] The authors describe a DRESS syndrome induced by osimertinib, in an advanced EGFR mutated lung cancer patient. This third-generation agent was initially associated with scarce skin toxicity in clinical trials, compared to standard agents. After FLAURA trial results showing higher efficacy of osimertinib compared to standard EGFR-tyrosine kinase inhibitors,[4] osimertinib became the first-line treatment of EGFR mutation-positive advanced NSCLC,[5] enhancing the number of patients potentially treated with this agent.

A sixty-year-old woman was initially admitted to the hospital with seizures. The brain scan showed intracranial space-occupying lesions. She started levetiracetam at the end of December 2018 and carbamazepine in January 2019. Investigation revealed a stage IV EGFR mutated (deletion on exon 19) lung adenocarcinoma with the involvement of the central nervous system. She was submitted to radiosurgery and she started systemic therapy with osimertinib (80 mg daily), in early March. After eight days, she was admitted to the hospital with a painful and itchy generalized skin rash on face, neck, trunk, and lower limbs, with preserved skin integrity and with no systemic symptoms. Osimertinib induced skin toxicity was assumed and the drug was stopped. She was discharged from the hospital with topic steroid therapy. But, three weeks after osimertinib suspension, she was readmitted to the hospital with widespread erythema, impaired skin integrity, with no mucosal involvement, and accompanied by fever (Fig. 1). Blood tests revealed eosinophilia (1240/μl; 12.7%)

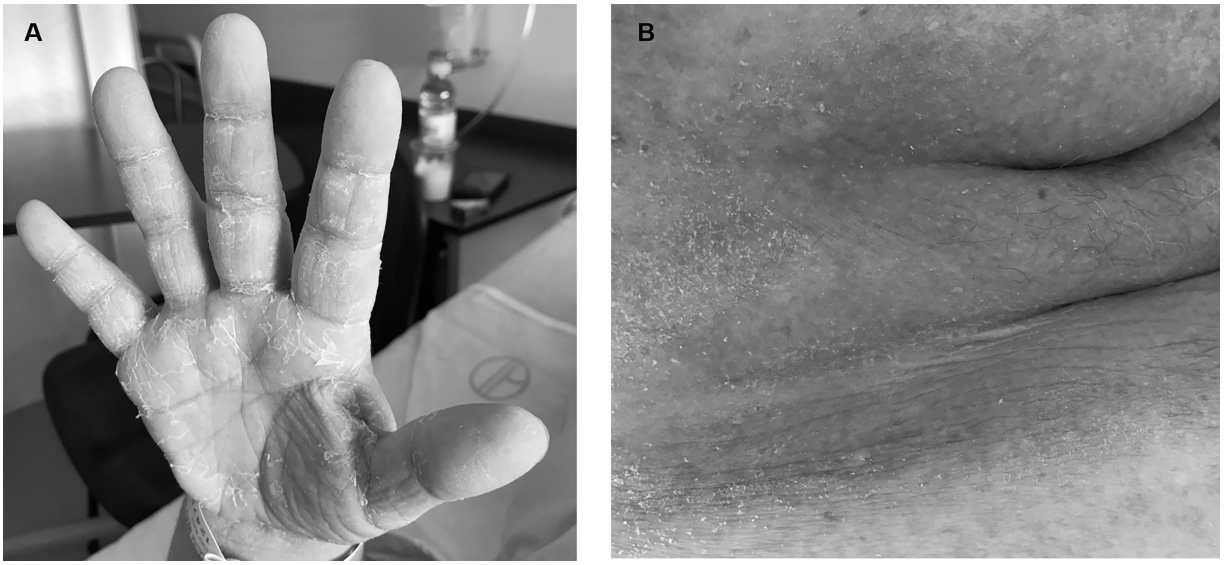

Figure 1 (A, B) — Osimertinib-induced skin lesions. Residual skin desquamation after acute dermatosis.

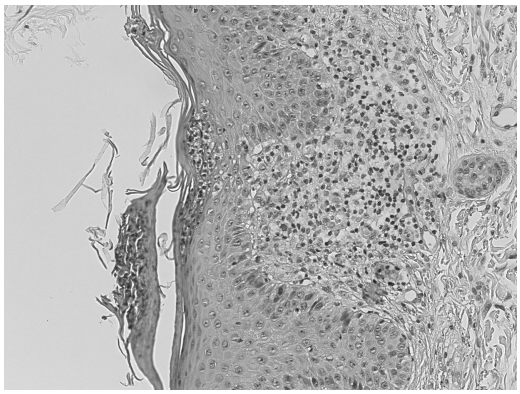

Figure 2 Skin biopsy. A lymphocytic infiltrate with some cells with big nuclei with irregular borders is seen at the superficial dermis. CD4+ and CD8+ cells are in an equilibrated number. Some CD8+ cells are positive for granzyme B. No eosinophils are seen. PAS coloration negative. Within an adequate clinic context, this biopsy is compatible with DRESS syndrome.

with no leukocytosis, acute kidney failure (AKIN II) with ionic changes, and elevation of alkaline phosphatase and lactate dehydrogenase, suggesting DRESS syndrome. She started systemic corticoid therapy (methylprednisolone 1 mg/kg day), teicoplanin, and fluid therapy, with clinical improvement. As skin involvement had worsened after osimertinib suspension, it was thought it could be related to carbamazepine, which was permanently suspended. Thus, after two weeks, with clinical improvement, and under systemic corticoid de-escalation, osimertinib was reintroduced with no evident adverse reaction. The patient remained hospitalized for two more weeks for surveillance. But, eighteen days after osimertinib reintroduction, she was readmitted to the hospital with a severe generalized rash all over the body with epidermal detachment and erosions greater than 30% of body surface area and no mucosal involvement. At that time, her blood tests revealed again a slight eosinophilia (660/μl; 7.3%) with no leukocytosis and acute kidney failure (AKIN II). Osimertinib was stopped again and systemic corticoid was escalated to prednisolone 40 mg daily. Skin biopsy was compatible with DRESS syndrome, showing a superficial dermal lymphocytic infiltrate, with similar counts of CD4+ and CD8+ cells (some granzyme B positive) and no eosinophils (Fig. 2).

In September 2019, after de-escalating systemic corticoid and with the resolution of skin lesions and normalized kidney function, she started gefitinib in the second line, with no skin toxicity. Unfortunately, gefitinib was suspended in early November due to disease progression, and the patient was kept under palliative care till the end of life.

The introduction of a new target agent in real-world clinical practice is always challenging as new toxicities may arise as the number of patients treated increases. The particularity of our case is that this skin toxicity was induced by a novel drug, initially reported as less associated with skin toxicity. Further, skin involvement had worsened after osimertinib suspension and the patient was under carbamazepine, a frequently DRESS syndrome associated drug, which made it difficult to associate osimertinib to this clinical situation. It is important to notice that skin toxicity can prevail after discontinuation of a target agent. To the best of our knowledge, this is the first case of DRESS syndrome induced by osimertinib described in literature till now.

Conflicts of interest

The authors have no conflicts of interest to declare.

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Serial autoantibody detection in interstitial lung diseases: should they be repeated at follow-up?

Interstitial lung diseases (ILDs) are a heterogeneous group characterized by progressive thickening of the lungs; they include a wide variety of lung pathologies of known and unknown cause. Idiopathic pulmonary fibrosis (IPF) and non-specific idiopathic pneumonia (NSIP) are the most common idiopathic ILDs.[1] The 2018 ATS/ERS international guidelines for the diagnosis of IPF recommend analysis of autoantibodies to exclude ILDs associated with connective tissue lung diseases (CTD-ILD).[1] The diagnosis of IPF requires exclusion of other ILDs and serological evaluation of C-reactive protein, erythrocyte sedimentation rate, antinuclear antibodies, rheumatoid factor, myositis panel, and anti cyclic citrullinated peptide in newly diagnosed ILDs. Many biomarkers have been proposed in the literature for differential diagnosis but they are not yet approved for clinical use.[2] The guidelines also underline that there is no clear agreement on the serological tests to perform in the initial screening.[1] Autoantibody determination is mainly required in cases with atypical IPF features, including women under 60 years of age, where interstitial lung involvement may be the first manifestations of CTD-ILD.[3]

We therefore wondered whether autoantibody determination should be repeated regularly under specific conditions in patients with UIP pattern and negative serological test at onset, in order to verify the initial diagnosis of IPF, since some patients develop CTD manifestations months or years after the initial diagnosis.[3] The question mainly concerns UIP and NSIP radiological patterns, i.e. the most frequent radiological features associated with rheumatoid arthritis, systemic sclerosis and Sjogren syndrome.[4]

We retrospectively evaluated a cohort of 91 patients (71 males, age 68.46 ± 7.70 years) diagnosed with IPF and treated with pirfenidone between August 2011 and January 2019: we selected patients who had undergone assay of serum autoantibodies. Five of them (2 males, age $69{,}8 \pm 13{,}1$ years) developed clinically evident CTD (2 Sjogren syndrome and 3 rheumatoid arthritis), that was confirmed by rheumatological tests and clinical evaluation. Concerning systemic manifestations of CTD, two patients reported sicca syndrome, one patient showed rheumatic nodules of the elbow and two patients complained of diffuse joint pain and stiffness. Mean time to CTD onset after diagnosis of IPF was $25{,}8 \pm 33{,}7$ months. The three patients with RA-UIP died 60 ± 31.74 months after diagnosis of ILD, showing a prognosis similar to that of IPF patients treated with pirfenidone, as already reported in the literature.[5]

Our results are in line with the first paper reporting this subtype of ILD patient.[5] Homma et al. observed a mean latency of 24 months between IPF diagnosis and CTD, which is considerably shorter than our figure.[6] This discrepancy may be due to inclusion of patients with various radiological and ILD patterns, not focused on UIP features as in our study. In confirmation of these assumptions, Kono et al. reported similar results to ours in a cohort of 111 patients diagnosed with IPF, where 9% of patients developed CTD.[7]

Here we reported our cases, initially diagnosed with IPF, who subsequently developed CTD. This subgroup is estimated to make up 8–10% of all IPF patients, raising the question of follow-up and sustaining the utility of taking a working diagnosis approach to ILD. We first provided survival data on these patients treated with pirfenidone; it could be worth extracting the population with UIP prior to diagnosis of CTD in order to investigate the effect of antifibrotic treatment in this cohort and the usefulness of serial determination of autoantibodies.

Conflict of interest

The present research was performed at Siena University without funding sponsors. The authors have no conflict of interest to declare.

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Rifampicin-induced disseminated intravascular coagulation: An antibody-mediated side effect

Dear Editor,

Rifampicin (RFM) remains an effective treatment of pulmonary tuberculosis. Gastrointestinal adverse effects and liver toxicity are common. However, more serious reactions such as haemolytic anaemia, acute renal failure, and disseminated intravascular coagulation (DIC) have only been rarely documented. DIC secondary to RFM is a consequence of a rare immunoallergic reaction caused by the intermittent administration of RFM. It is even more uncommon in the absence of neoplastic disease, severe infection or previous exposure to RFM. Clinical features of that reaction include fever, hypotension, abdominal pain, and vomiting within hours of ingestion. Future administration of RFM is life-threatening and is contraindicated.

The aim of this report is to describe a case of RFM-induced DIC and to perform a review of the previous reports of this uncommon finding. The *Pubmed*® database was searched for articles in English that were published between January 1990 and January 2020. We combined search terms RFM and DIC. We also manually searched the reference lists of the eligible studies.

The authors present the case of a 68-year-old man with a history of pulmonary tuberculosis diagnosed in 2007 which was reactivated in 2018. He started the treatment with RFM, isoniazid (IZD), pyrazinamide and ethambutol. Two months later, given the clinical improvement and negative acid-fast bacilli smear, he continued the treatment with RFM and IZD. However, due to gastrointestinal symptoms (nausea and abdominal pain), the patient was following treatment intermittently (on his own initiative).

After one week of interruption, the patient returned to the treatment with RFM and IZD. One hour after, he was admitted to the Emergency Department because of a sudden onset of dyspnoea, nausea, and abdominal pain. He was in respiratory distress, febrile, hypotensive, and tachycardic. The laboratory analysis revealed low platelets (28,000/μL) and d-dimer elevation (43,290 ng/ml) – Table 1.

Six hours after the RFM intake, the patient presented haemorrhagic dyscrasia with hemoptoic sputum, bleeding through the vascular accesses, haematuria, and haematochezia. The analytical study was compatible with DIC, showing low platelets (38,000/μL) and prolonged prothrombin time (PT) 37.8 s; a prolonged activated partial thromboplastin time (APTT) 81.1 s, and a very low fibrinogen level (not measurable) – Table 1. Chest angio-CT scan excluded pulmonary embolism and it revealed a ground-glass opacity infiltrate in the right lower lobe suggestive of inflammatory/infectious process.

DIC secondary to probable septic context, due to community-acquired pneumonia, was assumed. Samples were collected for cultural exams and ceftriaxone was initiated. The patient was admitted to the Intensive Care Unit (ICU).

During his stay in ICU, the patient presented good clinical and analytical recovery. On the 10th day of hospitalization, given the stability, the patient returned RFM. The analytical study (prior to RFM intake) showed no relevant changes – Table 1. Two hours after taking RFM, the patient started having nausea and abdominal pain. Five hours after RFM, a new episode of haemorrhagic dyscrasia was seen with hematemesis, bleeding through the vascular accesses and macroscopic haematuria. Hypotension refractory to fluids and vasopressor support was documented. Six hours after the RFM intake the patient presented cardiorespiratory arrest and death. Analytical study showed acute decrease in haemoglobin level (5.2 g/dL) and DIC criteria with low platelets (21,000/μL), coagulopathy (PT 26.8 s; APTT 79.9 s; low fibrinogen 157 mg/ml) and d-dimers elevation (65236 ng/ml) – Table 1. *Post mortem* study revealed anti-RFM positive antibodies (IgM and IgG) in the patient's serum.

The adverse effects of RFM, include IgE-mediated allergic reactions like rashes, mild gastrointestinal disorders, hepatotoxicity, and drug interactions.[1] In contrast, intermittent intake of RFM can produce more serious adverse effects induced by immunoallergic reactions mediated by IgG and IgM antibodies against erythrocytes, platelets and other target cells expressing blood antigen I, including renal tubular epithelial cells.[2] Clinical manifestations of these reactions begin within hours after the ingestion of RFM and include vomiting, abdominal pain, fever, and hypotension. Diagnostic investigations generally reveal the presence of renal dysfunction, intravascular haemolysis, and DIC. The review of the existing literature identified only 13 previously reported cases of RFM-induced DIC[2–4]; this is the 14th case described (Table 2).

In the case reported, as in 3 cases before, the fact that sepsis is a common source of DIC made diagnosis difficult.[2] This led to the re-exposure to RFM with a new episode of DIC and a fatal outcome. 3 other fatal cases have already been documented.[2] The prior treatment with RFM, the temporal association between the two episodes of DIC and the RFM intake, as well as the absence of new episodes after its interruption, pointed to the causal role of the drug in the case described. The suspicion was confirmed post mortem by the detection of anti-RFM IgG and IgM antibodies in the patient's serum. However, DIC due to RFM is a clinical diagnosis and it has been confirmed by antibodies in only two cases before.[5,6] The present case is intended to draw attention to a rare side effect of a commonly used drug.

Table 1 Laboratory data. Evolution of two DIC episodes.

Variable	Reference range, adults, this hospital[a]		1st episode of DIC					10th day (ICU)		2nd episode of DIC			
			1 h		6 h					2 h	5 h		
Haemoglobin (g/dL)	14.0–18.0	RFM	Sudden onset dyspnoea, nausea, and abdominal pain	13.7	Haemorrhagic dyscrasia	11.6	Recovery	8.5	RFM	Non-specific malaise, nausea, and abdominal pain	Haemorrhagic dyscrasia	5.2	Death
Platelets (/μL)	150–400,000			28,000		38,000		573,000				21,000	
PT (s)	9.4–13.4			11.9		37.8		15.3				26.8	
APTT (s)	24.0–37.0			28.8		8.1		30.2				79.9	
Fibrinogen (mg/mL)	200–400			–		Very low (not measurable)		981				157	
D-dimers (ng/mL)	0–250			43,290		-		1403				65,236	

[a] Reference values are affected by many variables, including the patient population and the laboratory methods used. The ranges used in Hospital do Divino Espírito Santo, Ponta Delgada; are for adults who are not pregnant and do not have medical conditions that could affect the results. They may therefore not be appropriate for all patients.

Table 2 Cases of RFM-induced DIC previously described in the literature.

Author	Study design	Case no. Author	Age (years)/gender	Diagnosis	Dosage	Prior exposure	Time to development of DIC	Clinical features	Outcome
Havey et al.[2]	Case report and review	1. Brasil et al.[2]	NA/M	L	600 mg/month	Yes	3 doses	NA	Death
		2. Denis et al.[2]	48/F	T	600 mg/day	NA	5 months	Fever, jaundice, vomiting, diarrhoea	Recovery
		3. Fujita et al.[2]	43/M	T	450 mg/day	NA	7 days	Bleeding	Recovery
		4. Ip at al.[2,5]	29/F	T	600 mg, three times a week	Yes	6 months	Fever, hypotension, vomiting, oliguria, pruritis	Recovery
		5. Luzzati et al.[2,6]	35/M	T	600 mg/day	Yes	1 dose	Fever, rash, hypotension, abdominal pain, vomiting, myalgias	Recovery
		6. Namisato and Ogawa[2]	64/M	L	600 mg/month	Yes	3 doses	Fever, hypotension, facial oedema, vomiting, abdominal pain	Recovery
		7. Nowicka et al.[2]	53/F	T	450 mg; dosing schedule unclear	Yes	3 doses	Lumbar and abdominal pain, anuria	Death
		8. Souza et al.[2]	46/F	L	600 mg/month	Yes	3 doses	Fever, haematuria	Death
		9. Havey et al.[2]	66/F	B	600 mg/month	Yes	6 doses	Fever, hypotension, vomiting, abdominal pain, oliguria	Recovery
Sadanshiv et al.[3]	Case report and review	10. Costiniuk et al.[3]	20/F	T	600 mg/day	Yes	3 weeks	Renal failure, non-bloody diarrhoea, hypotension, vomiting, decreased urine output, haemolysis	Recovery
		11. Soltani et al.[3]	71/F	B	600 mg/day	No	7 days	Renal failure, haemolysis, abdominal pain, vomiting, jaundice, decreased urine output	Recovery
		12. Sadanshiv et al.[3]	50/F	L	600 mg, single dose	Yes	1 day	Renal failure, haemolysis, dark-coloured urine, jaundice, fever, vomiting, decreased urine output	Recovery
Chen et al.[4]	Case report	13. Chen et al.[4]	22/M	T	450 mg/day	Yes	7 days	Epistaxis, haematochezia, haematuria, purpura, jaundice	Recovery
14. Present case			68/M	T	600 mg/day	Yes	3 months	Fever, hypotension, abdominal pain, haemolysis, hemoptoic sputum, bleeding through the vascular accesses, haematuria, haematochezia	Death

T – tuberculosis; B – brucellosis; L – leprosy; NA – not available.

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A PI*MS is not always a PI*MS. An example of when genotyping for alpha-1 antitrypsin deficiency is necessary

Dear Editor,

Alpha-1 antitrypsin (AAT) is a serum glycoprotein with functions which include neutrophil elastase inhibition in the lung (protecting it from destruction and emphysema), and antioxidant, anti-inflammatory, anti-infectious and immunomodulation effects. Alpha-1 antitrypsin deficiency (AATD) is an autosomal co-dominant disease and is considered one of the most frequent hereditary disorders; however, its epidemiology remains partially unknown owing to underdiagnosis.[1] At least 60 deficient proteinase inhibitor* (PI*) alleles have been described, the most common being PI*S (5%–10% in Caucasians) and PI*Z (1%–3%), which are associated with reduced serum AAT levels of 40 an escalation plan and ceilings care and 10%–20%, respectively. PI*ZZ is the most frequent genotype (95%) among individuals with severe deficiency.[2] Previous studies suggest that some areas of Portugal may have a very high frequency of deficient variants.[3] Other deficient variants (non-S, non-Z) are considered as ''rare'' because of their low frequency, they cannot be identified by the usual allele-specific genotyping methods and cannot always be characterized by isoelectrofocusing (IEF) for phenotyping; therefore they can only be detected by molecular biology techniques, such as genome sequencing.[4] Consequently, in cases with discordant plasma and phenotype results, it is important to continue diagnostic assessment since the identification of a severely deficient genotype supports the possible indication of augmentation therapy and the need for family screening.[1]

The PI*M_{Malton} variant is a rare deficient variant that differs from the normal M allele by deletion of the entire codon (TTC) for the residue Phe at position 51/52 (exon II). It is associated with severely reduced plasma AAT levels and hepatic inclusions by polymers and is characterized by a normal isoelectrophoretic pattern, which may be confounded with a normal M protein on IEF.[4]

Information about the frequency of rare alleles in Portugal is scarce. In a previous study including 1864 subjects, 9.5% of the AATD cases were related to a rare allele and null variants.[2] The majority of rare alleles (n = 64; 15.3%) corresponded to PI*M_{Malton} and PI*$M_{Palermo}$, including n = 16 PI*SM_{Malton} (3.8% of the individuals with AATD). However, the study sample might not be representative of the whole country, because most of the samples had been collected in the North and Central regions of Portugal.

Similarly, the PI*M_{Malton} variant is considered to be the second cause of severe AATD in Spain. A study including 3511 subjects over 12 years showed 1.6% of rare AAT variants, with PI*I (34%) and PI*M_{Malton} (20%) being the most frequent, accounting for 54% of all rare variants.[5] PI*M_{Malton} allele was also very common among the rare variants in other countries: 60% in Tunisia, 35% in Italy (particularly in Sardinia), and 8% in Switzerland. However, it has not been found in Finland, and is rare in Ireland.[4,5]

Augmentation therapy is indicated in severely deficient patients (AAT serum levels < 57 mg/dL) associated with deficient genotypes, including PI*SZ.[1] Since M_{Malton} is associated with levels similar to the Z variant, patients with genotypes such as PI*$M_{Malton}M_{Malton}$, PI*ZM_{Malton}, PI*SM_{Malton} and PI*NullM_{Malton} may be candidates for augmentation therapy. Therefore, it is crucial to identify these genotypes in patients with clinical manifestations, low AAT serum levels and inconsistent phenotypes on IEF.

We had the opportunity to treat the case of a 57-year-old man, ex-smoker of 40 pack-years, with severe chronic obstructive pulmonary disease (COPD) and extensive emphysema on computed tomography scan. He was diagnosed with severe AATD due to a serum AAT level of 46 mg/dL and ful-

filled all criteria for augmentation therapy.[1] However, the phenotype was reported as PI*MS. Due to the inconsistency between the plasma levels and phenotyping, genotyping was performed by SERPINA1 gene sequencing, showing a PI*SM$_{Malton}$ genotype.

This was an example of a patient with severe, early-onset emphysema with severe AATD defined by a serum level of AAT < 57 mg/dL, considered as the protective threshold, but with a PI*MS phenotype, consistent with a mild deficiency.

The patient was referred for evaluation for lung transplantation, and in the meantime was considered for augmentation therapy with intravenous AAT.

In conclusion, among the rare deficient variants of AAT, PI*M$_{Malton}$ is probably the most frequent on the Iberian Peninsula, although it still represents a challenge because it is not detected by the first line diagnostic tests (phenotyping/allele-specific genotyping). An PI*M$_{Malton}$ allele-specific genotyping assay has been developed for faster and cheaper diagnosis,[6] but it is not universally available. A larger registry database is needed for a better understanding of the characteristics and natural history of carriers of this rare variant.[7]

Conflicts of interest

Teresa Martin has received speaker fees from Menarini and GlaxoSmithKline. Marc Miravitlles has received speaker fees from AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, Menarini, Rovi, Bial, Sandoz, Zambon, CSL Behring, Grifols and Novartis, consulting fees from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Bial, Gebro Pharma, Kamada, CSL Behring, Laboratorios Esteve, Ferrer, Mereo Biopharma, Spin Therapeutics, Verona Pharma, TEVA, pH Pharma, Novartis, Sanofi and Grifols and research grants from GlaxoSmithKline and Grifols. Sofia Tello Furtado has received speaker fees from AstraZeneca, Boehringer Ingelheim, Bial, Novartis, Boehringer Ingelheim, and GlaxoSmithKline.

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Acute colonic pseudo-obstruction causing Acute Respiratory Failure in Duchenne Muscular Dystrophy

To the Editor,

Duchenne Muscular Dystrophy (DMD) is the most common inherited muscle disease diagnosed in children, with a prevalence ranging between 1.3 and 2.1 per 10,000 live male births. Caused by a mutation of the dystrophin encoding gene located at Xp21, the disease results in a relentless progression of muscle weakness and wasting of the skeletal and cardiac muscle cells. Even though implementing nocturnal and daytime long-term ventilation and cough assistance has reduced the risk of respiratory complications, Acute Respiratory Failure (ARF) is still a common occurrence in DMD patients and a leading cause of death in the very advanced stages of the disease. The pathogenesis of ARF has been attributed to an imbalance between increased respiratory load and reduced diaphragmatic capacity. Well-known aetiologies include pneumonia, otherwise benign

upper respiratory tract infection, and congestive heart failure.[1]

Acute colonic pseudo-obstruction (ACPO) is a rare disorder characterized by acute dilatation of part or all of the colon/rectum in the absence of any intrinsic or extrinsic mechanical obstruction. First described by Sir William Ogilvie in 1948, ACPO usually presents in hospitalized or institutionalized patients suffering from severe comorbid conditions, such as musculoskeletal abnormalities, trauma, surgery, or sepsis.[2] Patients affected with the disorder typically present worsening abdominal distension and some degree of abdominal discomfort/pain and constipation.[3] Abdominal overdistension can affect respiratory mechanics and blood gas exchange by causing a cranial shift of the diaphragm, reducing chest wall compliance and lung volume.[4]

DMD patients frequently present with intestinal motility disorders that have been attributed to immobility and weakness of the abdominal wall muscles. Altered dystrophin expression in the intestinal smooth muscle can also contribute to impaired gastrointestinal motility. As episodes of colonic pseudo-obstruction have been described in DMD patients,[5] we have hypothesized that ACPO could have some bearing on the onset of acute respiratory decompensation.

For this reason, we collected and reviewed all of the medical records of the DMD patients with ARF admitted to our 4-bed Respiratory Intensive Care Unit (RICU) between January 1, 2005 and August 31, 2019 after informed consent release forms were obtained. At the time of admission to the RICU, the clinical and physiological parameters of these patients were consistent with ARF; in particular, each presented at least one of the following: (1) difficulty in breathing; (2) hypoxemia and/or hypercapnia; (3) acute respiratory acidosis. The causes of ARF were determined taking into consideration the patients' clinical, radiological, hemodynamic, and laboratory test results. ACPO was diagnosed depending on the presence of abdominal distention and pain, nausea with vomiting, and/or constipation; the diagnosis was confirmed by radiographic evidence of colonic dilation >9 cm and the exclusion of any mechanical obstructions.[3]

48 DMD patients with a primary diagnosis of ARF were admitted to our RICU during the study period. ACPO was the cause of ARF in 2 of the patients (4.2%). The causes of ARF in the other patients were: pneumonia (16 cases); upper respiratory tract infection (12 cases); acute congestive heart failure (10 cases); gastroparesis/malnutrition (3 cases); pneumothorax (2 cases); tracheo-innominate fistula (2 cases); abuse of sedatives (1 case).

The baseline demographic, clinical and pulmonary function data, and the clinical and laboratory data at the time of their admission to the RICU of the 2 patients who were diagnosed with ACPO are outlined in Table 1; of note, patient 1 had been receiving home Non-Invasive Ventilation (NIV) administered by a pressure-limited ventilator, set on the assist/control mode, with Pressure Control (PC) at 18 cmH_2O, Respiratory Rate (RR) at 15 breaths/min, Inspiratory Time at 1.4 s, and PEEP at 4 cmH_2O. Both patients were receiving full-time ventilatory support on admission. In both cases of ACPO, distended bowel loops and marked diaphragmatic elevation were noted on an anteroposterior chest X-ray; parenchymal infiltrate, pleural effusion and/or pneumothorax were absent (Fig. 1).

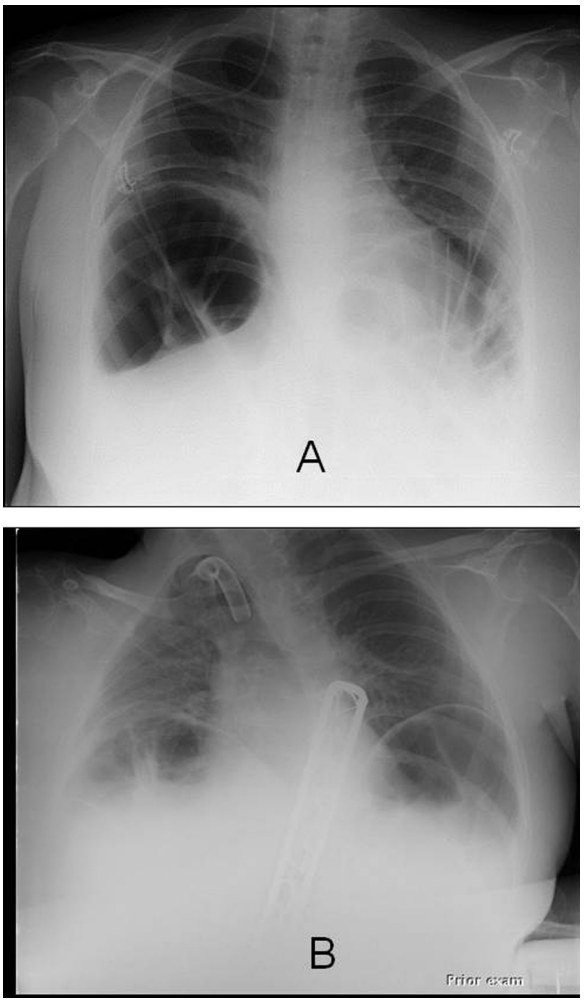

Figure 1 The radiograph of the chest and the upper abdomen of the two patients with Acute Colonic Pseudo-Obstruction (A = case 1; B = case 2).

Both patients were prescribed the standard treatment for ACPO consisting of: nothing by mouth, a nasogastric tube (in case 1), postural changes, i.v. fluids, and electrolyte replacement. In case 2, PEG tube was used to remove swallowed air from stomach. In addition, a polyethylene glycol (PEG) 3350 was administered via nasogastric or PEG tube, a broad-spectrum antibiotic was prescribed, and a rectal catheter was inserted. Neostigmine was excluded to avoid the risk of bronchoconstriction and/or increased bronchial secretions. In case 1, the ventilator setting was readjusted to a reduced insufflational pressure of 10 cmH_2O. As patient n. 1 did not respond to supportive treatment, endoscopic decompression of the colon was successfully carried out. Both patients showed progressive clinical improvement leading to recovery of spontaneous breathing during daytime. Time to recovery was shorter for case 1 compared to case 2 (4 and 10 days after admission, respectively).

Our findings demonstrated that the relevance of ACPO as a cause of ARF was similar to that of the other less frequent causes of acute respiratory decompensation in DMD

Table 1 Baseline demographic, clinical and pulmonary function data, and data at Respiratory Intensive Care Unit admission of the 2 patients who were diagnosed with ACPO. Blood gas analysis was performed during assisted ventilation (ACPO = Acute Colonic Pseudo-Obstruction; BMI = Body Mass Index; CRP = C-Reactive Protein; FVC = Forced Vital Capacity; MIP = Maximum Inspiratory Pressure; MEP = Maximum Expiratory Pressure; NIV = Non-Invasive Ventilation; PEG = Percutaneous Gastrostomy).

	Case 1	Case 2
Baseline demographic, clinical and pulmonary function data		
Age at RICU admission, yrs	25	34
Age at diagnosis of DMD, yrs	5	2
BMI, kg/m^2	22.34	18.37
History of constipation	y	y
Scoliosis	n	y, arthrodesis
Cardiomyopathy	n	y
NIV use at home	y	n
Tracheostomy tube	n	y; inflated cuff
PEG tube	n	y
FVC, L	0.95	NA
FVC, %	16	NA
MIP, cmH2O	17	37
MEP, cmH2O	20	24
Clinical, laboratory and blood gas data at RICU admission		
Clinical presentation	Abdominal distention, pain, nausea, dyspnea	Abdominal discomfort and distention, nausea, dyspnea
Physical examination	Distended, tympanitic abdomen; reduced bowel sounds; Pulmonary bibasilar rales	Distended, abdomen; reduced bowel sounds
Respiratory rate, breaths/min	20	19*
Heart rate, (beats/min)	100	115
Fever (Temperature >38 °C)	n	n
WBC count	6.53×10^9/L	8.76×10^9/L
Serum CRP, μg/ml	28.1	46.5
PaO2, mmHg	59.9	51.9
PaCO2, mmHg	55.6	30.5
Arterial pH	7.31	7.51
SaO2, %	90.0	89.2
Serum Na, mmol/L	138.0	139.0
Serum K, mmol/L	2.1	2.9
Serum Ca, mmol/L	2.3	2.07

patients. The development of ARF could be explained, we hypothesize, by severe diaphragmatic weakness (demonstrated by the marked reduction in MIP in both cases) that could have reinforced the physiological response to increased intra-abdominal pressure, usually consisting of relaxation and ascent of the diaphragm permitting cephalic expansion of the abdominal cavity.[6] Excessive diaphragmatic ascent could lead to a reduction in Respiratory System Compliance (Crs) shifting the lung volume to a lower portion of the volume–pressure curve. The result of reduced compliance would be increased work of breathing, potential fatigue of the respiratory muscles and, ultimately, acute respiratory decompensation.[7] The application of NIV in one of the ACPO patients (n. 1) may have contributed to the development of ARF as the release of positive pressure by a non-invasive route can lead to esophageal insufflation and in turn to gastro-intestinal distension. In particular, we hypothesize that insufflational airway pressure around 20 cmH_2O may have exceeded the lower esophageal sphincter pressure (approximately 20–25 cm H_2O, in a healthy adult).[8] Abdominal overdistension in turn may have caused CO_2 retention during NIV application, as delivered Tidal Volume decreases according to decreased Crs when the ventilator is set on a pressure-limited mode. In case 2, concomitant mild hypocalcemia may have facilitated impaired intestinal motility.

Worth noting, both of the patients presenting ACPO had a long-standing history of abdominal bloating and constipation. In the light of these findings, clinicians caring for DMD patients should be aware of the repercussions of intestinal dysmotility in these patients and prescribe appropriate measures to treat troublesome symptoms.

To conclude, although ACPO seems to be an infrequent cause of ARF, clinicians caring for DMD patients should be aware of the possibility of ''pulmonary-colonic syndrome'' and be prepared to identify and treat this potentially life-threatening condition precociously.

Conflicts of interest

The authors have no conflicts of interest to declare.

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LETTER TO THE EDITOR

Cigarette smoking and COVID-19

In a recent editorial published on tobacco and COVID-19, the Sociedade Portuguesa de Pneumologia raises doubts and caution about the data coming from the medical and scientific community regarding the hypothesis that cigarette smoking or nicotine could be ''protective'' against COVID-19, recommending that this information should not be taken as an invitation to start smoking or to delay giving it up to avoid SARS-CoV-2 infection or its complications.[1]

The role of cigarette smoking/nicotine (or whatever else is contained within cigarette smoke) in the scientific discussion on COVID-19 ignores the fact that smoke cessation has to be discouraged to avoid COVID-19 pulmonary complications (this seems obvious for scientists and physicians) but references the scientific importance of the strong epidemiological data coming from all the countries that hospitalized patients with SARS-CoV-2 related pneumonia show quite low percentages of active smokers.[2,3]

Based on this we have to strongly support the importance of understanding of the possible mechanisms characterizing these aspects, i.e. how cigarette smoking dampens the inflammatory response during infection by SARS-CoV-2 strongly reducing the severe complications of SARS-CoV-2 infection, mainly nterstitial pneumonia and ARDS. The reported evidence that among COVID-19 patients, those who are (and/or were) smokers show worse clinical progression with respect to never smokers is not in contradiction with the huge number of studies showing that there are few active smokers among hospitalized patients with SARS-CoV-2 related pneumonia.[4–6] However it is quite strange that a scientific society does not seem to understand the important scientific implications of such observations, bearing in mind that of course cigarette smoking has to be discouraged due to its well known dangerous effects.

Thus we have to consider, without any preconceived position, on the one hand the notorious unhealthy effects of cigarette smoking, and on the other the possible important scientific information coming from different countries in the world showing that active smokers are somehow 'protected' from the severe complications of SARS-CoV-2 infection, namely interstitial pneumonia and ARDS.

In this context a very recent paper reported decreased levels of the SARS-CoV-2 receptor ACE2 in both bronchial and alveolar epithelial cells from cigarette smoking-exposed versus air-exposed mice.[7] Furthermore and more importantly, cigarette smoking treatment did not affect ACE2 levels but potently inhibited SARS-CoV-2 replication in Calu3 cells in vitro.[7] On the other hand previous studies have reported the opposite effects of cigarette smoking on ACE2 expression in the lung,[8] thus underlying the urge for further investigations to finally clarify the role of cigarette smoking on SARS-CoV-2 infection and its severe respiratory complications.

Science proceeds by criticism and by analyzing objective data coming from scientists. In 1939 Winston Churchill said ''Criticism may not be agreeable, but it is necessary. It fulfils the same function as pain in the human body; it calls attention to the development of an unhealthy state of things. If it is heeded in time, danger may be averted; if it is suppressed, a fatal distemper may develop''.[9]

In the case of active smoking and COVID-19, to hide ones head in the sand will not help rapid scientific progress in the discovery of the pathophysiology of this disease and of its possible therapeutic strategies.

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Conflict of interest

The authors have no conflict of interest to declare.

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Tobacco and COVID-19: A position from Sociedade Portuguesa de Pneumologia. Authors' reply

We read with great interest the letter by Rossato and Di Vincenzo[1] commenting on our editorial ''Tobacco and COVID-19: A position from Sociedade Portuguesa de Pneumologia'' published in Pulmonology in December 2020.[2] We would like to thank the authors for the challenging discussion points and we acknowledge that, as in all fields of science, new data are continuously being collected and interpreted and we are still far from definitive conclusions about how smoking really impacts COVID-19.

The observations that report a low rate of smokers among COVID-19 patients are pertinent but have yet to be confirmed by good quality epidemiological studies designed to address this question. As we mentioned, a high number of studies does not report smoking status or does not distinguish never-smokers from missing data and this may pose considerable bias.[2] At the present time, we cannot rule out the hypothesis that smoking may not constitute a strong risk factor for COVID-19, but we have to further specify what questions we are posing: what is the difference in risk between present smokers and having a past history? Are smokers more prone to contract SARS-Cov-2 infection in general? We do not have enough information concerning asymptomatic infection and smoking, and we know there may be a bias toward higher testing rates in smokers,[3] due to higher rates of respiratory symptoms. An interesting study in *Nature*[4] shows that there are difficulties in correctly adjusting for other covariates — depending on the covariates included, a smoking history could either be associated with a higher risk of COVID-19 (age and sex adjusted only) or lower risk (fully adjusted model). After adjusting only for demographic factors (age, sex, deprivation and ethnicity), the authors found a non-significant positive hazard ratio for current smoking (HR 1.07 (0.98–1.18)), excluding any protective effect of nicotine and suggesting that any increased risk with current smoking is likely to be small.

Rossato and Di Vincenzo also quote the new paper by Tomchaney et al.,[5] reporting conflicting new results that show decreased expression of ACE2 receptors in both bronchial and alveolar epithelial cells exposed to cigarette smoke. These are puzzling data that still wait peer-review and publication. Animal studies are undoubtedly important to open new pathophysiologic hypothesis; however, we still face uncertainties as to the real role of ACE-2 receptor modulation and the risk of infection. One of the problems concerns tobacco smoke, a mixture of thousands of chemicals interacting together, and the presumptive role of nicotine. The studies by Russo et al.[6] have thrown some light on how isolated nicotine may facilitate SARS-Cov-2 infection: nicotine, even at low concentrations, increases ACE-2 levels in bronchial cells. Besides, they showed that ACE-2 increase is specifically mediated by α7-nAChR, suggesting that smoking may promote cellular uptake mechanisms of SARS-CoV-2 through α7-nAChR signaling. The presence of this receptor in neuronal tissues also raises questions about the impact of smoking in COVID-19 pathophysiology in several organs, including the brain.

In the absence of well-designed studies, with large populations, any hypothesis on the effect of smoking or nicotine in the risk of COVID-19 remains unproven. More than five decades of research in vast population-based studies were needed to establish the causative effect of tobacco in several deadly diseases. Our minds should be open to change, but in the present state of knowledge, we stand with the WHO and adopt a cautious recommendation against any putative protective effect of smoking.

Conflicts of interest

The authors have no conflicts of interest to declare.

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For a patient with severe asthma, every day may be his last *World Asthma Day*

KEYWORDS
Asthma;
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World Asthma Day

Dear Editor,

We read carefully the interesting article of Arrobas et al ''Cost-effectiveness of omalizumab in real world uncontrolled allergic asthma patients'' recently published on Pulmonology.[1]

We congratulate the authors for considering all important aspects for patients with severe asthma. They included real world patients with asthma that do not always match with those included in randomized placebo-controlled trials;[1] recognized that a significant percentage of patients have uncontrolled asthma, a rate that is particularly higher in severe asthmatic patients;[2] uncontrolled asthma, especially uncontrolled severe asthma, was associated with increased direct and indirect costs,[3] as previously found in our country including a representative sample of patients;[2] data that come from well-designed cost-effectiveness study like this is generally not considered in national healthcare plans for asthma; the specialist-based indication for biologic drugs such as omalizumab in severe allergic persistent asthma, as in the current study, allowed the reduction of exacerbation rates and increased patients' quality of life, at a societal acceptable cost.[1,4]

Nowadays, it is unacceptable to treat severe asthmatic patients with oral corticosteroids (OCS) on a daily basis or even during their almost permanent exacerbations.[1,4] Therefore, we need innovative drugs. The low price of OCS opposes the very high expenses in morbidity and mortality.[4]

We acknowledge the authors because this study will probably give important and relevant support to our national health authorities' decisions in severe asthma care, including our national investments. Similar to other patients with immune-related diseases, severe asthmatics from all ages have the right of equity. People living with severe asthma from all the regions must have access to treatments that, despite not being able to modify the natural history of the disease, can definitely modify their lives. Access to these treatments should be constant, even in a particularly difficult times related with the current Coronavirus Disease 2019 (COVID-19) outbreak.[5]

Patients with severe asthma are included in the high risk group for COVID-19 worse prognosis; it is time to maintain asthma under control. All treatments must be used, from inhaled corticosteroids to biologicals, as they were before the outbreak. No risk of increased viral infection susceptibility has been reported to date in previous placebo controlled trials and real world studies with omalizumab, mepolizumab, benralizumab, reslizumab and dupilumab in asthmatic patients. Regarding omalizumab, there is a possible anti-infectious effect. Thus, physicians must maintain biological treatments during the current pandemic.[5]

The World Asthma Day on May 5th 2020 is the first one in the COVID-19 era. Patients with severe asthma are once again concerned with COVID-19 morbidity and mortality, along with patients with other well-known chronic diseases, in particular metabolic, cardiovascular and chronic obstructive pulmonary disease.

It's time to celebrate asthma, in a different way, but it's time to action.

Conflicts of interest

The authors have no conflicts of interest to declare related with this letter.

Compliance with Ethics

This study did not involve any studies in human or animal subjects performed by any of the authors.

Authorship

The named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship of this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval for the version to be published.

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