Pulmonary Dysfunction in COPD

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Pulmonary Medicine

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Editorial Board

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Editorial

Pulmonary Dysfunction in COPD

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Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality all around the world. It has been identified as the fourth leading cause, which will rise globally to the third place, before the end of 2020. It is estimated that more than 12 million adults suffer from COPD in the USA and 24 million patients have an impaired lung function, which may lead to the development of COPD. Tobacco smoke is the predominant but not the only environmental risk factor for COPD. COPD is a burden for health providing systems as the estimated direct and indirect costs are constantly raising.

Chronic obstructive pulmonary disease, namely, pulmonary emphysema and chronic bronchitis, is a chronic inflammatory response of the airways to noxious particles or gases, with resulting pathological and pathophysiological changes in the lung. The main pathophysiological aspects of the disease are airflow obstruction and hyperinflation, which are discussed by D. Papandrinopoulou et al. The mechanical properties of the respiratory system and its component parts are studied by determining the corresponding volume-pressure (V-P) relationships. The consequences of the inflammatory response on the lung structure and function are depicted on the volume-pressure relationships.

Expiratory flow limitation is well discussed by Tantucci. When expiratory flow is maximal during tidal breathing and cannot be increased unless operative lung volumes move towards total lung capacity, tidal expiratory flow limitation (EFL) is said to occur. In any circumstances, EFL predisposes to pulmonary dynamic hyperinflation and its unfavorable effects such as increased elastic work of breathing, inspiratory muscles dysfunction, and progressive neuroventilatory dissociation, leading to reduced exercise tolerance, marked breathlessness during effort, and severe chronic dyspnea.

N. G. Koulouris et al. in their paper discuss the expiratory flow limitation in COPD patients at rest (EFLT). EFLT, namely, attainment of maximal expiratory flow during tidal expiration, occurs when an increase in transpulmonary pressure causes no increase in expiratory flow. EFLT leads to small airway injury and promotes dynamic pulmonary hyperinflation with concurrent dyspnea and exercise limitation. Among the currently available techniques, the negative expiratory pressure (NEP) has been validated in a wide variety of settings and disorders. Consequently, it should be regarded as a simple, noninvasive, most practical, and accurate new technique.

COPD is a complex pathological condition associated with an important reduction in physical activity and psychological problems that contribute to the patient's disability and poor health-related quality of life as it is stated in the paper of P. Santus et al. Pulmonary rehabilitation is aimed to eliminate or at least attenuate these difficulties, mainly by promoting muscular reconditioning. Pulmonary rehabilitation has a beneficial effect on dyspnea relief, improving muscle strength and endurance. Moreover, it appears to be a highly effective and safe treatment for reducing hospital

admissions, mortality, and improving health-related quality of life in COPD patients.

The paper of F. Krakontaki et al. attempts to show the impact of COPD on the cognitive functions of the patients. The findings provide evidence that stable COPD patients may manifest impaired information processing operations. Therefore, COPD patients should be warned of the potential danger and risk they face when they drive any kind of vehicle, even when they do not exhibit overt symptoms related to driving ability.

The deterioration of quality of life of COPD smokers is illustrated by S. Joseph et al. in a study population from Lebanon. The Clinical COPD Questionnaire (CCQ) demonstrated excellent psychometric properties, with a very good adequacy to a cross-sectional sample and high consistency. Smokers had a decreased respiratory quality of life versus nonsmokers, independently of their respiratory disease status and severity.

I. Tsangaris et al. show one of the most important complications of chronic hypoxemia in COPD, which is pulmonary hypertension. Interestingly, in types of PH that are encountered in parenchymal lung diseases such as interstitial lung diseases (ILDs), chronic obstructive pulmonary disease (COPD), and many other diffuse parenchymal lung diseases, some of which are very common, the available data is limited. The paper summarizes the latest available data regarding the occurrence, pathogenesis, and treatment of PH in chronic parenchymal lung diseases.

Finally, M. Pecchiari discusses the role of heliox, which has been administered to stable chronic obstructive pulmonary disease (COPD) patients at rest and during exercise on the assumption that this low density mixture would have reduced work of breathing, dynamic hyperinflation, and, consequently, dyspnea sensation. Contrary to these expectations, beneficial effects of heliox in these patients at rest have been reported only sporadically. On the other hand, when it is administered to COPD patients exercising at a constant work rate, heliox systematically decreases dyspnea sensation and, often but not always, increases exercise tolerance. Therefore, further studies, aimed to the identification of mechanisms conditioning the response of exercising COPD patients to heliox, are warranted, before heliox administration, which is costly and cumbersome, can be routinely used in rehabilitation programs.

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Review Article

Expiratory Flow Limitation Definition, Mechanisms, Methods, and Significance

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When expiratory flow is maximal during tidal breathing and cannot be increased unless operative lung volumes move towards total lung capacity, tidal expiratory flow limitation (EFL) is said to occur. EFL represents a severe mechanical constraint caused by different mechanisms and observed in different conditions, but it is more relevant in terms of prevalence and negative consequences in obstructive lung diseases and particularly in chronic obstructive pulmonary disease (COPD). Although in COPD patients EFL more commonly develops during exercise, in more advanced disorder it can be present at rest, before in supine position, and then in seated-sitting position. In any circumstances EFL predisposes to pulmonary dynamic hyperinflation and its unfavorable effects such as increased elastic work of breathing, inspiratory muscles dysfunction, and progressive neuroventilatory dissociation, leading to reduced exercise tolerance, marked breathlessness during effort, and severe chronic dyspnea.

1. Definition

Expiratory (air) flow limitation (EFL) during tidal breathing is a well-defined, mechanical pathophysiological condition occurring, either during physical exercise or at rest, before in supine and later on in sitting-standing position, when expiratory flow cannot be further increased by increasing expiratory muscles effort (i.e., by increasing pleural and alveolar pressure) because it is maximum at that tidal volume [1]. In other words, under the prevailing conditions, the respiratory system is globally limited as flow generator even during tidal expiration, and greater expiratory flow rates may be achieved just by increasing operating lung volumes, (i.e., moving progressively the end-expiratory lung volume (EELV) towards total lung capacity). In fact, the volume-related decrease of airway resistance and increase of elastic recoil are the only effective mechanisms to obtain higher expiratory flows in case of EFL [2].

As a consequence, the term airflow limitation widely used to indicate the abnormal decrease of maximal expiratory flow rates at a given lung volume, as compared to predicted (i.e., airflow reduction or airflow obstruction), is inappropriate and should not be adopted unless the condition previously described is present (Figure 1).

2. Mechanisms of EFL

Several mechanisms may contribute to the EFL development by reducing the expiratory flow reserve in the tidal volume range.

The age-related increment of closing volume and closing capacity may induce in the elderly the closure of dependent small airways above EELV, causing a functional amputation of lung volume with consequent decrease in maximal expiratory flow rates corresponding to tidal volume [3]. Actually, the lung senescence may predispose to EFL, especially in the supine position and in small sized, overweight women.

When supine, the relaxation volume of the respiratory system (V_r) is lower as a result of gravitational forces, and usually EELV decreases with recumbency [4]. Since the maximal flow-volume curve denotes minimal variation by assuming the supine position [5], this body position predisposes to EFL because tidal breathing occurs at lower lung volumes where maximal expiratory flow rates are necessarily less.

Breathing at low-lung volume (near residual volume), as frequently observed in great and massive obesity, chronic congestive heart failure, and sometimes in restrictive lung and chest wall disorders, intrinsically reduces the maximal

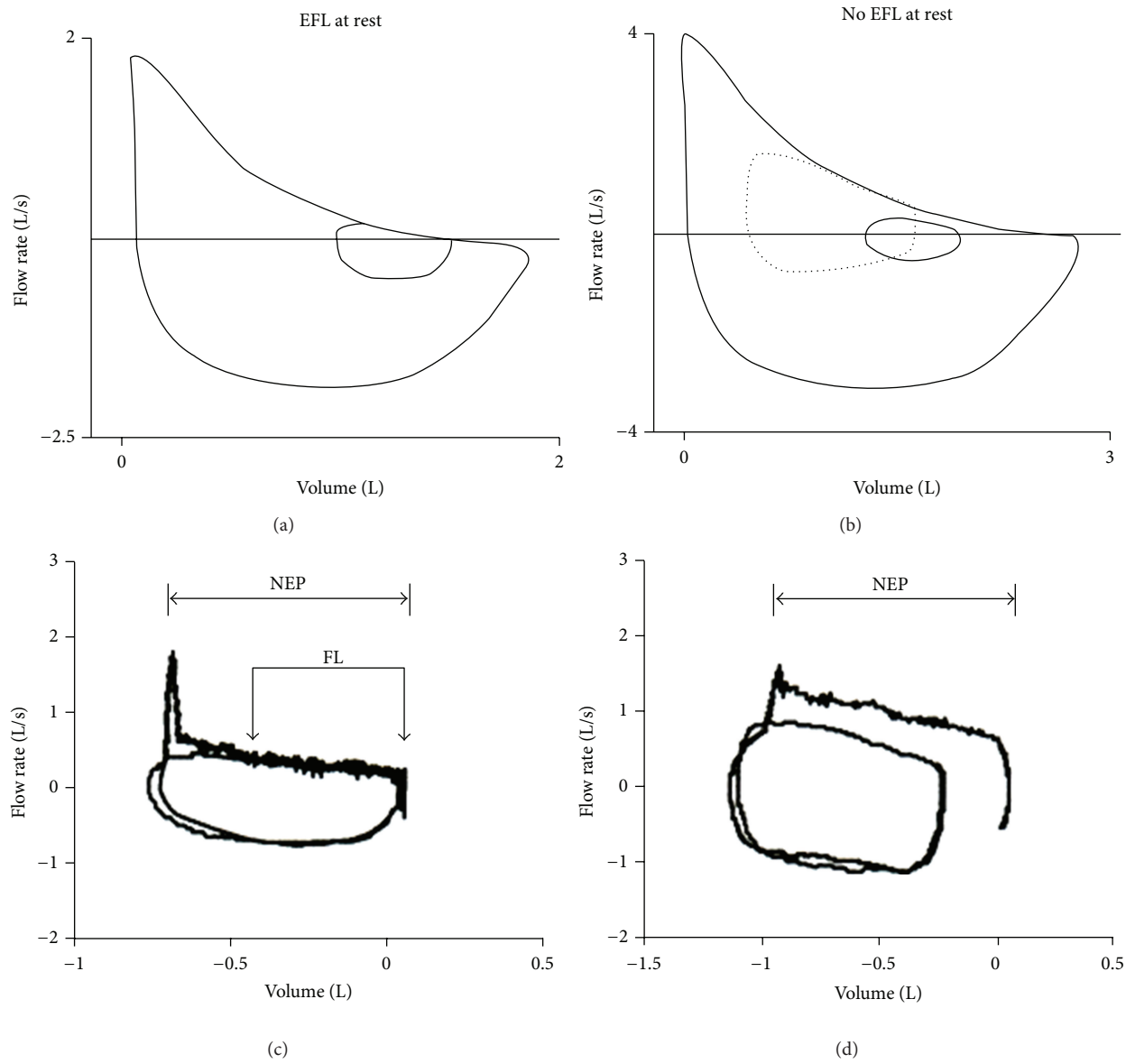

Figure 1: Maximal and tidal flow-volume curve in two representative COPD patients: one with airflow reduction and tidal expiratory flow limitation (EFL) at rest (a), the other only with airflow reduction at rest and potential EFL during exercise (b). The NEP application at rest does not increase expiratory flow in the first patient (c), while eliciting greater expiratory flow in the second one (d).

expiratory flow rates in the tidal volume range, facilitating the EFL occurrence, mainly in the supine position.

Higher ventilatory requirements with larger tidal volume (for similar respiratory rate and expiratory time), faster respiratory rate and shorter expiratory time (for similar tidal volume), or both, as expected during exercise or observed even at rest in various conditions, do increase mean tidal expiratory flow and reduce expiratory flow reserve during tidal breathing, making easier to have EFL.

On the other hand, EFL is linked inescapably to the presence of airflow reduction, no matter what is the prevailing mechanism (increased airway resistance, augmented cholinergic bronchial tone, decreased lung elastance, airway-parenchyma uncoupling, and airways collapsibility) in the obstructive lung diseases such COPD (Figure 2), chronic asthma, cystic fibrosis, constrictive bronchiolitis [6, 7]. In this respect, predominant reduction of maximal expiratory flow rates at lower lung volumes appears more crucial in promoting EFL. However, the site where the system becomes entirely flow-limited and flow limiting segment develops can be located centrally or peripherally. When EFL originates in the peripheral airways, it is mainly due to the viscous, density-independent, flow-limiting mechanism, while the speed wave, density-dependent, flow-limiting mechanism is substantially involved, when the EFL originates in the central airways [8].

Therefore, aging, body position, exercise, hyperpnea-tachypnea, low-volume breathing, or airflow reduction represents, alone or more often combined together, the main factors that favor the development of EFL in humans.

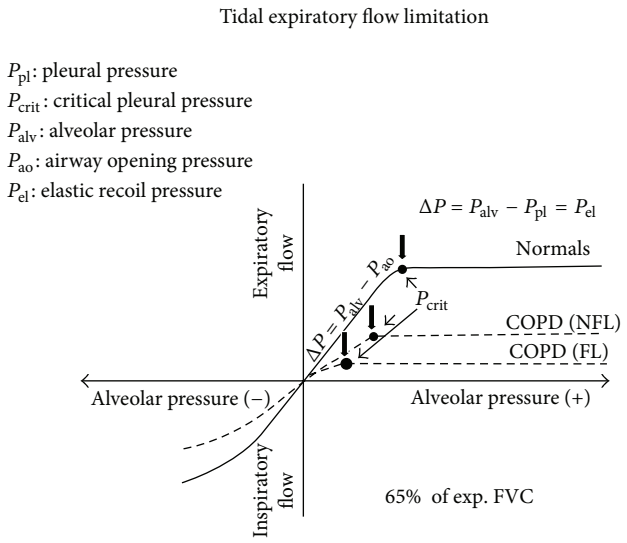

Figure 2: Isovolume (low-lung volume) flow-pressure relationship in normal subjects, COPD without expiratory flow limitation (NFL) and COPD with expiratory flow limitation (FL). In any case, after P_{crit}, expiratory flow does not increase further on, and its driving pressure becomes P_{el}. In COPD patients with high airflow resistance and very low P_{el}, the P_{crit} occurs early, limiting expiratory flow in the tidal volume range.

3. Methods for EFL Detection

Classically, flow limitation may be detected looking at isovolume pleural (or alveolar) pressure-flow relationship, and it occurs, when expiratory flow rate does not change (or even is reduced) despite the increasing pleural (alveolar) pressure [9]. Therefore, if increasing pleural pressure at lung volume corresponding to tidal breathing induces no change in expiratory flow, EFL is documented. Comparison between full (or partial) maximal and resting flow-volume loops has been used to detect EFL which is assumed when expiratory tidal flow impinges on or is even greater than maximal expiratory flow at the same lung volume [10]. This method that, however, should be performed by body plethysmography to avoid artifacts due to the thoracic gas compression [11] is fatally flawed by the sequential emptying of the lung regions with uneven time constant and by different time and volume history of the lung parenchyma and airways in the preceding inspiration [12, 13]. In fact all these factors influence the corresponding expiratory flow rates that are going to be compared in the two maneuvers. To respect time and volume history with similar lung-emptying sequence and to limit (or avoid by using body plethysmography) thoracic gas compression, comparison between submaximal (i.e., with gentle expiratory effort) and resting tidal flow-volume curve has been suggested for assessing EFL. Obviously this technique demands high cooperation and uncommon ability from the patients and cannot be standardized.

More than 15 years ago, to overcome all these problems, the Negative Expiratory Pressure (NEP) method has been introduced in the research and clinical practice [14]. A negative pressure of few cmH_2O (usually 5 cmH_2O) is applied at the mouth at the beginning of expiration to establish a pressure gradient between the alveoli and airway opening. During NEP that lasts for the whole expiration, there is an increase in expiratory flow in the absence of EFL, while the expiratory flow does not increase over the flow of the preceding control expiration, throughout the entire or part of the tidal expiration, in the presence of (total or partial) EFL (Figure 1). The NEP method that has been validated by using isovolume pressure-flow curves [15] does not require cooperation from the subjects and use of body plethysmography, can be performed at rest in any body position and during effort, and usually is devoid from interpretative problems. The only limit is the upper airway collapse possibly induced by the NEP application, as observed in snorers and OSAH patients, that can be partially controlled by reducing the negative pressure and repeating the measurements. The excessive spontaneous breath-to-breath changes in EELV can, however, lead to unclear results by using this technique.

This inconvenience is absent during the manual compression of abdominal wall (CAM) that, performed at rest or during exercise simultaneously with the start of tidal expiration, allows to increase expiratory flow rates over those of the preceding control expiration in the absence of EFL. In contrast, failure to increase expiratory flow rates during CAM indicates EFL [16]. The ability of the physician or technician, the cooperation of the patients, and the glottic reflex possibly elicited by this maneuver that cannot be standardized limit the utility of CAM for assessing EFL.

Recently the use of forced oscillation technique (FOT) during tidal breathing has been used to detect EFL breath-by-breath, both at rest and during exercise [17]. Briefly, when the oscillatory pressure applied at the mouth does not reach the alveoli during expiration because a flow limiting segment is present in the bronchial tree, the reactance signal, instead of reflecting the mechanical properties of the lung parenchyma and airways, is influenced only by those of the airways and becomes much more negative with a clear within-breath distinction between inspiration and expiration. This application of the FOT is very promising to identify EFL during tidal breathing, but the closure of intrathoracic airways eventually occurring at EELV must be considered as an important limiting factor of this technique, because the distortion of the reactance signal is similar.

4. EFL, Dynamic Hyperinflation, and Dyspnea

The development of EFL is functionally relevant because under the prevailing conditions (e.g., during exercise or at rest either in the supine or seated position) EFL is associated or promotes dynamic pulmonary hyperinflation (DH) by fixing, for a given expiratory tidal volume, the time required for the respiratory system to reach its relaxation volume (V_r) [18]. Indeed, in the presence of EFL at rest, although DH can be avoided if the expiratory time is long enough, EELV is more often dynamically raised [19] and invariably increases with increasing ventilatory request (greater tidal volume and faster respiratory rate) [20]. When EFL develops during exercise, EELV starts to increase and inspiratory capacity to decrease,

both signaling the occurrence of progressively greater DH [21].

DH promotes neuromechanical dissociation and implies a positive alveolar end-expiratory pressure (PEEPi) with a concomitant increase in inspiratory work, due to PEEPi acting as an elastic threshold load, impairment of the inspiratory muscles function, and adverse effects on hemodynamics [22]. These factors together with dynamic airway (downstream from the flow-limiting segment) compression during expiration may contribute to the dyspnea sensation [23, 24].

5. Clinical Aspects

In healthy subjects EFL occurs neither at rest nor during strenuous exercise [25], with the exception of highly fit old individuals in whom EELV tends to increase at high levels of exercise because of elevated values of minute ventilation they can reach before stopping [26]. Since maximal expiratory flow rates are reduced near EELV because of lung volume functional reduction due to age-related increase of closing capacity, EFL may develop under these circumstances [3]. Recently, however, for the same reasons EFL has been found by using the NEP technique also at rest in a large number of very old subjects, especially in small sized elderly women. Among these aged subjects chronic dyspnea was frequently reported in the absence of obvious cardiopulmonary diseases [27].

EFL may occur during tidal breathing at rest in COPD patients and has been found in more than 50% of the patients with moderate-to-severe-to-very-severe airway obstruction [6, 14, 19, 28]. Despite this general picture, changes in conventional indices of airway obstruction such as FEV_1, PEF, and FEV_1/FVC derived from maximal flow/volume curve are not useful to predict EFL, and special techniques must be adopted to accurately detect EFL in these patients [7]. In COPD EFL at rest has been found to correlate with chronic dyspnea better than routine spirometric parameters [7]. In fact, EFL more than airway obstruction *per se* entails a greater risk of dynamic pulmonary hyperinflation (DH), and DH has been recognized as an important cause of dyspnea either during exercise or at rest, due to its negative consequences on work of breathing, inspiratory muscle function, and, above all, neuromechanical coupling [21, 23].

It has been postulated that, in COPD for similar degrees of airflow obstruction, as measured by FEV_1 reduction as percent predicted, EFL could be more easily observed, both during exercise and at rest, in patients with emphysematous phenotype in whom reduction of lung elastic recoil and loss of airway-lung parenchyma interdependence are thought to be the main determinants of airflow reduction. Under these conditions the peripheral small airways should be more compliant and prone to collapse during expiration favoring EFL that might partly explain the greater dyspnea reported by pink puffers. Recently, in a cohort of stable COPD patients with moderate-to-severe airflow obstruction, EFL assessed by the NEP technique was detected significantly more in those with lower values of DL_{CO} and K_{CO}, but only when appraised in the supine position, suggesting an earlier appearance of EFL in emphysematous COPD patients (Figure 3). Interestingly, in these patients, chronic dyspnea, as measured by the modified MRC scale, was significantly greater (personal data). Further studies are needed to confirm this observation than links supine EFL and emphysema phenotype (pink puffer) in broader groups of COPD patients.

During episodes of acute exacerbation and respiratory failure, COPD patients are prone to develop DH even in the absence of EFL because of increase in airway resistance with longer time constant in the respiratory system and rapid and shallow breathing with reduction of expiratory time [29]. Moreover, higher ventilatory requirements due to fever and/or anxiety, increased physiological dead space, and deterioration of gas exchange may contribute to DH. In the presence of EFL, however, all these factors cause a catastrophic increase in DH that cannot be longer sustained during spontaneous breathing without unbearable dyspnea and risk of acute fatigue of the respiratory muscles, leading to acute ventilatory failure (ARF) and adoption of mechanical ventilation [30]. With this regard, it should be stressed that almost all COPD patients mechanically ventilated for ARF exhibit EFL, since further increase in expiratory flow resistance is induced by endotracheal tube and expiratory circuit of the ventilator [31]. This is relevant when assisted mechanical ventilation is started because under these circumstances the inspiratory work could be very high yet, and the application of PEEP to counterbalance PEEPi can reduce the elastic threshold load without increasing EELV.

Conversely, apart from patients with severe chronic asthma who have uninterrupted, long-lasting, marked airway obstruction [7], EFL at rest is seldom observed in asthmatic patients, unless under severe and prolonged bronchoconstriction [32].

In clinically stable patients with restrictive ventilatory disorders EFL is very uncommon during tidal breathing at rest [33].

In obese subjects and in patients with stable chronic heart failure EFL at rest is rarely present in seated position. However, recent studies showed that in massive obese subjects and patients with acute worsening of chronic congestive heart failure of EFL was frequently detected in the supine position [34, 35]. In all instances the development of EFL with recumbency prevents EELV to reach supine V_r, leading to supine DH with concomitant PEEPi. Since this elastic threshold load imposed to shorter (and functionally weaker) inspiratory muscles has been related to dyspnea sensation, the occurrence of supine EFL may be associated with the onset of orthopnea either in massively obese subjects and patients with chronic heart failure [34, 35].

6. Conclusions

EFL is a very important mechanical constraint that frequently occurs in COPD patients, even with mild-to-moderate airflow obstruction, during exercise, fatally inducing the onset of DH and its progressive worsening, with the well-known negative mechanical, muscular, cardiovascular, and symptomatic consequences. Even worse in the natural history of

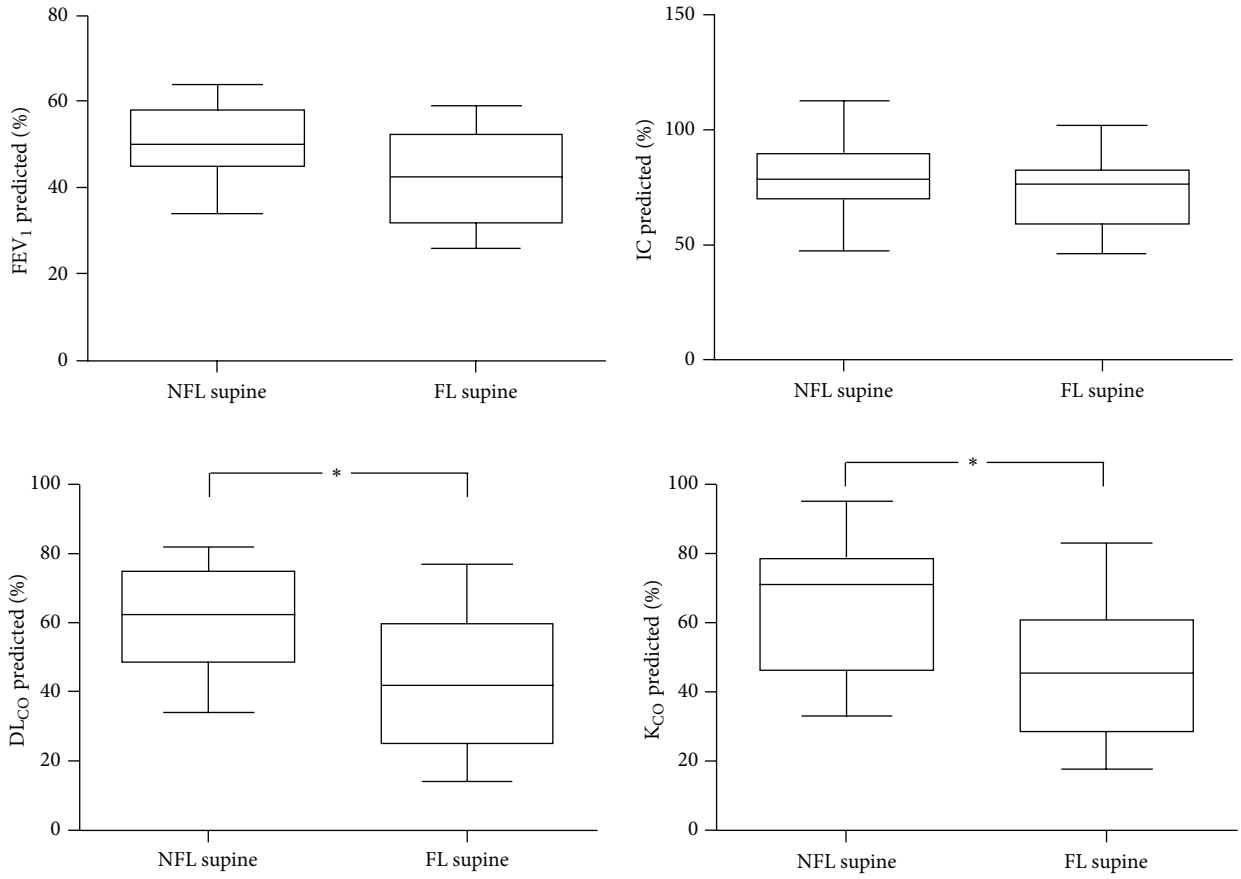

FIGURE 3: Comparison of FEV_1, IC, DL_{CO}, and K_{CO} in COPD patients who exhibit tidal expiratory flow limitation (EFL) in the supine position (FL; $n = 14$) versus those who do not (NFL; $n = 13$). Both DL_{CO} and K_{CO} are significantly lower in FL patients ($^*P < 0.05$), suggesting that emphysematous patients are more prone to develop recumbent EFL.

COPD is the presence of EFL at rest, initially only in the supine position, contributing to orthopnea (and probably to more severe symptoms in early morning) in these patients and subsequently in the sitting-standing position limiting their daily physical activity and causing (very often) DH during resting tidal breathing with persistent volume-related mechanical stress in the lung parenchyma. Physicians who take care of COPD patients should be aware of this severe functional condition that, once established, rarely can be reversed with the present educational, pharmacological, and rehabilitative therapy and try to avoid it treating much earlier and more aggressively airflow obstruction and its determinants.

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Research Article

Driving-Related Neuropsychological Performance in Stable COPD Patients

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Background. Cognitive deterioration may impair COPD patient's ability to perform tasks like driving vehicles. We investigated: (a) whether subclinical neuropsychological deficits occur in stable COPD patients with mild hypoxemia ($PaO_2 > 55$ mmHg), and (b) whether these deficits affect their driving performance. *Methods*. We recruited 35 stable COPD patients and 10 normal subjects matched for age, IQ, and level of education. All subjects underwent an attention/alertness battery of tests for assessing driving performance based on the Vienna Test System. Pulmonary function tests, arterial blood gases, and dyspnea severity were also recorded. *Results*. COPD patients performed significantly worse than normal subjects on tests suitable for evaluating driving ability. Therefore, many (22/35) COPD patients were classified as having inadequate driving ability (failure at least in one of the tests), whereas most (8/10) healthy individuals were classified as safe drivers ($P = 0.029$). PaO_2 and FEV1 were correlated with almost all neuropsychological tests. *Conclusions*. COPD patients should be warned of the potential danger and risk they face when they drive any kind of vehicle, even when they do not exhibit overt symptoms related to driving inability. This is due to the fact that stable COPD patients may manifest impaired information processing operations.

1. Introduction

It is increasingly recognized that chronic obstructive pulmonary disease (COPD) is a multicomponent disease, but relatively little attention has been paid to its impact on neuropsychological function. Several studies have identified neuropsychological deficits in COPD patients [1–3]. The extent of this dysfunction appears to be related to the level of hypoxemia [4–8]. Subclinical cognitive deficits can even be detected in COPD patients with mild hypoxemia ($PaO_2 > 55$ mm Hg) [9, 10].

Neuropsychological tests aim to provide standardized and objective measurements is the function of specific cognitive domains. The tasks, performed as part of the neuropsychological testing, often closely resemble mental challenges encountered in everyday life. One of the commonest mental challenges in everyday life is driving performance. The latter is a complex task highly dependent on the cognitive function, involving perceptual, motor, and decision making skills. Therefore, our hypothesis was that driving ability may be impaired even in stable COPD patients with mild hypoxemia.

Road testing *per se* is the gold standard for assessing driving ability [11], but it is time consuming, expensive, and potentially hazardous. Simulators, which reproduce real driving [12, 13] conditions, are complex, very expensive, and not widely available. Nowadays, with advances in computer technology, various off-road neuropsychological tests have been developed to assess driving capacity. These tests are easier, obviously safer than on-road testing, and cheaper than using driving simulators. These tests measure an individual's ability to maintain attention, alertness, and proper reaction, the three key components of safe driving performance.

Table 1: Anthropometric characteristics and respiratory function data of normal subjects and COPD patients.

Parameters	Normal subjects ($n = 10$)	COPD patients ($n = 35$)	P value
Age, (yrs)	55 (5)	59 (7)	NS
Gender, M/F	8/2	26/9	NS
Ht, (m)	1.7 (0.05)	1.7 (0.07)	NS
Wt, (kg)	78 (8)	77 (14)	NS
Wt, (% pred)	109 (10)	106 (15)	NS
BMI	27.4 (2.7)	26.5 (3.7)	NS
FVC, (% pred)	105 (12)	86 (20)	$P = 0.007$
FEV_1, (% pred)	100 (11)	45 (22)	$P < 0.001$
FEV_1/FVC, %	77 (4)	40 (14)	$P < 0.001$
IC, (% pred)	103 (18)	81 (17)	$P < 0.001$
TLC, (% pred)	93 (8)	100 (15)	NS
FRC, (% pred)	89 (12)	120 (0.0)	$P = 0.002$
RV, (% pred)	74 (14)	123 (42)	$P < 0.001$
DL_{CO}, (% pred)	103 (12)	60 (22)	$P < 0.001$
PaO_2 (mm Hg)		77 (12)	
$PaCO_2$ (mm Hg)		41 (6)	
SpO_2%	98 (97–99)	95 (94–96)	$P < 0.001$
IQ (% ile)	90 (75–95)	80 (63–95)	NS

Values are mean (SD) or median (range).
Abbreviations: Ht: height; Wt: weight; BMI: body mass index; SpO_2 %: arterial oxygen saturation measured with pulse arterial oximeter; IQ: intelligent quotient; $P \leq 0.05$, statistically significant; NS: nonsignificant.

The aim of this work was to assess cognitive neuropsychological performance in a group of normal subjects and in a group of stable COPD patients with mild hypoxemia (i.e., $PaO_2 > 55$ mm Hg) with a battery of pertinent neuropsychological tests, especially designed to evaluate driving-related ability.

Therefore, we conducted this preliminary study to investigate (a) whether the cognitive neuropsychological performance was impaired in COPD patients with subclinical levels of hypoxemia, that is, $PaO_2 > 55$ mm Hg (primary outcome), and (b) whether this impaired performance was related to driving ability (secondary outcome).

Figure 1: A subject performing neuropsychological testing for evaluating driving-related ability with the Vienna Test System.

2. Methods

The population of the study consisted of 35 patients with COPD (26 males) and 10 normal subjects (8 males) who served as controls. The COPD patients referred to our laboratory for lung function testing. At study time, their clinical and functional state had been stable for at least four weeks. COPD severity was classified using postbronchodilator spirometric values according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines [14] (4 patients in stage I, 7 in stage II, 15 in stage III, and 9 in stage IV). Controls were never-smokers healthy volunteers with no medical history. The two groups were matched for age, gender, education, and intelligence quotient (IQ) as assessed by Raven's progressive matrices intelligence test (RPM) [15]. Subjects with history of neurological or psychiatric disease, head injury, uncorrected visual or acoustic impairment, shaking hands, chronic sedative intake, or alcohol abuse were excluded. Subjects with a history of asthma, allergic rhinitis, and BMI > 32 were also excluded.

None of our patients participating in the study reported any symptoms and signs related to sleep apnoea syndrome. Although the Epworth Sleepiness Scale was not formally filled by the patients, all the pertinent questions were asked during the strict and detailed history taking. Therefore, a formal sleep study was not justified. On the other hand, any patients reporting suspicious symptoms or signs for OSAHS were excluded from the study.

Randomly allocated, half of our patients have taken their daily dose of bronchodilator, but half of them have not taken it for at least 24 hours before neuropsychological testing. Any other medication was not allowed for at least 48 hours before testing. COPD patients were mildly hypoxemic (PaO_2 > 55 mm Hg). Only 7 of them were hypercapnic ($PaCO_2$ > 45 mm Hg). The characteristics of all subjects are presented in Table 1.

The study was approved by the local Medical Ethics Committee of Sotiria Hospital. All subjects gave their informed consent, and none of the participants received any financial compensation for their participation in the study.

2.1. Respiratory Function Tests. All control subjects and COPD patients underwent routine pulmonary function tests, that is, spirometry, static lung volumes, and lung diffusion capacity (DL_{CO}), according to the ATS/ERS guidelines [16–19]. The severity of chronic dyspnea was rated according to the modified Medical Research Council (mMRC) [20]. Arterial blood gases were measured only in COPD patients, and oxygen saturation (%SpO_2) using a pulse oximeter was measured in all subjects.

2.2. Neuropsychological Tests. Neuropsychological assessment took place on the same day after the pulmonary function tests. Every patient and healthy individual underwent an attention/alertness battery of tests for evaluating driving-related performance based on the Vienna Test System [21, 22] (http://www.schuhfried.co.at). Each test began with standardized instructions while the subject was comfortably seated in front of a computer's screen (Figure 1).

2.3. Reaction Time to Single Visual (RT-V) and Acoustic Stimuli (RT-A). The subject places his forefinger on a detector and when a color flashlight (yellow light) appears on the screen he has to push a button 10 cm ahead in the fastest possible way (Figure 1). The use of a rest and a reaction key makes the splitting into reaction and motor time possible. So, two parameters are recorded: (a) the period of time between the flash light and the moment the subject takes his forefinger away from the detector-rest key (reaction time: RT-V), and (b) the period of time the subject takes his forefinger away from the detector and pushes the button (motor time: MR-V). The sum of the two times above is the total reaction time (total RT-V). Totally, 28 stimuli are presented, and the test duration is 7 minutes.

Reaction time to acoustic stimuli is performed in the same way, except that the flashlight is replaced by a sound presented to the subject via headphones. The total reaction time (total RT-A) is the sum of the reaction time (RT-A) and motor time (MR-A) to acoustic stimuli.

2.4. Selective Attention Test (SA). It is a test for the assessment of concentration. The program presents four geometrical shapes on the top of the screen and asks from the subject to compare these shapes with a geometrical shape shown at the bottom of the screen. The number of given tasks is 80, and the duration of the test is 20 min.

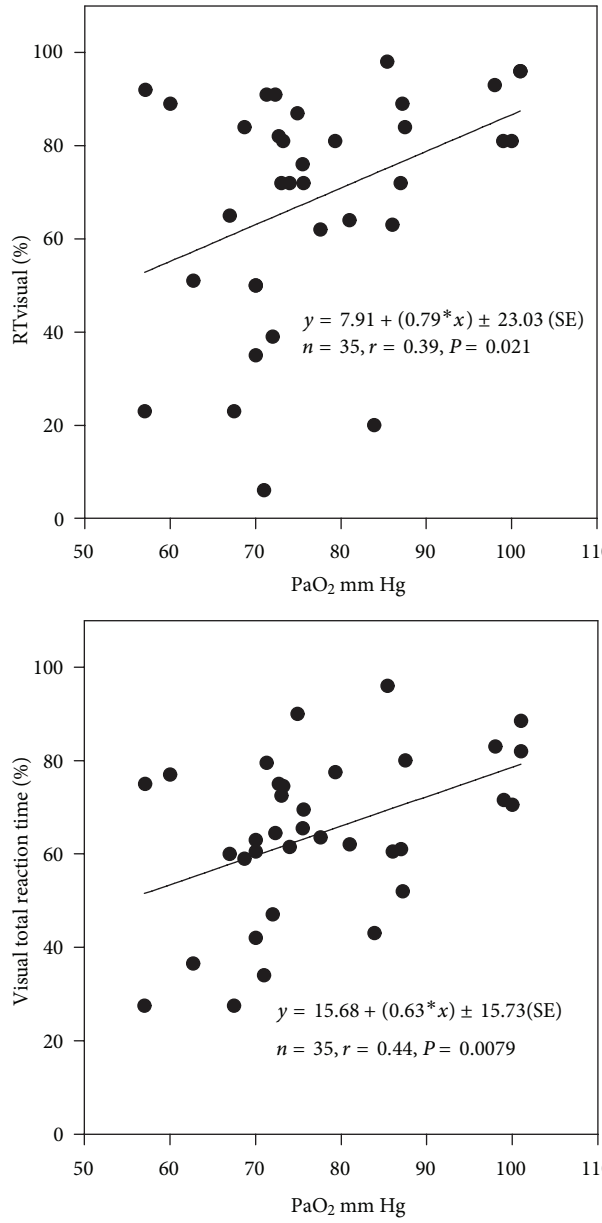

Figure 2: Relationship of PaO_2 to simple reaction time (RT-V%) and total reaction time (total RT-V%) to visual stimuli.

2.5. Permanent Attention Test (PA). This test assesses reaction under stress. The subject has to match quickly color figures with the equivalent color buttons on a keyboard, react to acoustical signs of high or low frequency by pushing predetermined corresponding buttons, and press foot pedals when the figure of a foot pedal appears on the screen. The total number of presented stimuli is 150, and the test duration is 30 min.

2.6. Tachistoscopic Traffic Test (TAVTMB). This test assesses visual perception. The subject is confronted with 20 pictures of traffic situation for 1 second each. Then, he has to indicate what he has seen in the picture. The test duration is 10 min.

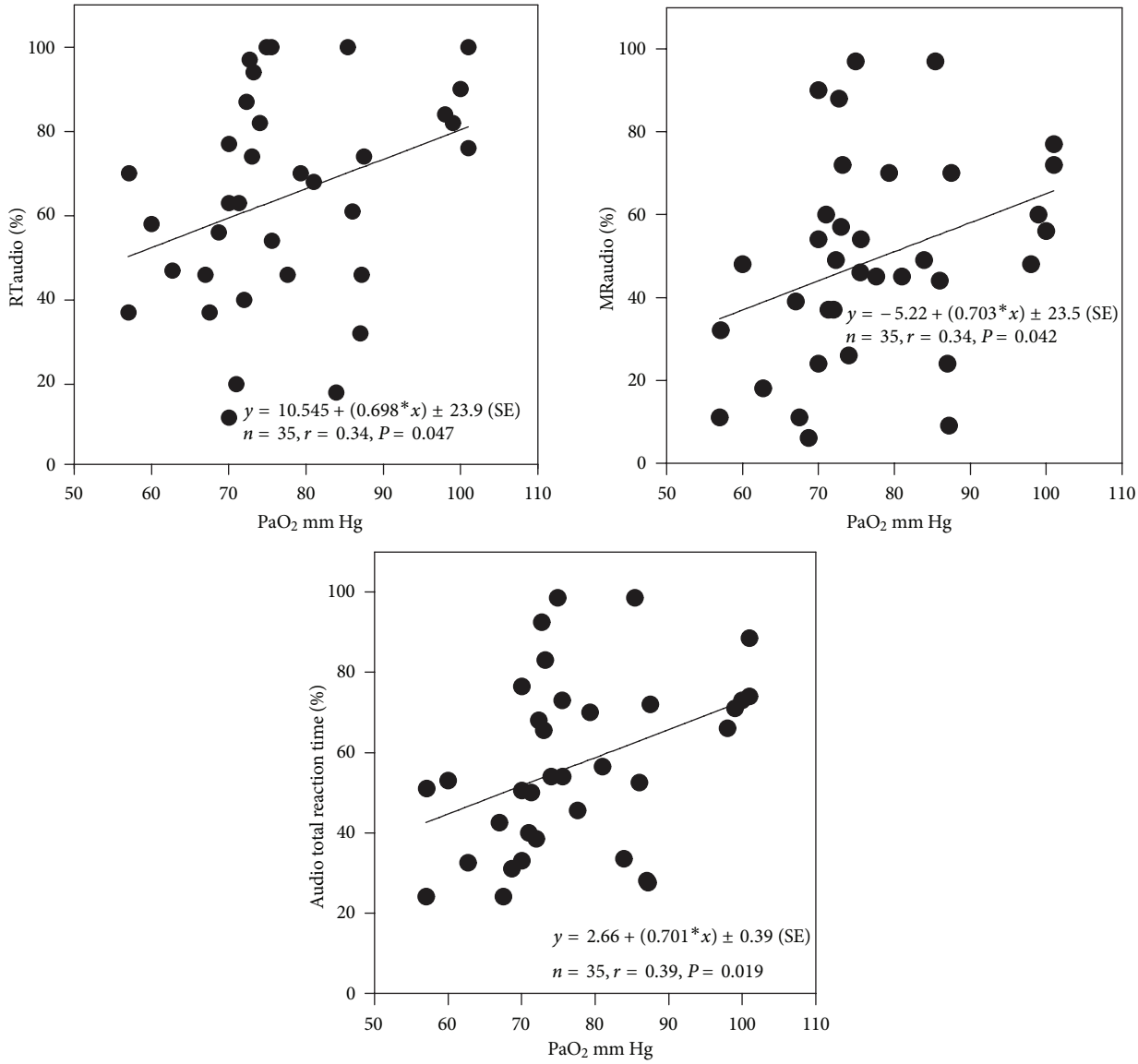

Figure 3: Relationship of PaO_2 to simple reaction time (RT-A%), motor reaction time (MR-A%), and total reaction time (total RT-A%) to audio stimuli.

According to the results of the tests, the subject is classified in a percentile of preexisting normative values of age-matched controls. Normative data exists from general adult population from all over Europe, of different social-economical and educational groups, with age distribution of 18–80 years old (http://www.schuhfried.at).

Control subjects and COPD patients were also evaluated according to Raven's intelligence test [15]. This IQ test consists of 60 items. Each item contains a figure with a missing piece and alternative pieces to complete the figure, only one of which is correct. The raw score is typically converted to a percentile rank by using the appropriate norms. Subjects had at their disposal 30 minutes to complete the test. Subjects with IQ scores <50% ile were not acceptable in order to avoid wrong answers in all other neuropsychological tests because of the difficulty to understand them.

In addition, both patients and control subjects underwent ophthalmologic and audiologic examinations before the tests to exclude hearing or visual deficits compromising the reliability and validity of neuropsychological testing.

According to the European diagnostic criteria for the assessment of driving ability based on the Vienna Test System, subjects have to pass all the tests in order to be classified as having adequate driving-related ability and obtain a professional driving licence. An expert in traffic psychology evaluates patients' performance on all the tests and identifies who are fit or unfit to drive [16].

2.7. Statistical Analysis. The statistical analysis and related graphs were performed using SigmaStat V3.5 and SigmaPlot V10.0 (Jandel Scientific, CA, USA). For comparisons between groups, the Student's unpaired t-test was used. If there was

Table 2: Driving-related neuropsychological testing performance data in normal subjects and COPD patients.

Parameters	Normal subjects ($n = 10$)	COPD patients ($n = 35$)	P value
SA, (% ile)	32.5 (19–39)	23.9 (9.3–34.8)	NS
RT-V, (% ile)	89 (82–89)	76 (53.8–88.5)	$P = 0.035$
MR-V, (% ile)	79.2 (12.2)	59.8 (18.7)	$P = 0.004$
Total RT-V, (% ile)	82 (79–87.5)	64.5 (59.3–76.5)	$P < 0.0001$
RT-A, (% ile)	84.5 (70–97)	68 (46–83.5)	$P = 0.035$
MR-A, (% ile)	72.6 (22)	49.2 (24.7)	$P = 0.01$
Total RT-A, (% ile)	78.3 (14.2)	56.9 (21.6)	$P = 0.0052$
PA, (% ile)	26.5 (17–38)	18 (6–34)	NS
TAVTMB, (% ile)	25 (21–62)	18 (7–24)	$P = 0.003$
Driving ability, accepted/rejected	8/2	13/22	$P = 0.029$

Values are mean ± SD or median (range).
Abbreviations: SA: selective attention; RT-V: reaction time to visual stimuli; MR-V: motor time to visual stimuli; Total RT-V: the sum of reaction and motor time to visual stimuli; RT-A: reaction time to audio stimuli; MR-A: motor time to audio stimuli; Total RT-A: the sum of reaction and motor time to audio stimuli; PA: permanent attention; TAVTMB: tachistoscopic traffic test; $P \leq 0.05$, statistically significant; NS: nonsignificant.

Table 3: Characteristics and attention/alertness performance data for COPD patients who have been accepted and those who have been rejected as safe drivers.

	Rejected ($n = 22$)	Accepted ($n = 13$)	P
AGE, (yrs)	61.5 (6.6)	55.7 (6.6)	0.017
Ht, (m)	1.68 (0.1)	1.73 (0.1)	0.042
Wt, (% pred)	104.8 (92–117)	111 (96–122)	NS
BMI	26.1 (3.5)	27.1 (4)	NS
FVC, (% pred)	79.7 (18.7)	96.8 (18.2)	0.013
FEV_1, (% pred)	35.4 (14.9)	59.8 (24.5)	<0.001
FEV_1/FVC, %	45.6 (13)	63.2 (20.5)	0.004
IC, (% pred)	75.6 (13.4)	90.2 (20)	0.015
TLC, (% pred)	101 (16.6)	98.4 (10.4)	NS
RV, (% pred)	133.4 (47.6)	104.1 (20.3)	0.044
RV/TLC (%)	47.9 (10.6)	36.5 (8.9)	0.003
DLCO, (% pred)	50.6 (15.3)	74.8 (24)	<0.001
PaO_2 (mm Hg)	72.2 (68.7–79.3)	86 (74.9–99.3)	0.005
$PaCO_2$ (mm Hg)	41.6 (6)	38.7 (4.13)	NS
SaO_2, (%)	94.2 (2.3)	96.4 (1.9)	0.006
SpO_2, (%)	93.5 (2.4)	96.5 (2.0)	<0.001
mMRC, grade	3 (2–4)	1 (1–2.5)	0.002
IQ (% ile)	75 (50–85)	90 (80–95)	0.009
SA, (% ile)	19.5 (17.1)	36 (23.5)	0.021
RT-V, (% ile)	63.3 (27.9)	78.3 (14.1)	NS
MR-V, (% ile)	57.5 (20.8)	63.7 (14.5)	NS
Total RT-V, (% ile)	61.3 (47–75)	71.5 (65–80.5)	0.047
RT-A, (% ile)	59.5 (27.4)	73.2 (18.2)	NS
MR-A, (% ile)	47.2 (28.9)	52.6 (15.8)	NS
Total RT-A, (% ile)	53.4 (24.3)	62.9 (15)	NS
PA, (% ile)	8.5 (5–16)	43 (33.8–51.8)	<0.001
TAVTMB, (% ile)	9 (5–14)	25 (21–30)	<0.001

Values are mean (SD) or median (range).
Abbreviations as in Table 3.

no normality in the distribution in any of our parameters, a Mann-Whitney U-test for unpaired values was used. Where appropriate, Spearman correlation analysis, linear regression analysis, one-way ANOVA on ranks, multiple regression, and forward stepwise regression were used.

3. Results

All subjects' anthropometric and lung function data are shown in Table 1. Controls and COPD patients had comparable age, height, weight, BMI, and IQ. COPD patients were

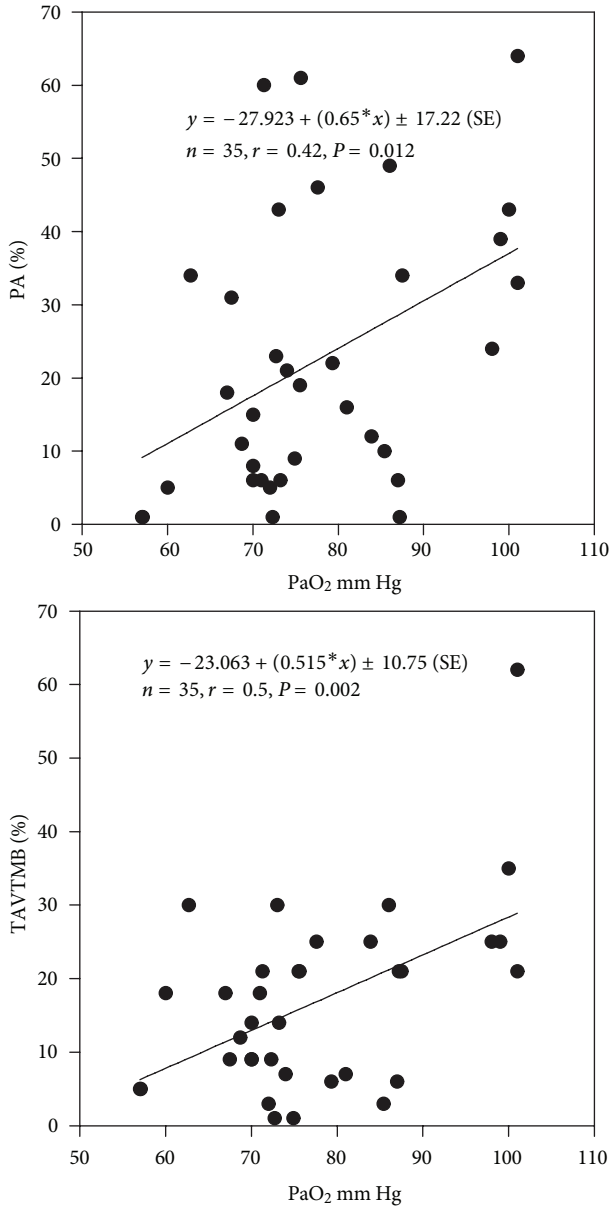

Figure 4: Relationship of PaO_2 to permanent attention (PA%) and tachistoscopic traffic (TAVTMB%) tests.

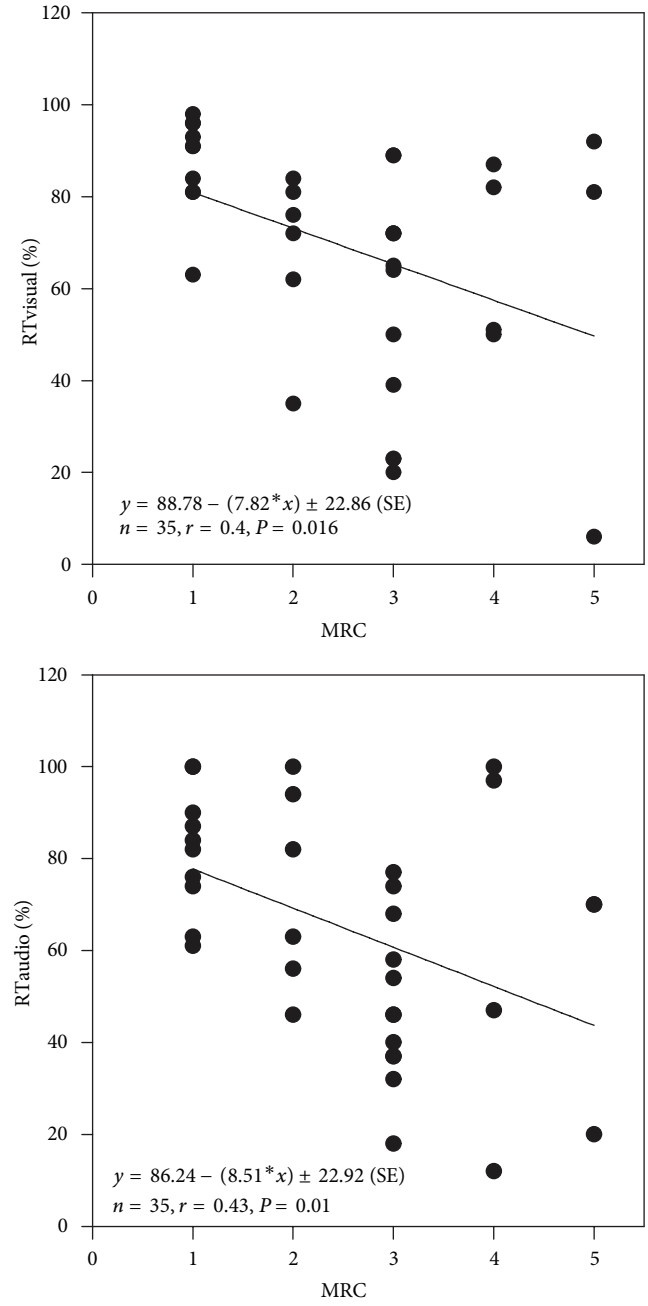

Figure 5: Relationship of dyspnea severity according to the modified Medical Research Council (mMRC) to reaction time to visual (RT-V%) and audio (RT-A%) stimuli.

significantly different to controls in pulmonary function data and oxygen saturation.

Table 2 summarises the results obtained in the attention/alertness battery of tests for the two groups. All the results are expressed as percentile of preexisting normative values. The faster the performance, the higher the score. Patients had significantly longer reaction and motor times in response to visual and acoustic stimuli and so, lower scores. They also presented significantly reduced visual perception (TAVTMB). Patients tended to score worse than controls for selective and permanent attention test, but this difference did not reach statistical significance. So, COPD patients scored worse than healthy volunteers in five of the seven neuropsychological tests for assessing driving-related performance. Among 35 COPD patients, only 13 successfully completed all the tests, and these 13 were classified as safe drivers. Among 10 controls, only 2 failed to complete all the tests and were classified as unsafe drivers ($P = 0.029$).

All neuropsychological tests were significantly ($P < 0.05$) correlated with PaO_2, except for the selective attention test (SA) (Figures 2, 3, and 4). SA test was correlated only with a lower IQ. The severity of dyspnea rated according to the mMRC score seems to influence significantly the performance on RT-V, RT-A, PA, and TAVTMB tests (Figures 5

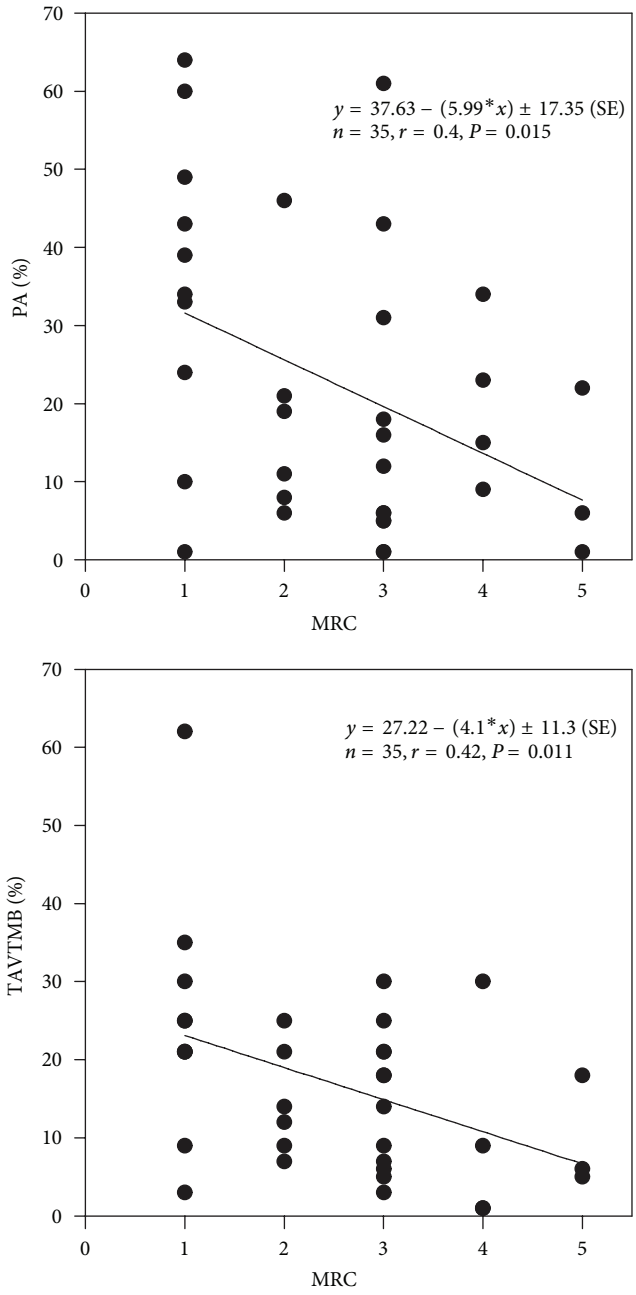

Figure 6: Relationship of dyspnea severity according to the modified Medical Research Council (mMRC) to permanent attention (PA%) and tachistoscopic traffic (TAVTMB%) tests.

and 6). The performance on the same tests, except for the PA test, was significantly correlated with FEV_1% pred (Figure 7). The effect of FEV_1 especially on visual perception (TAVTMB) can be verified if we divide patients into GOLD stages. In stage I, the median value of visual perception is 25%, the same as for the control group. In stage II, it is 21%, in stage III, 12%, and in stage IV, 9%. There is a statistically significant difference among the groups ($P < 0.003$).

With simple correlations, we could not find any effect of $PaCO_2$ on psychomotor tests. To further investigate the real effect of PCO_2 on psychomotor performance, we divided our patients into two groups: those in whom PCO_2 was normal (≤45 mm Hg) ($n = 28$) and those whose PCO_2 was >45 mm Hg and were hypercapnic ($n = 7$). The two groups had similar scores on the tests except for the motor reaction time to visual and acoustic stimuli. Hypercapnic COPD patients scored lower than nonhypercapnic on these tests, and this difference remained significant after adjustment for potential confounders such as PaO_2 and age.

As we have already mentioned, randomly allocated, half of our patients ($n = 17$) have taken their daily dose of an inhaled drug (6 patients have taken a b_2 bronchodilator and 11 a combination of a b_2 bronchodilator and anticholinergic or corticosteriod) at least one hour before testing, and half of them have not taken it, at least 24 hours before testing ($n = 18$). The two groups showed no significant differences on the neuropsychological tests. So, it appears that bronchodilators do not influence driving-related psychomotor performance.

Finally, we divided the 35 COPD patients into two groups: those who have been accepted ($n = 13$ patients) and those who have been rejected ($n = 22$ patients) as safe drivers. The two groups showed statistically significant differences for PaO_2, SpO_2, FEV_1, FVC, IC, RV, and DLCO. They also showed statistically different scores in SA, total RT-V, PA, and TAVTMB tests (Table 3). They were not matched for age and IQ, and after correction for age and IQ with logistic regression, they remained different in the last two tests, that is, permanent attention and visual perception.

4. Discussion

In this study, we have shown that, except of the well-known cognitive dysfunction in severe hypoxemic patients [23–25], cognitive performance is also impaired in mildly hypoxemic COPD patients when compared to normal subjects matched for age, education level, and IQ. One of the main practical effects of this deterioration is the impairment of a patient's ability to perform tasks requiring increased vigilance and alertness like driving any kind of vehicle [26]. To the best of our knowledge, there are no reports dealing with the problem of impaired driving ability in COPD patients by using especially designed computer-based neuropsychological tests [27].

There are sparse publications and controversial reports for COPD patients with mild hypoxemia [9, 10]. The practical effect of the cognitive deterioration to the daily lives of these patients is still not known. Driving is an essential part of everyday life for most people, and the withholding of a private or professional driving licence has major implications for social functioning and employment. According to traffic psychology, accident proneness has strong relationships with a number of perceptual, cognitive, and motor skills. In our study, COPD patients demonstrated markedly delayed reaction times to visual or acoustic stimuli and impairments in motor activity and perceptive speed in traffic situations. These Subclinical neuropsychological deficits may explain the worse driving-related performance of COPD patients compared to normal subjects. More than half of our COPD

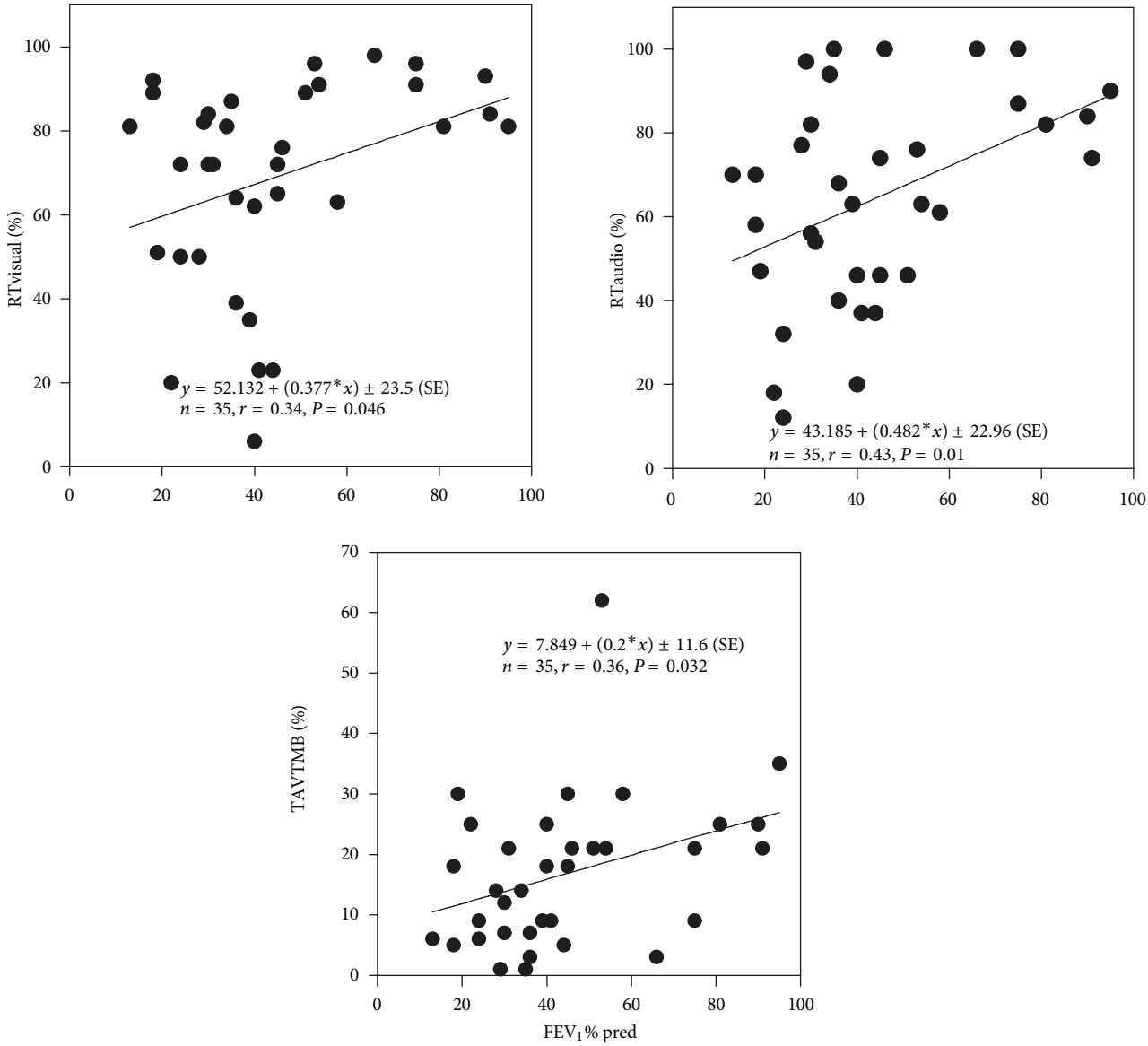

Figure 7: Relationship of FEV_1% pred to reaction time to visual (RT-V%) stimuli, reaction time to audio (RT-A) stimuli, and tachistoscopic traffic test (TAVTMB%).

patients (22/35) were classified as unsafe drivers based on failing to at least one from a battery of neuropsychological tests pertinent to any driving situation.

The explanation for the impaired functioning in COPD patients can be the mildly low levels of blood oxygenation, given the fact that the brain is the most sensitive organ to oxygen lack. This level of hypoxemia could lead to mild-to-moderate inefficiencies in neural functioning and thus to the modest subclinical impairment. In this study, we have included mildly hypoxemic patients ($PaO_2 > 55$ mm Hg); therefore, it is possible that a not fully normal PaO_2 or at the lower limits of normal (between 55–80 mm Hg) still leads to an impaired subclinical cognitive performance.

In addition, these patients usually have nocturnal desaturation or hypoxemia during sleep [27, 28], chronic pulmonary disease could enhance vascular disease, leading to reduced cerebral blood flow and oxygen consumption, even in normoxemic COPD patients, and COPD *per se* could lead to an acceleration of the aging process so that brain functions are impaired in a fashion similar to that seen in the elderly. This process could lead to a reduction in cortical neuronal density and a subsequent less efficient performance on neuropsychological tests. All these factors could be at work and have additive effects [29].

Impairments of cognitive performance in patients with COPD can be predicted on the basis of the severity of the disease. The partial pressure of arterial oxygen and the degree of pulmonary impairment may be major factors contributing to cognitive deficit among COPD patients. The partial pressure of arterial dioxide seems to affect the performance on motor reaction time to visual or acoustic stimuli, which require motor muscle activity. The muscle weakness that

is frequently seen in patients with COPD may explain the previous observation [30]. However, the permanent attention test, another test requiring motor muscle performance, does not seem to be influenced by $PaCO_2$. So, impairments in motor ability cannot simply be explained by weak muscle activity. Irrespective of the cause, these deficits may have negative impact on driving performance of any kind of vehicle ranging from a bicycle to heavy lorries, in real traffic settings.

Possible limitations of the present study lie in whether these findings represent state rather than trait effects, which appears to be reasonable target for future research. In this sense, future research should replicate the main findings in independent samples as well as further explore whether the findings are associated in task-specific manner or across tasks.

Driving fitness may be assessed with reasonable accuracy using off-road tests minimizing the expense and risk associated with on road assessment. However, computer-based testing does not provide the real changes that occur when turning a steering wheel and the vehicle changes course. Also, missing in the laboratory environment is the subject's knowledge that the consequences of driving control responses affect his/her own safety.

Although there are disadvantages in computer-based testing, these are easy and simple tests that might be useful for giving insight about driving performance in COPD patients and make an important contribution to transport safety. These preliminary data need to be confirmed with further studies before simple computer-based testing can be used to decide whether or not an individual is safe to drive in every day life.

We conclude that probably stable COPD patients should be warned of the possible danger and risk they face when they drive any kind of vehicle, even when they do not exhibit overt symptoms related to driving ability.

Abbreviations

ATS:	American Thoracic Society
BMI:	Body mass index
COPD:	Chronic obstructive pulmonary disease
DLCO:	Lung diffusion capacity
FEV_1:	Forced expiratory volume in one second
FRC:	Functional residual capacity
GOLD:	The global initiative for chronic obstructive lung disease
IC:	Inspiratory capacity
IQ:	Intelligence quotient
mMRC:	Modified Medical Research Council
MR-A/MR-V:	Motor reaction time to audio/visual stimuli
PA:	Permanent attention
RT-A/RT-V:	Reaction time to audio/visual stimuli
RPM:	Raven's progressive matrices
SA:	Selective attention
TAVTMB:	Tachistoscopic traffic test
TLC:	Total lung capacity.

Conflict of Interests

The authors report no conflict of interests.

Authors' Contribution

All authors made measurements on the subjects participating in the study, analysed the data, and contributed in lengthy discussions during the writing of the paper. F. Karakontaki and N. G. Koulouris wrote the paper.

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Review Article

Pulmonary Rehabilitation in COPD: A Reappraisal (2008–2012)

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Chronic Obstructive Pulmonary Disease (COPD) is a complex pathological condition associated with an important reduction in physical activity and psychological problems that contribute to the patient's disability and poor health-related quality of life. Pulmonary rehabilitation is aimed to eliminate or at least attenuate these difficulties, mainly by promoting muscular reconditioning. The scope of this paper has been the analysis of the literature on pulmonary rehabilitation in COPD patients has appeared in the last five years, focusing on the principal outcomes obtained. The results demonstrate that pulmonary rehabilitation has a beneficial effect on dyspnoea relief, improving muscle strength and endurance. Moreover, pulmonary rehabilitation appears to be a highly effective and safe treatment for reducing hospital admissions mortality and improving health-related quality of life in COPD patients. It represents, therefore, a very important therapeutic option that, along with standard pharmacological therapy, can be used to obtain the best patient management. The favourable results obtained with pulmonary rehabilitation programs should stimulate researchers to improve our understanding of the mechanisms that form the basis of the beneficial effects of this therapeutic intervention. This would in turn increase the effectiveness of pulmonary rehabilitation in COPD patients.

1. Introduction

Pulmonary rehabilitation is defined by the American Thoracic Society and the European Respiratory Society as an "evidence-based, multidisciplinary, and comprehensive intervention for patients with chronic respiratory diseases who are symptomatic and often have decreased daily life activities." As such it is an integral part of the clinical management and health maintenance of those patients with chronic respiratory disease who remain symptomatic or continue to have decreased lung function despite standard medical treatment. Integrated into the individualised treatment of the patient, pulmonary rehabilitation is designed to reduce symptoms, optimise functional status, increase participation, and reduce health care costs by stabilising or reversing systemic manifestations of the disease [1]. All together these considerations underline the general implications and the importance of this respiratory treatment, which should be considered fundamental during the management of chronic obstructive pulmonary disease (COPD). In the last few years, medical literature has provided evidence that pulmonary rehabilitation favourably affects outcomes in COPD [2]. In spite of these important achievements, there is a need of further improvements in pulmonary rehabilitation programs, because COPD is still a major cause of disability worldwide, besides mortality [3].

COPD is characterised by complex and diverse pathophysiologic manifestations. The inflammatory pulmonary process, principally triggered by cigarette smoke, induces a series of molecular and cellular reactions with detrimental effects on lung tissue [4]. The main and more important manifestations of respiratory relevance are expiratory flow

limitation with dynamic collapse of the airways, air trapping, and lung hyperinflation [5]. The increase in respiratory rate that occurs during exercise further amplifies lung hyperinflation, leading to or worsening the "dynamic hyperinflation" due to tidal expiratory flow limitation. Various bronchodilator drugs have proven able to improve pulmonary function, promoting reduction of lung hyperinflation at rest and during exercise: thus, acute administration of tiotropium or budesonide/formoterol increased inspiratory capacity and decreased intrathoracic gas volume by about 0.4 L in 20 COPD patients [6]. Helium-oxygen mixtures (heliox) are also being used to reduce lung hyperinflation in COPD patients on the assumption that if turbulent flow occurs during tidal breathing, a less dense gas mixture would reduce airway resistance and prevent expiratory flow limitation. However, heliox did not abolish expiratory flow limitation in 26 stable COPD patients but reduced exercise dynamic hyperinflation in 25% of the patients and decreased exercise dyspnoea in all of them [7]. This decrease was largely independent of changes in dynamic hyperinflation and tentatively related to the fall of inspiratory resistance which follows the reduction of turbulent flow in the upper airways with heliox.

In spite of the patient's attempt to adopt more convenient breathing patterns, these adaptations are generally overwhelmed during exercise, when there is an acute increase in the ventilatory demand. Acute and chronic hyperinflation have been shown to contribute to exertional dyspnoea, reduced ventilatory capacity, and worsened exercise performance in COPD [8, 9]. Wasted ventilation further increases the already high ventilatory demand requested for the maintenance of blood gas homeostasis.

Although the initial pathology of COPD is confined to the lung, the reduction in physical activity and psychological problems associated to the progress of the disease increasingly contribute to the patient's disability and poor health-related quality of life. This forms the basis of the most important clinical manifestations of COPD, such as muscle dysfunction, cardiac impairment, skeletal and sensory deficits, malnutrition, and steroid-related myopathy [10], besides respiratory muscle fatigue, sleep disorders, and psychological alterations such as anxiety, depression, sense of guilt, and carer dependency. The importance of the psychological profile has been clearly demonstrated, particularly as far as anxiety and depression are concerned, both being common occurrence in COPD patients, even when their disease is mild in terms of respiratory function and symptoms [11]. Indeed, depression has a prevalence rate of about 45% in patients with moderate to severe COPD [12]. Hence, care should be taken to design an adequate psychological and social support within the pulmonary rehabilitation settings.

Exercise training is an important aspect of pulmonary rehabilitation, as it represents the best available means of improving muscle performance, with remarkable favourable impact on exertional dyspnoea, exercise tolerance, and improvement of daily activities [1]. Traditionally pulmonary rehabilitation has focused on lower extremity training, little or no attention being paid to training of upper limb muscles, although they are regularly involved in all daily activities. The minimum duration of exercise training in pulmonary rehabilitation has not been extensively investigated; however, the ERS/ATS Statement suggests 20 sessions of a comprehensive treatment as the best option.

Education of the patient is a core component of a complete rehabilitation program, together with the prevention and early treatment of respiratory exacerbations, implementation of breathing strategies, and bronchial cleaning. The combination of postural drainage, percussion, and forced expiration improve airway clearance, while the use of a positive expiratory pressure mask and assisted coughing have proven to be more effective than assisted coughing alone in COPD patients during an exacerbation [13]. In fact, for some patients mucus hypersecretion and impaired mucociliary transport represent distinctive features of their lung disease, and for these reasons they require particular and appropriate instructions.

Pulmonary rehabilitation programs should also address body composition abnormalities, which are frequently present but underrecognised in chronic lung diseases. Interventions relating to these aspects may be in the form of caloric supplementation, physiological interventions, pharmacological strategies, or combination therapy in order to induce weight gain without an overall fat mass increase. All of these interventions have resulted in an improvement in quality of life and justify the decision taken by official organisations to recommend pulmonary rehabilitation as an integral part of the long-term management of COPD [14–17].

While the utility of pulmonary rehabilitation is undisputed, no general consensus exists regarding the parameters that should best represent the improvements achieved with pulmonary rehabilitation. Indeed, the various research groups have focused on different parameters, like exercise performance, endurance, dyspnoea, and quality of life, while little or no attention have been paid to a number of parameters concerned with respiratory mechanics and gas exchange. The absence of homogeneity regarding the study endpoints largely limits the comparison among the various studies, besides evaluation of their results. With this in mind, we have analysed the literature on pulmonary rehabilitation in COPD patients that has appeared in the last five years, focusing on the main outcomes used and their evaluation.

2. Selection Criteria

We conducted a MEDLINE search using the keywords "pulmonary rehabilitation" and "COPD": of the resulting 1294 articles, 574 had been published in the last five years, but only 398 had pulmonary rehabilitation as the relevant issue. These papers could be classified as follows: 121 clinical trials, 78 randomised clinical trials, 10 meta-analyses, 4 practical guide lines, 131 reviews, and 54 systematic reviews (Figure 1). Guide lines and reviews were discarded. Among clinical trials, we took into consideration those that were performed following a randomisation design and those which included a representative number of patients (>200). Two additional studies involving a smaller number of patients were included in the analysis: one because it addresses the results obtained

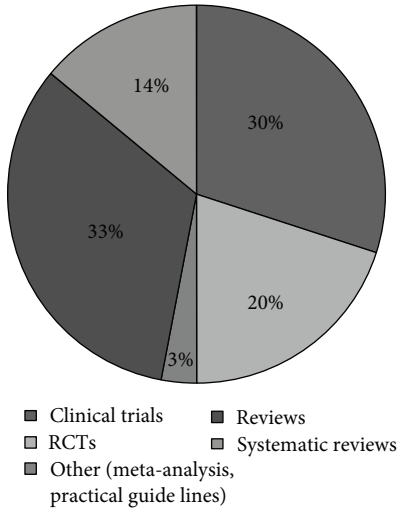

Figure 1: Distribution of scientific literature about pulmonary rehabilitation.

in an out-patient pulmonary rehabilitation program [18], the other because it deals with a new approach, namely, the home exercise video program [19]. With these restrictions, only 19 papers could be taken into consideration (Table 1).

3. Results

In all studies, the duration of the pulmonary rehabilitation programs was six-to-twelve weeks. Furthermore, all programs were based on a multidisciplinary approach: exercise training, patient education, psychosocial and behavioural interventions, and nutritional therapy to contrast weight loss and muscle wasting. It is important to underline that only three papers made the distinction between primary and secondary outcomes. Furthermore, two of them have evaluated the improvement of the quality of life after the Saint George Respiratory Questionnaire (SGRQ) score as the primary outcome [20, 21], whereas the third one has used the Chronic Respiratory Disease Questionnaire (CRQ) [22].

The conclusion common to all papers listed in Table 1 is that pulmonary rehabilitation improves the 6 MWTD, maximal oxygen consumption, treadmill endurance time, exertional and overall dyspnoea, and self-efficacy for walking, in line with studies performed in the 90s [37–39]. Briefly, the assessment of pulmonary rehabilitation has been made according to three perspectives: functional outcomes, dyspnoea perception, and quality of life.

3.1. Functional Outcomes. Twelve studies have analysed the six-minute walking test distance (6 MWTD) as a functional parameter; all of them concluded that pulmonary rehabilitation of COPD patients leads to an increase of the covered distance. Nine of those papers also evaluated other variables such as the incremental shuttle test, leg strength, and the peak oxygen intake and found that they were correlated with the 6 MWTD. Moreover, in a retrospective analysis involving a cohort of 815 severe or very severe COPD patients undergoing a pulmonary rehabilitation program based on increasing exercise tolerance, transfers, and stair climbing, Enfield et al. [28] found that the 6 min walking distance was increased by an average 90 metres and that these changes were positively associated with the increase of survival rate. Therefore, the 6 MWTD appears to be an important, simple, and repeatable parameter to evaluate the functional improvement obtained with a pulmonary rehabilitation program, independent of the severity of the disease.

Only 3 studies have considered *Forced Expiratory Volume in the first second* (FEV_1) as a functional parameter. Stav et al. [31] reported a consistent reduction of the rate of FEV_1 decline or even a suppression of that decline after three years of pulmonary rehabilitation, while Ergün et al. [18] and Chang et al. [20] found no significant changes in FEV_1 after 8 weeks of pulmonary rehabilitation.

3.2. Dyspnoea Perception. Four studies evaluated dyspnoea using the MRC or Borg scale. Ergün et al. [18] demonstrated a decrease in dyspnoea sensation by an average of 1.2 units of the MRC scale, both in the early and the late-stage group of COPD patients. Similarly, no significant differences in dyspnoea score were observed between those two groups in a randomized, controlled, prospective study on 78 COPD patients aiming to assess the effectiveness of a pulmonary rehabilitation program performed in a community hospital [34]. On the contrary, Scott et al. [30], using the Borg scale to assess dyspnoea severity in a prospective, observational study, concluded that patients with higher baseline FEV_1 were more likely to enjoy an attenuation of breathlessness, besides greater improvement of both subjective (SGRQ) and objective outcomes (6 MWD).

Few data are available concerning the effectiveness of pulmonary rehabilitation on dyspnoea relief in less severe COPD patients. In a 2-year randomised controlled trial on patients with moderate airflow obstruction but impaired exercise capacity, it was found that a significantly greater decrease of MRC dyspnoea score from baseline occurred in the group of patients subjected to active treatment [21].

3.3. Quality of Life. Ten studies have evaluated the improvements in quality of life using either the SGRQ, CRQ, or Hospital Anxiety Depression (HADs) scale. Van Wetering et al. [21] have conducted a 2-year randomised controlled trial in which the efficacy of the conventional treatments was compared with that of a newly designed Interdisciplinary Community-based (INTERCOM) COPD management program, consisting in a 4-month rehabilitation phase and a 20-month active maintenance phase. The primary outcomes were the change from baseline in disease-specific quality of life as assessed by the SGRQ total score and the total number of exacerbations. At 12 months, the SGRQ score in the INTERCOM group had almost returned to baseline, whereas in the conventional care group it remained stable up to 12 months and worsened thereafter. The authors concluded that INTERCOM proved to be a feasible approach to improve disease-specific quality of life, dyspnoea, and functional

Table 1: Selected studies for the review and used outcomes.

Main author/year	Type of study	Outcomes
van Ranst et al. 2011 [23]	Retrospective, observational	(i) Peripheral muscle performance (ii) Respiratory muscle strength (iii) Cycle exercise endurance and 6 MWDT (iv) CRQ, SGRQ, SF-36
Yoshimi et al. 2012 [24]	Prospective, observational	(i) Respiratory muscle strength (ii) 6 MWDT (iii) SGRQ
Murphy et al. 2011 [22]	Single-blind cluster randomised trial	(i) 1°: CRQ (ii) 2°: ISWT, Self-efficacy for Managing Chronic Disease 6-Item Scale
Fischer et al. 2012 [25]	Prospective, observational	(i) 6 MWDT (ii) Correlation between concerns about exercise and 6 MWDT
Gale et al. 2011 [26]	Prospective cohort study	(i) PWV, BP, IL-6, fasting glucose and lipids (ii) ISWT
Riario-Sforza et al. 2009 [27]	Number needed to treat study	6 MWDT
Enfield et al. 2010 [28]	Retrospective, observational cohort study	Relationship between 6 MWD and survival
Cheikh Rejbi et al. 2010 [29]	Prospective, observational	6 MWDT and peak oxygen uptake in COPD and healthy subjects
Ergün et al. 2011 [18]	Prospective, observational	(i) MRC, BORG dyspnea scale (ii) ISWT, ESWT, FEV_1 (iii) SGRQ, HADs (iv) Body composition: BMI, FFM
Scott et al. 2010 [30]	Prospective, observational	(i) Compliance (ii) SGRQ (iii) 6 MWDT (iv) BORG dyspnea scale
Stav et al. 2009 [31]	Matched controlled trial	(i) FEV_1 (ii) 6 MWDT (iii) BMI
Moore et al. 2009 [19]	Randomised pilot study	(i) ISWT (ii) CRQ
Steele et al. 2008 [32]	Randomised clinical trial	(i) Daily activity with accelerometer (ii) Exercise adherence with diary (iii) 6 MWDT
Eaton et al. 2009 [33]	Prospective randomized controlled study	Risk of readmission at 3 months after an exacerbation
Chang et al. 2008 [20]	Three-group randomised controlled trial	(i) 1°: SGRQ (ii) 2°: FAI, IPAQ, ISWT, FEV_1
Elçi et al. 2008 [34]	Randomized, controlled, prospective study	(i) MRC (ii) 6MWDT (iii) SF-36 (iv) HADs (v) SGRQ
Van Wetering et al. 2010 [21]	Randomised controlled trial	(i) 1°: SGRQ, n ° of exacerbations (ii) 2°: subscores of SGRQ, MRC, 6 MWDT, muscle strength, FFM, lung function
Gottlieb et al. 2011 [35]	Single-centre, randomized, placebo-controlled, unblinded clinical trial	(i) 6 MWDT (ii) Leg strength (iii) SGRQ
Sabit et al. 2008 [36]	Retrospective case note study	Identifying variables that affect poor attendance to PR programme

6 MWDT: 6-minute walking distance test, CRQ: chronic respiratory disease questionnaire, SGRQ: St George's respiratory questionnaire, SF-36: medical outcomes study short-form survey, PWV: aortic pulse wave velocity, BP: blood pressure, IL-6: interleukin-6, ISWT: incremental shuttle walk test, ESWT: endurance shuttle walking test, HADs: hospital anxiety depression scale, BMI: body mass index, FFM: fat free mass, FEV_1: forced expiratory volume in one second, FAI: Frenchay activities index, IPAQ: international physical activity questionnaire.

exercise capacity. On the other hand, the frequency of exacerbations was not significantly different between the groups during the 2-year period of observation. The other two studies that used quality of life as primary outcome also concluded that pulmonary rehabilitation is effective in improving the health-related quality of life in COPD patients [20, 22], and a similar conclusion was reached in the studies that have used quality of life as an additional or secondary outcome [18, 19, 23, 24, 30, 34, 35].

It should be stressed, however, that these studies were carried out on patients with a stable disease, while it is well known that exacerbations are an important and negative prognostic element in the natural history of the disease [40], becoming more frequent as the disease progresses [41]. This should be taken into account for a comprehensive evaluation of the impact of pulmonary rehabilitation programs. Indeed, randomised controlled trials performed over a 2-year period have shown that pulmonary rehabilitation has no impact on incidence of exacerbations and health-care utilization, although there were improvements in disease-specific quality of life, dyspnoea scores, and exercise capacity [21, 33].

4. Discussion

The purpose of this paper has been to analyse the outcomes used in studies on pulmonary rehabilitation in COPD patients published over the last five years, besides the efficacy of these treatments in improving the quality of life and the ability in carrying out daily life activities. Almost all studies have assumed as a primary outcome for the evaluation of the pulmonary rehabilitation programs the distance covered during the six-minute walking test and the peripheral muscle strength, with less attention paid to the impact on the quality of life.

A growing amount of literature advocates home-based rehabilitation as a useful adjunct for COPD management [42, 43]. Home-based interventions are a cheaper, more cost-effective method of care than traditional hospital treatment [44–46] and enable patients to remain in their own environments, close to the family, where exercise training specific to their daily activities can be applied [42, 47, 48]. It must be noted, however, that home-based interventions are principally focused on respiratory muscle training, whereas pulmonary rehabilitation performed in the hospital tackles additional aspects, such as quality of life, breathlessness sensation, psychological profile, and effectiveness of therapeutic interventions [49]. Furthermore, hospital-based, multidisciplinary pulmonary rehabilitation programs include interventions that promote airway clearance, as accumulation of secretions in COPD contributes substantially to airway obstruction. Application of positive end-expiratory pressure has been shown very effective to remove bronchial secretions and reduce atelectasis. It is also the most effective treatment available in reducing the need for increased ventilatory assistance and duration of hospital stay after an exacerbation [50], while concomitant bronchodilation therapy can also help mobilisation of secretions, as it positively affects the ciliary beat frequency of respiratory epithelium [51]. Furthermore, several studies have investigated the nonadherence to inhalatory medications of COPD patients; it has been in fact reported that to 18% of patients spontaneously discontinue the respiratory therapy [52], and it is reasonable to suppose that the incidence would be greater in patients involved in a home-based rehabilitation program. On the other hand, there is a paucity of data regarding the adherence in attending pulmonary rehabilitation programs. In a retrospective analysis, Sabit et al. [36] have concluded that COPD patients are less likely to complete a pulmonary rehabilitation program if they are current smokers, attend a long lasting program, suffer frequent exacerbations requiring hospital admission, and have higher MRC score. There is therefore the need for a worldwide multicentre investigation to better understand what kind of COPD patients should be assigned to pulmonary rehabilitation programs, also in connection with the available resources.

Of particular interest is the hypothesis that pulmonary rehabilitation, through the exercise and nutritional intervention, could reduce the risk of cardiovascular accidents [26], because it is well known that patients with COPD have an increased risk of cardiovascular disease. The hypothesis was supported by the observation that following rehabilitation, the aortic pulse wave velocity (PWV) was reduced together with a marked fall in systemic blood pressure [26]. Moreover, there was a modest reduction in total cholesterol. This study, the first that evaluates the effect of a standardised multidisciplinary pulmonary rehabilitation program on cardiovascular risk factors in patients with COPD, indicates that pulmonary rehabilitation could represent an opportunity to identify and treat cardiovascular and metabolic dysfunction in these patients, thus providing additional benefits.

The primary goal of pulmonary rehabilitation should be, however, the improvement of lung mechanics, in order to lower the work of breathing and restore ventilation-perfusion distribution, with enhanced gas exchange and exercise performance. These pathogenetic cornerstones of COPD should be treated both with pharmacological bronchodilation and pulmonary rehabilitation, in order to reduce respiratory symptoms in stable patients and during exacerbations [51, 53]. There are, in fact, clear indications for performing pulmonary rehabilitation after acute exacerbations in COPD patients, besides conventional community care, as this treatment appears to be safe and highly effective in reducing hospital admissions and mortality and in improving health-related quality of life [54].

5. Conclusion

Current literature supports the notion that pulmonary rehabilitation provides clinically relevant improvements in quality of life, breathlessness, exercise performance, and psychological status. Also the usefulness of the association of conventional pharmacological treatment and pulmonary rehabilitation has been repeatedly proven [49]. However, uncertainties remain regarding some elements of pulmonary rehabilitation programs, such as duration and yearly frequency of the

cycles, training intensity, and degree of supervision, for which further investigations are required. Furthermore, the present analysis has shown that only very few studies have considered pulmonary function parameters among expected outcomes. This, together with lack of assessment of absolute lung volume partitioning and tidal expiratory flow limitation, largely prevents the possibility to better understand the effects of pulmonary rehabilitation on the respiratory system, urging for further studies in this area.

Conflict of Interests

The authors declare that they have no conflict of interests.

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Review Article

Lung Compliance and Chronic Obstructive Pulmonary Disease

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Chronic obstructive pulmonary disease, namely, pulmonary emphysema and chronic bronchitis, is a chronic inflammatory response of the airways to noxious particles or gases, with resulting pathological and pathophysiological changes in the lung. The main pathophysiological aspects of the disease are airflow obstruction and hyperinflation. The mechanical properties of the respiratory system and its component parts are studied by determining the corresponding volume-pressure (P-V) relationships. The consequences of the inflammatory response on the lung structure and function are depicted on the volume-pressure relationships.

1. Introduction

Chronic obstructive pulmonary disease (COPD), a common preventable and treatable disease, is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases [1]. Airway limitation is attributed to three different mechanisms: (1) partial block of the lumen (e.g., due to excessive mucous production forming semisolid plugs), (2) thickening of the airway wall, which occurs because of edema or muscle hypertrophy, and (3) abnormality of the tissue surrounding the airways (destruction of the parenchyma and narrowing of the airway due to loss of radial traction). Both entities of COPD, namely, chronic bronchitis and emphysema, are characterized by the former mechanisms. Chronic bronchitis is characterized by partial block of the lumen and airway wall thickening, while emphysema by radial traction loss [2].

The most common risk factor for COPD globally is cigarette smoke. Cigarette smokers show a higher prevalence of respiratory symptoms and lung function abnormalities than nonsmokers. As a consequence, the annual rate of decline in FEV_1 is higher than the expected FEV_1 decline with decreasing age. Passive exposure to smoke is also an important aspect of the disease. We should take under consideration the occupational exposures, including organic and inorganic dusts, chemical agents and fumes, and of course the indoor pollution from the biomass during cooking and heating in poorly ventilated houses [3–5].

2. COPD Pathology

Pathological changes are found in large and small airways, in the parenchyma and the pulmonary vasculature, resulting from repeated injury and repair. The inflammatory response may be genetically determined, or may be caused by noxious particles, such as cigarette smoke. However, some patients develop COPD without exposure to cigarette smoke. The oxidative stress and the imbalance between proteases and antiproteases, which have a role in protection of connective tissue from breaking down, amplify the inflammatory response of the disease. The inflammatory response is aggravated by the inflammatory cells CD8+ cytotoxic Tc1 lymphocytes and the inflammatory mediators (chemotactic factors, proinflammatory cytokines and growth factors) [6].

A scenario which is under experimental exploration exposes an attractive model for initiation of inflammation, comprising oxidative DNA damage of LEBCs and host immune response. According to that, noxious particles induce oxidative DNA damage of the lung epithelial barrier cells (LEBCs), and the acquired mutations are expressed at

the microsatellite DNA level of LEBCs. The altered LEBCs are recognized by dendritic cells (DCs) as "nonself" DCs travel with the new information to the lymph nodes, presenting it to the naïve T lymphocytes, and after that a predominant CD8+ cytotoxic T-lymphocyte proliferation occurs. The CD8+ T lymphocytes release perforin and granzymes and attract the altered LEBCs, activating cell death cascades [7].

3. Pathophysiological Aspects in COPD

3.1. Airflow Obstruction. Airflow during exhalation is the result of the balance between the elastic recoil of the lungs promoting flow and resistance of the airways that limits flow. The factors that lead to the obstruction of the lumen and the increased resistance, with the consequence of flow limitation, are the presence of secretions, the increased tone of bronchial smooth muscle, the hypertrophy of submucosal glands, and the protrusion towards the internal part of the lumen of the dorsal part of trachea during expiration. These factors are involved in airflow obstruction due to the great difference between intraluminal pressure and the pressure in the surroundings. The loss of elastic recoil concerning the wall of the small airways, due to the reduction of elastic tissue in the pulmonary parenchyma, is an evident mainly in emphysema. The absence of cartilage in the wall of the small peripheral airways contributes further more to the loss of the elastic recoil [8]. Patients with COPD are said to be flow limited when the expiratory flow that they generate during tidal respiration represents the maximal possible flow that they can generate at that volume. In flow-limited patients, the time available for lung emptying (expiratory time) during spontaneous breathing is often insufficient to allow end expiratory lung volume (EELV) to decline to its natural relaxation volume. This leads to lung hyperinflation [9].

3.2. Hyperinflation. The loss of the elastic recoil, especially in the case of emphysema, the fact that the COPD patient breaths in "a higher level" which means that the functional tests show a functional residual capacity (FRC) which exceeds the predicted one, in order to maintain the airways open and the air trapping during premature closure are all aspects of lung hyperinflation [8].

In normal subjects, lung volume at end expiration approximates the relaxation volume of the respiratory system. However, in patients with airflow obstruction, the end-expiratory lung volume may exceed the predicted FRC. Indeed, lung emptying is slowed, and expiration is interrupted by the next inspiratory effort, before the patient has reached the static equilibrium volume [11]. This is termed dynamic hyperinflation and is affected by VT, expiratory time, resistance, and compliance. It is also called intrinsic positive end-expiratory pressure (auto-PEEP) and was firstly described by Bergman in 1972 [12] and Johnson et al. in 1975 and represents the positive intrapulmonary pressure at the end of expiration [13]. The presence of auto-PEEP means that the inspiratory muscles must firstly overcome the combined inward recoil of the lung and the chest wall before inspiratory flow can be initiated. Thus, auto-PEEP acts essentially as an inspiratory threshold load and has been measured to be as much as 6–9 cmH_2O during quiet breathing at rest in clinically stable but hyperinflated COPD patients [14, 15].

During severe airflow obstruction episodes, increased expiratory efforts simply raise alveolar pressure without improving expiratory airflow. When tidal volume (VT) is increased or the expiratory time is short because of a high respiratory rate, the lung cannot deflate to its usual resting equilibrium between breaths. This raise in alveolar pressure and lung volume results in several events which affect the dynamic status of the lung. Breathing takes place near the total lung capacity [16]. Tidal breathing during an exacerbation in a patient with COPD may be shifted upwards close to the total lung capacity as a consequence of dynamic hyperinflation [17].

Hyperinflation has detrimental effects on the function of diaphragm that increase the work of breathing. First of all, the diaphragm is displaced into a flattened position which results in the decrease of the zone of apposition between the diaphragm and the abdominal wall. Secondly, the muscle fibers of the flattened diaphragm are shorter and are less capable of generating inspiratory pressures that will overwhelm the transpulmonary pressure [18]. The positive pressure within the hyperinflated lung raises the mean intrathoracic pressure and causes the inspiratory muscles to operate at a higher than resting lung volume [19]. The sarcomere length of the diaphragm in COPD patients is shorter and indirectly proportional to the TLC and the RV. This adjustment improves the capability of the diaphragm to generate force in "higher lung volumes." The ideal length of inspiratory muscles during relaxation is considered to be near the level of residual volume (RV). In COPD patients, however, because of hyperinflation, the length of the muscle fibers is even shorter. Furthermore, an increase in the relative proportion of the type I fibers which are slow twitch and fatigue resistant [20, 21] and an increase in mitochondrial concentration and efficiency of the electron transport chain which improves oxidative capacity are other structural adaptations to chronic intrinsic mechanical loading [22]. As a result, the developing force produced by the muscles is even more reduced on the expense of a considerable mechanical disadvantage which further impairs respiratory muscle function rendering this way the diaphragm more weak [18].

The ventilatory muscles partially adapt to chronic hyperinflation to preserve their force generating capacity during resting breathing. During COPD exacerbations, these adaptations can become overwhelmed [20–22]. The already burdened inspiratory muscles become subject to increased elastic loading, which means that they require a greater effort for a given change of volume. Acute dynamic hyperinflation further shortens the inspiratory muscles, particularly the diaphragm, and causes functional muscle weakness [23–25]. Exposure to oxidative stress and local activation of proteases may also result in diaphragmatic injury during periods of increased inspiratory loading and result in inspiratory muscle dysfunction [26, 27]. The net effect of this increased loading and functional weakness of the inspiratory muscles

is that the effort required for tidal inspiration represents a relatively high fraction of the maximal possible effort that the patient can develop at that lung volume [28].

4. Lung Compliance

The respiratory system owns its elastic property to the function of the respiratory muscles, which supply the whole system with the necessary pressure difference so that air moves into the airways. The static mechanical properties of the respiratory system and its component parts are studied by determining the corresponding pressure-volume (*P-V*) relationships. The *P-V* curves that are obtained as volume is changed in progressive steps from residual volume (RV) to total lung capacity (TLC) and back again are loops. The elastic properties of the lung and chest wall as well as the changes in lung units between inflation and deflation are responsible for the presence of these loops [16]. The lung elasticity is depicted by the static volume-pressure curve. The fact that the *P-V* curve is nonlinear practically means that as lung volume increases, the elastic elements approach their limits of distensibility [29].

In COPD, because of the resting and dynamic hyperinflation which is equal to a further increase in the end-expiratory lung volume (EELV), the exercise tidal volume (VT) encroaches on the upper alinear extreme of the respiratory system's *P-V* curve where there is increased elastic loading. In COPD, the ability to further expand VT is reduced, so inspiratory reserve volume (IRV) is reduced. In contrast to health, the combined recoil pressure of the lungs and chest wall in hyperinflated patients with COPD is inwardly directed during both rest and exercise. This results in an inspiratory threshold load on the respiratory muscles (Figure 1) [30]. Intrapulmonary pressures do not return to zero, representing this way the auto-PEEP which imposes extra load to the inspiratory muscles. During the subsequent respiratory cycle, auto-PEEP must be overcome in order to generate inspiratory flow [17].

The static compliance (C) of the lung is the change in lung volume per unit change in the transpulmonary pressure; that is, the pressure difference between the interior of the alveoli and the pleural surface of the lungs required to affect a given change in the volume of air in the lungs:

$$C = \frac{\Delta V_L}{\Delta(P_A - P_{\text{Pl}})}, \tag{1}$$

where C is the compliance, ΔV_L is the change in lung volume, and $\Delta(P_A - P_{\text{Pl}})$ is the change in the transpulmonary pressure.

Strictly speaking, the transpulmonary pressure is equal to the pressure in trachea minus the intrapleural pressure. Thus, it is the pressure difference across the whole lung. However, the pressure in the alveoli is the same as the pressure in the airways (including the trachea) at the beginning or at the end of each normal breath. That is, the end-expiratory or end-inspiratory alveolar pressure is 0 cm H_2O. Therefore, at the beginning or at the end of each lung inflation, alveolar distending pressure can be referred to as the transpulmonary pressure [31].

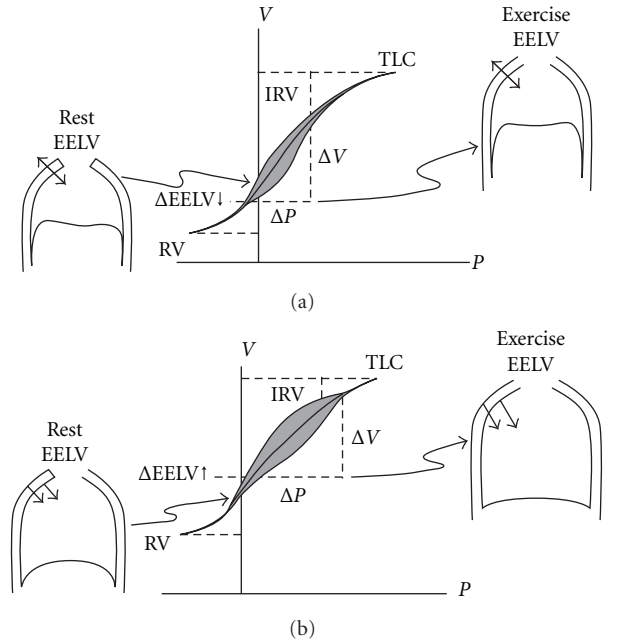

Figure 1: Pressure-Volume (*P-V*) relationships of the total respiratory system in (a) normal and (b) chronic obstructive pulmonary disease (COPD). Tidal *P-V* curves during rest and during exercise are shown. In COPD individuals, there is a resetting of the respiratory system's relaxation volume to a higher level than in the healthy individuals. Hyperinflation in COPD leads to increased EELV, RV and a corresponding reduction in IRV, in comparison to normal condition. In contrast to normal lung, the combined recoil pressure of the lungs and chest wall in hyperinflation is inwardly directed during rest and during exercise. This results in inspiratory threshold load on the inspiratory muscles with consequential decrease in the zone of apposition (shown in *P-V* curve (b) during rest and exercise). EELV: end-expiratory lung volume, RV: residual volume, IRV: inspiratory reserve volume, TLC: total lung capacity. From O'Donnell and Laveneziana [30].

The volume that corresponds to zero pressure (0 cm H_2O) is the resting volume of the respiratory system, where the pressure at the level of the mouth is 0 cm H_2O. This is the level of functional residual capacity (FRC) where there is no airflow in the airways and the pressure at the level of the mouth when performing spirometric studies equals the airway and the alveolar pressure (0 cm H_2O). In the *P-V* curve, the horizontal distance from the point 0 represents the elastic pressure of the whole respiratory system (P_{pl}) which is negative below the FRC and positive above the FRC level (Figure 2) [32]. The pressure difference between the pressure at the level of the mouth and the atmospheric pressure represents the pressure needed to expand the respiratory system during the respiratory cycle.

The looped *P-V* curve practically means that as lung volume increases, the elastic elements approach their limits of distensibility and a given change in transpulmonary pressure produces smaller and smaller increases in lung volume. As a result, the compliance of the lung is the least at high lung volumes and greatest as the residual volume (RV) is approached [18]. A lung of high compliance expands

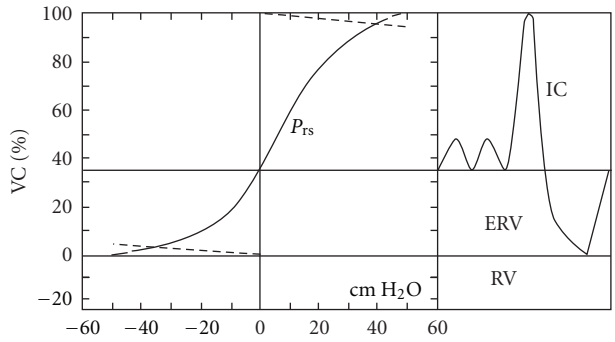

Figure 2: Quasistatic *P-V* curve of the respiratory system, with a spirogram showing subdivisions of lung volume. ERV: expiratory reserve volume, IC: inspiratory capacity, VC: vital capacity. Adapted from Agostini and Hyatt [32].

to a greater extend than one of lower compliance when both are exposed to the same increase in transpulmonary pressure [10]. Hyperinflation and tidal breathing towards the total lung capacity force the respiratory system to operate on the flatter part of the compliance curve where progressive pressure increases generate smaller incremental volume changes [17].

The lung compliance is normally measured as static, when the lungs are stationary. The distensibility estimated during normal tidal breathing from measurements of lung volume and esophageal pressure made at the end of inspiration and expiration when the lungs are apparently stationary has an index as a result, which is called dynamic compliance. In subjects with healthy lungs, the two measurements yield similar results [10].

Since the pressure-volume curve of the lung requires estimation of the pressures in the airways and around the lung, this can be obtained by measurement of the esophageal pressure. A small balloon on the end of the catheter is passed down through the nose or mouth, and the difference between the mouth and the esophageal pressures is recorded as the patient exhales in steps of 1 liter from the total lung capacity (TLC) to RV [2].

Some factors that influence the static lung compliance (including emphysema) are listed in Table 1.

Table 1

Aspect	Low compliance	High compliance
Lung of normal structure	Small person	Large person
Lung surfactant	Respiratory distress syndrome. Surfactant protein B deficiency	
Fibrous stroma	Disorders of lung parenchyma	Age, emphysema, and semicarbazide
Visceral pleural	Thickening secondary to TB, Asbestos exposure, and haemothorax	
Tone in muscle of alveolar ducts	Histamine Serotonin, hypoxia	Bronchodilator drugs
Pulmonary blood volume	Mitral stenosis Left ventricular failure	isocapnoeic hypoxia Pulmonary stenosis

Source: [10].

5. *P-V* Curve and Emphysema

Most of the early studies describing the *P-V* relationship in COPD were done to diagnose and establish the severity of emphysema. However CT was more convenient as a method. Most of the early study were done on spontaneously breathing COPD subjects [33].

Gibson et al. found that the *k* factor was increased in COPD patients. The *k* factor describes the concavity of the exponential fit and is independent of lung volume. Therefore, an increase in *k* means the curve has concavity toward the pressure axis, without regard to its position [34]. This was confirmed by the study of Greaves and Colebatch who studies normal and emphysematous lungs. They found that when emphysema was present, *k* was increased by more than two standard deviations above the mean predicted value for age. They also found a direct relationship between *k* and mean alveolar size [35]. Osborne et al. studied the relationship between *k* and mean alveolar size in emphysematous undergoing lung resection. They found that *k* correlates with severity of COPD until the contribution of large air spaces to the shape of the curve was lost due to airway closure [36].

Compliance is increased in obstructive lung disease like pulmonary emphysema, less in asthma and at a minor degree in chronic bronchitis. In emphysema, the elastic recoil is decreased and the *P-V* curve is shifted up and left. This is due to the loss of elastic tissue as a result of alveolar wall destruction. In chronic bronchitis without emphysema, however, the *P-V* curve may be normal since the parenchyma is minimally affected.

In practice the measurement of compliance and its result has limited clinical value. As mentioned previously, the resulting curve is non linear and the value of compliance is measured according to the change in pressure. The measurement above the level of FRC, approaching the TLC, shows lower values of compliance and increased lung stiffness due to the collagen fibers in the lung parenchyma, which influence the lung distension in high volumes. Thus, the measurement of compliance should be carried out close to the FRC level, otherwise, close to the TLC and RV levels, the results have limited clinical value [37].

The natural history of the development of lung hyperinflation in COPD patients according to clinical experience indicates that it is an insidious process that occurs over decades. It would appear that RV is the first volume component to increase, reflecting increased airway closure. EELV increases thereafter, reflecting the effects of EFL and alteration in lung mechanics, and eventually TLC increases as lung compliance increases. However, it is likely that the time

course of change in the various volume compartments is highly variable among patients [30, 38].

The *P-V* curve shows different configuration during the respiratory cycle, that is, during inspiration and expiration. This phenomenon is called hysteresis and is a property of elastic structures. The difference in configuration occurs due to the fact that close to the RV (small lung volumes) further pressure is required during inspiration to open the small distal airways. In greater lung volumes, the phenomenon of hysteresis is possibly attributed to the resistance of elastic fibers in the parenchyma [37].

6. Conclusion

The static and dynamic studies of the lung in chronic obstructive pulmonary disease differ according to the pathological aspects of the disease. The loss of elastic recoil of the lung affects the pressure difference between the interior of the alveoli and the pleural surface of the lungs, that is, the transpulmonary pressure. As a result, a lung of high compliance, like the emphysematous lung, expands to a greater extent than the one of low compliance, when both are exposed to the same increase in transpulmonary pressure.

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Review Article

Effects of Heliox in Stable COPD Patients at Rest and during Exercise

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Heliox has been administered to stable chronic obstructive pulmonary disease (COPD) patients at rest and during exercise on the assumption that this low density mixture would have reduced work of breathing, dynamic hyperinflation, and, consequently, dyspnea sensation. Contrary to these expectations, beneficial effects of heliox in these patients at rest have been reported only sporadically, and the majority of the studies performed until now suggests that heliox is not a therapeutic option in spontaneously breathing resting COPD patients. On the other hand, when it is administered to COPD patients exercising at a constant work rate, heliox systematically decreases dyspnea sensation, and, often but not always, increases exercise tolerance. For these reasons, heliox has been evaluated as a non pharmacological tool to power rehabilitation programs. The conflicting results provided by the published trials probably point at a substantial heterogeneity of the COPD patients population in terms of respiratory mechanics and gas exchange. Therefore, further studies, aimed to the identification of mechanisms conditioning the response of exercising COPD patients to heliox, are warranted, before heliox administration, which is costly and cumbersome, can be routinely used in rehabilitation programs.

1. Introduction

The clinical use of helium-oxygen mixtures (heliox) in patients with asthma or with larynx or trachea obstruction was first described in 1934 by Barach [1]. From then, the interest in the clinical use of heliox declined, in part because of the discovery of bronchodilators and in part because of the loss of many locations of natural helium during the Second World War [2]. The enthusiasm for heliox resurged in the late 1980s, concomitantly with increased mortality from asthma [3]. At present, the use of heliox has been advocated for a number of conditions, like upper airway obstruction, croup, acute asthma, and postextubation stridor [4]. Heliox has been administered in chronic obstructive pulmonary disease (COPD) patients on the assumption that this gas mixture, because of its low density, is able to reduce pulmonary resistance. It is thus worth to briefly revise the physical properties of heliox and their impact on the dynamics of the respiratory system.

2. Physical Properties of Helium

Helium is the lighter element after hydrogen and it heads the noble gas series in the periodic table, with an atomic number of 2 and an atomic weight of 4 g mol^{-1}. Due to its low melting and boiling point, at ambient temperature and pressure it exists as a gas. Helium is considerably less dense and slightly more viscous than air: dry, at 37°C and 1 atm, its density is 0.157 Kg m^{-3} and its viscosity 204 μP (for comparison, in the same conditions air density and viscosity are 1.134 Kg m^{-3} and 190 μP, resp.). The solubility coefficient of helium in water is very low compared to nitrogen, oxygen, and carbon dioxide (at 37°C 0.0014, 0.014, 0.03 and 1 g/L, resp.).

Because of its low solubility, helium passes the alveolar-capillary membrane very slowly, despite its diffusibility is greater than that of oxygen, carbon dioxide, and even nitrogen. The single orbital of helium is completely filled by two electrons, so helium does not form compounds. It is regarded as metabolically inert and appears as a colourless,

odourless, and tasteless gas. Unlike xenon, it is devoid of anesthetic properties. As a therapeutic gas, helium is used to replace nitrogen as a carrier gas for oxygen. The percentage of oxygen in heliox (which will be indicated from now on as subscript) should be at least 20% to prevent hypoxia, and no more than 40%, because beyond this value heliox is not likely to exert any relevant clinical effect [5]. The density of a helium-oxygen mixture can be obtained as the weighted mean of oxygen and helium densities [6]. At 37°C and 760 mmHg, 20%, 30%, and 40% O_2 in He have densities of 0.377, 0.488, and 0.600 $\mathrm{Kg\,m^{-3}}$, respectively. In contrast, the viscosity of heliox mixtures cannot be obtained as the weighted mean of oxygen and helium viscosities, because the viscosity of a gas mixture is higher than the average viscosity of individual gases. By using the semiempirical formula of Wilke [7], at 37°C and 760 mmHg, the viscosities of 20%, 30%, and 40% O_2 in He result 225, 226, and 226 μP, respectively.

From a technical point of view, it is worth to note that because of the different viscosity of air and heliox, Fleish type flowmeters should be calibrated with each gas mixture. At 20°C, the ratio between the viscosities of water vapour saturated heliox_{21} and air is ~1.15, so, if the flowmeter is not recalibrated before use with heliox_{21}, flow will be overestimated by ~15%. Moreover, a considerable error can be introduced if the flowmeter is calibrated using dry heliox_{21} without previous humidification, because the viscosity of the dry mixture is greater than that of the water saturated mixture. In this case, expiratory flow will be underestimated by ~8% [8].

3. Fluid Dynamics

Consider a tube of diameter D in which a fluid of density ρ and viscosity η flow steadily. The regime of the flow inside the tube (laminar, transitional, or turbulent) depends on a dimensionless quantity called Reynolds number (Re), which is the ratio of inertial to viscous forces as

$$\mathrm{Re} = \frac{\rho D v}{\eta} = \frac{4}{\pi}\frac{\rho \dot{V}}{\eta D}, \tag{1}$$

where v is the velocity and $\dot{V}$ is the flow. Indicatively, flow is laminar if Re is less than ~2300, overtly turbulent if Re is more than ~4000, and transitional if Re is between ~2300 and ~4000. The pressure difference required to generate a given flow is greater if the flow regime is turbulent than if it is laminar, because in the former condition (a) the boundary layer is thinner and the shear near the wall is increased, and (b) the fluid elements experience accelerations which are dissipated as heat. Using the description of the conductive airways provided by Weibel [9] to calculate Re for each generation at a given flow, it can be predicted that, at rest, transitional or turbulent flow is confined to the trachea, because only in this location Re is greater than 2300. When ventilation is increased as during exercise, Re increases in each generation and turbulence extends distally in the central airways.

Predicting the flow regime in the tracheobronchial tree on the basis of the Reynolds number actually overestimates the amount of laminar flow present, because the establishment of Poiseuille flow is not immediate at the entrance of each airway generation. Assuming a flat velocity profile of airflow at the entrance of an airway, a fully established laminar flow can be found only after a certain length from the entrance (L_e) given by

$$L_e = k_2 \frac{\rho D v}{\eta} D = k_2 \,\mathrm{Re}\, D, \tag{2}$$

where k_2 is a constant depending on Re. For Re less than 2300 and greater than 50, k_2 is ~0.03; for Re less than 50, the ratio L_e/D is constant and ~1.5. As L_e so calculated is greater than the anatomical length of the large conducting airways, the part of the tracheobronchial tree in which flow is turbulent or transitional should be substantially greater than that estimated solely by the computed Re.

Because the kinematic viscosity of heliox_{21} is ~4 times that of air, substitution of air with heliox_{21} causes a 4 times decrease of Re in each airway generation, possibly causing the transition of turbulent to laminar flow at some locations. Moreover, by reducing L_e, heliox can further reduce the extension of the part of the tracheobronchial tree involved by turbulence.

The ability of heliox to keep the airflow laminar is not the sole reason of its favourable effects on respiratory mechanics. Actually, heliox is able to decrease airway resistance even if the flow regime remains turbulent.

Independently of the flow regime, the relation between the flow ($\dot{V}$) and the pressure difference between the inlet and the outlet of a circular tube (ΔP) is given by

$$\dot{V} = \pi \sqrt{\frac{1}{8}\frac{\Delta P}{L}\frac{D^5}{\rho f}}, \tag{3}$$

where f is the friction factor [6]. The relation between f and Re is graphically represented in the Moody's diagram.

For fully established laminar flows, $f = 64/\mathrm{Re}$. In this case (3) becomes the well-known Poiseuille's equation as follows

$$\dot{\mathrm{V}} = \frac{\pi}{128 \mathrm{L} \eta} \Delta \mathrm{P} \mathrm{D}^4. \tag{4}$$

In the region of transition between laminar and turbulent flow, f depends on both wall roughness and Re. For a fully established turbulent flow, if the wall of the tube is rough, f is independent on the Reynolds number and dependent only on wall roughness; if the wall is smooth, f is proportional to $\mathrm{Re}^{-1/4}$.

As ρ appears in the denominator of (3) and f is proportional to ρ^{-1} only when laminar flow is present, the replacement of air with heliox should decrease the pressure difference necessary to generate a given flow, even if the flow regime remains overtly turbulent. Therefore, if the flow is transitional or overtly turbulent, density dependence is always present at some variable degree, according to the flow regime and to the characteristics of the airways. If the airflow is purely laminar, no benefit of heliox should be expected; conversely, airway resistance should increase, because of the increased viscosity of heliox relative to air.

4. Density-Dependence of Maximal Expiratory Flow in Normal Subjects and COPD Patients

Beside reducing the pressure difference between the alveoli and the mouth which should be developed in order to generate a given flow and, consequently, the metabolic cost of breathing, heliox is potentially able to increase the maximal ventilation available to a subject. This effect is highly desirable in COPD subject, in whom ventilation can be a constraint of physical performance. In contrast, most normal subjects do not use the maximal flows available even at peak exercise [10].

The density-dependence of the maximal flows can occur only if certain conditions are met. During forced expirations, dynamic compression of the intrathoracic airways takes place, and flows become effort-independent when the pulmonary volume is less than 80% of the vital capacity. In this volume range, expiratory flow limitation occurs.

Flow limitation may result from two mechanisms: (a) the coupling between airways compliance and convective acceleration of gas (wave-speed theory) [11], or (b) the coupling between airways compliance and viscous pressure losses [12]. In case (a), the maximal flows are inversely proportional to the square root of the gas density, as the wave-speed theory states that the maximal flow ($\dot{V}_{\max}$) inside a compliant tube is that at which the local velocity of the fluid is equal to the propagation velocity of a small disturbance travelling on the wall of the tube, according to the following equation:

$$\dot{V}_{\max} = A\sqrt{\frac{A}{\rho}\frac{dP_{\text{tm}}}{dA}}, \tag{5}$$

where $A(dP_{\text{tm}}/dA)$ is the elastic module of the tube and A the cross section.

Conversely, in case (b) the maximal flows are density-independent, as the viscous pressure losses are determined solely by the viscosity and by the geometrical characteristics of the airways, as long as the flow-regime remains laminar.

When a normal subject forcedly expires, as long as lung volume stays in the upper two-thirds of his vital capacity, the choke point, that is, the part of the airways where dynamic compression actually limits expiratory flow, is found in the central airways, where the cross-sectional area is small, and the lateral pressure drop is largely due to convective acceleration. In this volume range, flow limitation is due to the wave-speed mechanism, and if air is replaced by heliox, maximal flows increase. In the lower third of the vital capacity, the choke point moves upstream in the peripheral airways, where the cross-sectional area is large, the flow is laminar, and the viscous mechanism is predominate. In this case the maximal flows become density-independent.

During the evolution of the disease, COPD patients experience a progressive reduction of their maximal expiratory flows that may become so low that flow-limitation is present even at rest. It is believed that the disease first arises in the peripheral airways, which are the major site of increased resistance in many COPD patients [13–15]. In line with this assumption, when air is replaced by heliox_{21} the increase of maximal expiratory flow at 50% of VC ($\dot{V}_{\max,50\%\text{VC}}$) is generally lower in smokers than in nonsmokers [16]. However, contrary to the expectations, in COPD patients a reduced density-dependence is not a rule. In a sample of 22 COPD patients, density-dependence, defined as an increase of $\dot{V}_{\max,50\%\text{VC}}$ greater than 20% when air is replaced by heliox_{21}, was present in 11 patients [17]. In this study, patients with decreased density-dependence differed from those with normal density-dependence because of smaller vital capacity, large ratio of residual volume to total lung capacity, higher resistance, and lower static lung recoil at total lung capacity. These results suggest that different patterns of airways lesions are present in the COPD population. Even if the disease starts peripherally, central airways can be affected with variable degree, so that their mechanical properties change in a way that during maximal expiration the choke point moves in some patients to the peripheral airways, and in some others remains in the central airways.

5. Heliox Breathing at Rest in COPD Patients

In healthy human subjects at rest, the end-expiratory volume corresponds to the relaxation volume of the respiratory system. In COPD patients, pulmonary hyperinflation, that is, an increase of functional residual capacity above the predicted normal value, is often present, because of reduced lung recoil, as in emphysema, and/or because of dynamic hyperinflation. The latter occurs when the duration of expiration is not sufficient to allow the respiratory system to deflate to its relaxation volume prior to the next expiration, possibly because the time-constant of the respiratory system has increased (increased airway resistance) or the respiratory rate is too high. In COPD patients, dynamic hyperinflation is mainly due to the presence of tidal expiratory flow-limitation, that is, the inability to increase expiratory flow by further increasing the transpulmonary pressure during tidal breathing. The assessment of changes of dynamic hyperinflation is usually made by measuring the opposite changes of inspiratory capacity [18]. Dynamic hyperinflation and concomitant intrinsic positive end-expiratory pressure increase inspiratory work, impair inspiratory muscles function, and adversely affect hemodynamics [19]. All these factors, together with dynamic airways compression, may contribute to dyspnea [20, 21].

Currently, dynamic hyperinflation can be decreased by bronchodilators [22] or, in hypoxemic patients, by oxygen administration, which reduces ventilation. Heliox, by decreasing airway resistance and increasing maximal expiratory flows, could provide further relief to COPD patients.

Unfortunately, in resting COPD patients, airway resistance during heliox_{21} breathing can decrease [23], or remain substantially unchanged [24]. In contrast, heliox_{21} has been regularly found to decrease airways resistance in healthy subjects at rest [25, 26], in line with the notion that, in a normal respiratory system, the resistance of the central airways, where airflow is transitional or turbulent, accounts for a substantial part of total airway resistance [27].

Conflicting results have been obtained also regarding the effects of $heliox_{21}$ administration on dynamic hyperinflation in COPD patients at rest. Grapè et al. [23] reported no effect of $heliox_{21}$ on dynamic hyperinflation; conversely, a significant fall of end-expiratory lung volume was detected by Swidwa et al. in 15 patients [28]. It should be noted that some of these patients were studied after hospital discharge for bronchitic exacerbations or coronary artery disease, and most had a forced expired volume in one second (FEV_1) response to the bronchodilator greater than 20%, an unusual finding in COPD patients. Afterwards, a lack of effect of $heliox_{21}$ on dynamic hyperinflation in COPD patients at rest has been repeatedly reported [29–34]. Recently, one study by Chiappa et al. [35] documented an average 17% increase of inspiratory capacity at rest when air was replaced by $heliox_{21}$. Their 12 COPD patients showed a marked density-dependence of maximal expiratory flows, as $heliox_{21}$ increased peak expiratory flow by 31% and forced expiratory flow between 25 and 75% of the forced vital capacity by 46%.

The effects of $heliox_{21}$ on tidal expiratory flow-limitation and dynamic hyperinflation have been assessed by Pecchiari et al. and compared to those of a bronchodilator in 22 stable COPD patients at rest [29]. In all the patients who were flow-limited, $heliox_{21}$ did not decrease dynamic hyperinflation, independent of posture. In 9 out of 13 patients who were flow-limited in the sitting posture, and in all 18 patients flow limited in the supine position, the tidal expiratory $\dot{V} - V$ loops on air and $heliox_{21}$ were essentially superimposed, indicating that the choke point was located in the peripheral airways. In 4 flow-limited patients in the sitting position, $heliox_{21}$ actually abolished flow-limitation, pointing at a central localization of the choke point. In these patients, flow-limitation actually involved the last fraction of the tidal volume (V_T), so that no increase of inspiratory capacity was detected during $heliox_{21}$ breathing. All the flow-limited patients remained flow-limited after salbutamol administration, nevertheless dynamic hyperinflation decreased as documented by the increase of inspiratory capacity, in line with what was previously reported [22]. As ventilation did not change after bronchodilator, the increase of inspiratory capacity was entirely due to higher maximal expiratory flows in the V_T range. In the non flow-limited patients at rest, neither $heliox_{21}$ nor salbutamol caused inspiratory capacity to increase, simply because in these patients little or no dynamic hyperinflation is present at rest [36].

6. Heliox Breathing during Exercise in COPD Patients

COPD patients are limited in their daily activity because of exercise intolerance due to dyspnea and/or leg fatigue. As the disease worsens, physical activities are progressively reduced, causing further deconditioning and worsening quality of life. Rehabilitation can potentially interrupt this vicious cycle. To be effective, rehabilitation should be performed at a sufficiently high level of exercise, and heliox has been regarded as a promising non pharmacological tool to improve exercise tolerance of COPD patients during rehabilitation programs.

A number of different experimental approaches have been used to assess the effects of $heliox_{21}$ breathing in exercising COPD patients, namely, (a) incremental work rate test on a cycle ergometer [37–40] or on a treadmill [41, 42], (b) constant work rate test on a cycle ergometer [30–35, 37, 43, 44], and (c) endurance shuttle walking test [45].

In COPD patients cycling at increasing work rates, $heliox_{21}$ increased maximal work rate in one study only [39] out of six [37–42], and ventilation at peak exercise in three studies [38–40] out of five [37–41]. At peak exercise, dyspnea [39, 40] and leg discomfort sensations [39] were not affected by $heliox_{21}$.

When COPD patients cycled to exhaustion at constant load, $heliox_{21}$ increased exercise tolerance in five [30, 31, 33–35] out of six studies [30, 31, 33–36]. At isotime, ventilation was usually unaffected by $heliox_{21}$ [30–33, 43], being, relative to air, increased in only two studies [35, 44] and decreased in only one [34]. In contrast, at peak exercise, ventilation was increased during $heliox_{21}$ breathing [30, 31, 34, 35] except than in two studies [33, 37]. Dyspnea sensation was constantly decreased by $heliox_{21}$ at isotime [30–35, 43, 44], while leg discomfort was decreased [33–35, 43, 44] or unchanged [30, 31]. At isotime, $heliox_{21}$ was able to decrease exercise-induced dynamic hyperinflation in five studies [30, 31, 33, 34, 43] out of eight [30–35, 43, 44]. Of these eight trials, Vogiatzis et al. [44] did not observe any dynamic hyperinflation on air. In the COPD patients studied by Chiappa et al. [35], $heliox_{21}$ markedly increased inspiratory capacity at rest (from 1.85 L in air to 2.17 L in $heliox_{21}$). At isotime and peak exercise inspiratory capacity decreased relative to the rest value more during $heliox_{21}$ breathing (-0.22 and -0.25 L, resp.) than during air breathing (-0.10 and -0.13 L, resp.).

A negative correlation between heliox-induced changes of dyspnea and inspiratory capacity at isotime has been found by Palange et al. [30], as expected according to the strict relation between dynamic hyperinflation and dyspnea. Eves et al. found that the decrease of dynamic hyperinflation with $heliox_{21}$, together with the increase of peak expiratory flow and the reduction of total work of breathing, explained 99% of the variance associated with increased endurance time [31]. Similar results concerning the relation between dynamic hyperinflation and exercise tolerance have been obtained by other studies [34, 35].

$Heliox_{21}$ breathing increased markedly the endurance shuttle walking distance [45], to the same extent than 28% oxygen in nitrogen. In the same study, $heliox_{28}$ provided further improvement relative to $heliox_{21}$ or to 28% oxygen in nitrogen alone. The additive effects of helium and hyperoxia on exercise tolerance were later confirmed by Eves et al. [31]. In another research [46], $heliox_{30}$ improved the 6-min walking distance more than 100% oxygen. A study in which training on $heliox_{40}$ was compared with training on air was promising [47], showing that training on $heliox_{40}$ increased exercise tolerance and quality of life more than training on air. A following study, however, did not confirm these results [48].

Even if part of the contrasting results obtained can be related to differences in the experimental methodology

[49, 50], most of the discrepancies probably depend on the heterogeneity of COPD patients. A potential confounding factor is the eventual presence of tidal expiratory flow-limitation [18], which has been investigated, using the negative expiratory pressure technique [51], only in one instance [32]. This study assessed, in 26 stable COPD patients, tidal expiratory flow-limitation, inspiratory capacity, breathing pattern, and dyspnea sensation during air and heliox_{21} breathing at rest and during exercise at 1/3 and 2/3 of the maximal work rate. On air, the patients who were flow-limited at rest remained flow-limited during exercise. In contrast, 4 and 7 of the patients who were not flow-limited at rest became flow-limited at 1/3 and 2/3 of maximal work rate, respectively. Dynamic hyperinflation was absent in the non flow-limited patients and developed only in the presence of flow-limitation. At rest, no difference was found between the breathing pattern of flow-limited and non flow-limited patients, while during exercise tidal volume increased more in non flow-limited patients. Heliox_{21} did not abolish flow-limitation, had no systematic effect on breathing pattern, and reduced dynamic hyperinflation in only 25% of the flow-limited patients. A positive correlation was found between the increase of end-expiratory lung volume on air and the reduction of dynamic hyperinflation induced by heliox_{21}. This finding suggests that the heliox_{21} responders are those patients who during exercise increase their operational lung volume enough so that the choke point moves from peripheral to more central airways, where the maximal flows are determined by the wave-speed mechanism and are density-dependent.

Dyspnea sensation was relieved by heliox_{21} in both flow-limited and non flow-limited patients, regardless of the presence or the absence of dynamic hyperinflation. In this connection, it should be underlined that dyspnea is not necessarily related to dynamic hyperinflation, in fact, in normal subjects, dyspnea may not change with heliox_{21} even if dynamic hyperinflation decreases [26], and, in COPD patients, dyspnea can decrease even in the absence of dynamic hyperinflation [32, 44]. The reduction of dyspnea documented by D'Angelo et al. [32] could thus be related to a decrease of the inspiratory work, which, depending on the extent of turbulence in the airways, can amount up to 50%–60% [6, 52].

7. Modelling Heliox Effects on the Respiratory System

Because of the complex behaviour of the respiratory system especially in the presence of expiratory flow-limitation and the difficulty to directly assess the relevant variables in the human subject, mathematical models of the respiratory system have been developed and used to interpret the result of experimental research. Recently, a nonlinear dynamic mathematical model of the respiratory system, including both wave-speed and viscous mechanisms determining flow-limitation, was developed by Barbini et al. [53], on the basis of Weibel symmetrical morphometric description of the tracheobronchial tree [9] and on the mechanical characteristics of airway generations reported by Lambert [54]. This model has been used to simulate the response of the respiratory system to heliox_{21} in the presence of different obstructive conditions, all causing tidal expiratory flow-limitation [52]: (A) moderate to marked increase of the collapsibility of the peripheral airways (i.e., airways beyond the 7th generation); (B) marked increase of the collapsibility of peripheral airways with moderate involvement of the central ones (form the 4th to 7th generation); (C) markedly increased collapsibility of the central and peripheral airways; (D) markedly increased collapsibility of the central airways with moderate involvement of the peripheral ones. The effects of heliox_{21} have been evaluated in terms of inspiratory interrupter resistance (R_{int}), intrinsic positive end-expiratory pressure (PEEPi), dynamic hyperinflation and expiratory flow-limitation.

Heliox_{21} administration reduced R_{int} in all cases except case A, where the viscous pressure loss was entirely due to laminar flow. The decrease of R_{int} in case B, C, and D was considerable, amounting to 22% in case B and 27% in case C and D. Thus heliox_{21} should reduce the inspiratory work of breathing, accounting, at least in part, for the reduction of dyspnea sensation which has been reported in COPD patients especially during exercise [29].

In no instance heliox_{21} abolished expiratory flow-limitation.

PEEPi and dynamic hyperinflation decreased with heliox_{21} only trivially in case A ($\sim$1 and $\sim$7%, resp.), where flow was limited by the viscous mechanism. Similar results were obtained for case B, even if the relative contribution of the viscous over the wave speed mechanism becomes relevant in the last part of the expiration only. In case C, the decrease of PEEPi and dynamic hyperinflation was modest (22 and 23%, resp.) because the contribution due to peripheral resistance to the total resistance of the upstream segment remained elevated. The fall of PEEPi and dynamic hyperinflation was remarkable (41 and 41%, resp.) in case D only, where flow limitation was dominated by the wave speed mechanism and the resistance of the peripheral airways was only slightly increased.

Note that case A, B, and C can be regarded as three subsequent stages of chronic obstructive pulmonary disease, which initially involves the peripheral airways and then spreads to the whole tracheobronchial tree. Conversely, case D may represent severe asthma with mild involvement of peripheral airways or mild chronic obstructive pulmonary disease affecting mostly the central airways.

8. Conclusions

The administration of heliox, which is costly and cumbersome, to stable COPD patients at rest with moderate to severe disease is not warranted, because no beneficial effect in terms of breathing pattern or dynamic hyperinflation has been observed in most of the published trials. In contrast, heliox could be effective as non pharmacological tool to enhance the efficacy of rehabilitation programs, since its administration to COPD patients usually enhances their exercise tolerance,

at least at constant work rate, and thus can be useful to increase the level of physical training. The conflicting results which have been obtained so far suggest that further research is needed in order to identify the COPD patients potentially able to benefit from this kind of rehabilitation programs.

Conflict of Interests

The author has no conflict of interests to declare.

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Review Article

Pulmonary Hypertension in Parenchymal Lung Disease

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Idiopathic pulmonary arterial hypertension (IPAH) has been extensively investigated, although it represents a less common form of the pulmonary hypertension (PH) family, as shown by international registries. Interestingly, in types of PH that are encountered in parenchymal lung diseases such as interstitial lung diseases (ILDs), chronic obstructive pulmonary disease (COPD), and many other diffuse parenchymal lung diseases, some of which are very common, the available data is limited. In this paper, we try to browse in the latest available data regarding the occurrence, pathogenesis, and treatment of PH in chronic parenchymal lung diseases.

1. Introduction

Pulmonary arterial hypertension (PAH) is defined as mean pulmonary artery pressure (mPAP) ≥25 mmHg at rest, with a mean pulmonary capillary wedge pressure (PCWP), left atrial pressure or left ventricular end-diastolic pressure (LVEDP) less than or equal to 15 mmHg validated by right heart catheterization (RHC) [1]. These values are being used by all PAH registries and in all randomized controlled trials (RCTs) [2–7]. Pressure measurements during exercise are no longer recommended or supported by data for pulmonary hypertension (PH) diagnosis. As of 2009, based on the latest Dana Point Classification [1], PH due to underlying parenchymal diseases, such as COPD and interstitial lung disease (ILD), remains in group 3. Other diseases with multisystemic, and more importantly pulmonary, manifestations such as connective tissue diseases (CTDs), or sarcoidosis are categorized separately (groups 1.4.1 and 5.2, resp.).

In patients with parenchymal lung disease, PH is reported likely modest (mPAP = 25 to 35 mmHg), although in some subjects PAP can be markedly increased (mPAP = 35 to 50 mmHg) [8, 9]. In such patients, especially in those who have mild-to-moderate impaired lung mechanics, this pressure increase is considered as "out-of-proportion" PH. As an example, in a retrospective study regarding RHC measurements in COPD patients, moderate-to-severe PH (mPAP > 40 mmHg) has been found in only 1% of the study population [9].

Recently, the German consensus group attempted to define severe PH in patients with chronic lung disease according to the following criteria (at least two out of three have to meet): (a) mPAP > 35 mmHg, (b) mPAP ≥ 25 mmHg with limited cardiac index (CI < 2.0 L/min/m^2), and (c) PVR > 480 dyn/s/cm^{-5} [10]. This definition describes less than 5% of patients with lung disease and gives a quantitative dimension to the "out-of-proportion" approach.

Epidemiological input on the prevalence of "out-of-proportion" PH is not available, except for few scattered data from subgroup analyses out of large studies. In a survey by a cardiac echo laboratory, the prevalence of all-cause PH (determined as systolic PAP > 40 mmHg) was 10.5% [11]. Among those subjects, only 9.7% had underlying lung diseases and hypoxia. In general, there is limited, albeit adding up data (Figure 1) regarding "out-of-proportion" PH due to chronic lung disease.

2. Pathophysiology

The pathophysiological mechanism in "out-of-proportion" PH due to parenchymal lung disease is multifactorial and depending on the underlying type of lung parenchymal

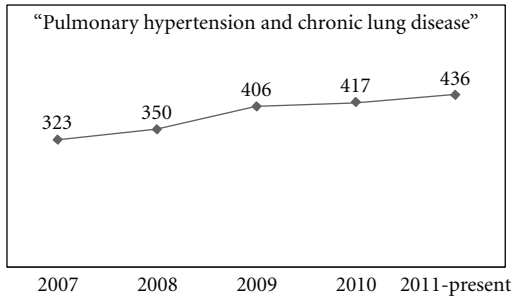

Figure 1: Distribution of PubMed search results within the last 5 years, per calendar year, with the search terms "Pulmonary hypertension and chronic lung disease." Results contain original research articles, experimental articles, reviews, and case reports.

involvement. In general, mechanisms include chronic hypoxic vasoconstriction (which is a major factor), mechanical lung stress, capillary loss, smoking habit effects, and inflammation. The acute hypoxic effect in systemic circulation is vasodilation, whereas in pulmonary circulation it triggers an acute vasoconstrictive process regulated by endothelin, serotonin, and other compounds and mediated by ion-channel activity in pulmonary arterial smooth muscle cells (SMCs) [12]. Additively, pulmonary vascular endothelial cells appear to exhibit a paracrine-like activity, metabolizing and uptaking vasoactive compounds that act on the pulmonary vascular tone under hypoxic state, probably contributing to hypoxic vasoconstriction [13].

On the other hand, in chronic hypoxia, which is the case in parenchymal lung disease, it seems that multiple pathological changes may occur in pulmonary vasculature, such as fibrous remodeling and an increase in both the number and mass of SMCs in the arterial wall, resulting in higher PVR over time and development of PH [14, 15]. In animal models, acute and chronic hypoxia appears to share causative intercessors in the disease cascade [16]; therefore, hypoxia may not only start the PH process but also encumber the disease, if not reversed.

In idiopathic pulmonary arterial hypertension (IPAH) and other forms of PH, it is widely accepted that a key histological finding is the plexiform lesion seen in the vast majority of patients [17, 18]. The plexiform lesion develops when capillary formations produce a network that spans in the lumens of dilated thin-walled, small pulmonary arteries. Medial hypertrophy also can be present in smaller arterioles, caused by intimal thickening attributable to the accumulation of one or more layers of myofibroblasts and fibrous matrix proteins within the neointimal space between the endothelium (tunica intima) and the internal elastic lamina. In more advanced stages, small pre- and intra-acinar arterioles predominantly exhibit complex lesions, that cause occlusion of the vessel's lumen, including concentric laminar intimal proliferation, called "onion skin" or concentric-obliterative lesions, and glomeruloid-like plexiform lesions [19]. Interestingly, this lesion was found to be similar in histological appearance with those occurring in limited cutaneous systemic sclerosis (lc-SSc) [20]. However, almost a decade later, it was reported that lc-SSc lesions were all polyclonal, in contrast with plexiform lesions in IPAH which were mainly monoclonal (80%) [21].

3. Diagnostic Approach

Due to the limitations of the invasive, albeit consistent, and accurate RHC, transthoracic tissue Doppler echocardiography (TTE) has emerged to fill the diagnostic gap and noninvasively assess the systolic pulmonary artery pressure (sPAP) in order to detect PH at an earlier stage. This technique, when applied by well-trained experts, can be very useful as a "sentinel" study prior to RHC. On the other hand, there is a possibility of misinterpretation which may lead to PH misdiagnosis and devastating consequences [38]. It should be emphasized that TTE can provide only estimates of pulmonary arterial pressures and that RHC is needed in order to establish PH diagnosis. The technique of TTE has been used widely not only as the study of choice in PH screening, but also as the "gold standard" frequent follow-up study in patients under treatment [39]. In a recent prospective trial assessing TTE and RHC measurements in 155 PH patients, there was a significant correlation between RHC and TTE [40]. More specifically, single TTE parameters performed well in predicting final PH diagnosis in this cohort, such as sPAP (area under the curve (AUC) 0.63, $P = 0.025$), the lateral apical RV longitudinal strain (RVaSl) (AUC 0.76, $P = 0.001$), and the ratio of transmitral Doppler early filling velocity to tissue Doppler early diastolic mitral annular velocity (E/E′) (AUC 0.84, $P < 0.001$). In addition, TTE showed a sensitivity of 33.33% and specificity of 100% in all-type precapillary PH identification, as well as 84.72% negative predictive value (NPV) to rule out the disease. However, in a recent analysis of subjects from the REVEAL (Registry to Evaluate Early and Long-term PAH Disease Management) study by Farber et al. [41], in 1883 patients that underwent both RHC and TTE, with the reservation that there were cases where several months have passed in between the tests, there was little association between serial TTE and RHC values. Additionally, repeat TTE measurements alone have shown to be insufficient to accurately monitor changes in PAP or disease progression.

Nowadays, TTE remains unable to replace RHC in establishing PH diagnosis, although it is very reliable for screening, following up, and providing indices of disease severity [42]; furthermore, TTE may distinguish pre- from postcapillary PH in certain cases.

4. Pulmonary Arterial Hypertension Associated with Connective Tissue Diseases That Affect Lung Parenchyma

Pulmonary hypertension is an increasingly recognizable complication and a major cause of death in patients with connective tissue diseases (CTDs), notably occurring in systemic sclerosis (SSc), systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and mixed CTD (MCTD), overall affecting 3% to 13% of such patients [43–46]; these

pathologies may develop solely or in association with ILD [47, 48].

Originally, pulmonary hypertension in IPAH and CTD was thought to share similar histologic and pathophysiologic characteristics [49, 50]. However, there is growing clinical evidence regarding differences in the disease process between CTD-PH and IPAH, in terms of endothelial and metabolic functions, as well as histological trails [51, 52]. In a study regarding the expression and activity of pulmonary endothelial angiotensin-converting enzyme (ACE), endothelial metabolic dysfunction was noticed in CTD-PH, compared to a group of IPAH patients. There was also functional evidence that a reduced DLCO value in patients with PAH-CTD was related to the degree of functional capillary surface area (FCSA) loss [53]. It is of interest that pulmonary endothelial dysfunction, based on the aforementioned techniques, was seen in patients with limited and diffuse systemic sclerosis at early disease stages, prior to PH development [54]. These findings could at least partly justify the worse prognosis in such patients, despite their hemodynamic semblance with IPAH [55, 56].

Beside direct involvement of pulmonary vasculature (i.e., group 1), pulmonary hypertension in CTDs may be due to left heart disease, lung parenchyma involvement, chronic thromboembolism (related to groups 2, 3, and 4 resp.), or even venoocclusive disease, often presenting a difficult diagnostic challenge.

4.1. Polymyositis/Dermatomyositis and Pulmonary Hypertension. These myopathies are part of the idiopathic inflammatory myopathies family, characterized by proximal muscle weakness, elevated serum creatine kinase, abnormal appearance in electromyography, and inflammatory cell infiltration in muscles. In polymyositis and dermatomyositis (PM/DM), involvement of multiple organs is common [57–59]. The most common affected site, apart from muscles, is the lung, with the general pulmonary complications reaching 40% in such patients, resulting in significantly high mortality rates [60].

Pathogenesis is incompletely understood, with the obvious factor being the autoimmunity as PM/DM commonly presents along with other autoimmune diseases. Recent data suggest a genetic base of the disease that might predispose to autoimmunity [61–63]. In PM specifically, the muscle fiber seems to be the main target. On the other hand, DM is characterized by deposition of membrane attack complex in muscle capillaries. Interestingly, antinuclear and anticytoplasmic autoantibodies are found in up to 90% of patients with PM and DM, allowing clinicians to define homogenous cohorts of PM/DM patients [64].

Pulmonary hypertension occurrence in PM/DM is not thoroughly designated, with available data only in a case report basis. The majority of patients present with breathlessness in effort and pulmonary function test restriction or DLCO decrease. It is of interest that PH in PM/DM affects mainly females [65, 66]. In one autopsy series, 20% of patients with PM had pulmonary arterial medial and intimal hypertrophy, a clue that could be linked to PH pathogenesis in such patients [67]. Another major factor in the PM/DM-PH pathogenesis could be the presence of ILD, that is quite common in the disease (5% to 65%) [68, 69]. True prevalence of PM/DM-PH is still not known, underlining the need for earlier referral of patients and RHC diagnosis confirmation.

4.2. Systemic Sclerosis and Pulmonary Hypertension. Systemic sclerosis (SSc) is a chronic systemic autoimmune disease characterized by fibrosis, vascular alterations, and autoantibodies. It is mainly expressed in two forms, (i) the limited systemic sclerosis-scleroderma with cutaneous manifestations such as CREST (calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, telangiectasias) syndrome, a term recently quite abandoned, and (ii) the diffuse systemic sclerosis-scleroderma, which is rapidly progressive and is characterized by multiple internal organ involvement usually including interstitial lung disease of progressive severity [70].

The prevalence of PH in patients suffering from SSc is reported to be 7% to 35%, depending on the cohort studied [46, 71, 72]. Unfortunately, at the time of SSc-PH diagnosis, the plurality of these patients has been reported to be already in New York Heart Association (NYHA) functional class (FC) III or IV, which is of poorer survival compared to NYHA-FC II patients [1, 73–75].

Interestingly, in recent data reported by the French PAH-SSc Network [76], a considerable number of patients in NYHA-FC II with mild symptoms at the time of diagnosis had already severely impaired hemodynamic profile (mPAP > 35 mmHg, cardiac index of less than 3 L/min/m^2). In the same study, the 3-year survival in NYHA-FC II patients was 80%, higher than previously reported (>66%) by the UK PH research group [74].

In a recent subgroup analysis of the largest known to date US cohort of RHC-confirmed PH patients [77] (REVEAL study), SSc-PH patients did not differ in hemodynamics at the initial diagnostic RHC compared to other CTDs, with an exception in the right atrial pressure (RAP) (SSc-PH group RAP was 9.1 ± 5.9 versus 8.1 ± 5.0 mmHg, $P = 0.05$). In addition, a higher percentage of patients with SSc-PH were in NYHA-FC IV at the time of enrollment, compared with patients suffering from other CTDs ($P = 0.04$), but the 6-minute walking distance test (6MWD) was not significantly different. In relation to pulmonary arterial pressure estimates by TTE at the time of enrollment, SSc-PH patients were significantly better than in other CTDs, with a lower percentage of RV enlargement and LV systolic dysfunction. The 1-year survival for SSc-PH patients was 87%, comparing to 93% of IPAH. In a 3-year survival followup, rates dropped to 47% for SSc-PH. Having in mind that these patients were treated under the current guidelines, their high 3-year mortality raises questions about the effectiveness of their current management. It should be noted that systemic sclerosis associated PH may be multifactorial: true PAH, left heart disease associated PH, and ILD-associated PH might sometimes overlap in the same patient.

4.3. Systemic Lupus Erythematosus and Pulmonary Hypertension. Systemic lupus erythematosus (SLE) is a complicated autoimmune disease of unclear pathogenesis, affecting multiple organs [78]. The pulmonary involvement, which results in SLE-PH, appears commonly in adult patients.

The theory of vasculitis, *in situ* thrombosis, and SMCs proliferation also applies in SLE-PH pathophysiology, with the exact causal relationship being still under investigation [79–82]. Several factors are incriminated for the induction of SLE-PH, such as hypoxic vasoconstriction, pulmonary venous hypertension resulting from left heart disease, antiphospholipid antibody-induced chronic or acute thrombosis, and pulmonary venoocclusive disease (PVOD) [83–88]. There are several pathological similarities in SLE-PH and IPAH, including SMCs hypertrophy, hyperactivation of transcription factors like hypoxia inducible factor-1 alpha and nuclear factor of activated T-lymphocytes, decreased expression of certain voltage-gated potassium channels, and *de novo* expression of antiapoptotic proteins [89]. Interestingly, immunoglobulin and complement deposition has been found in the pulmonary arterial wall of SLE patients [90]. In addition, mitral and aortic valve damage (also known as Libman-Sacks endocarditis) might occur in SLE patients, cause regurgitation, and subsequently provoke pulmonary venous hypertension. The exact incidence of this complication has not been effectively determined.

The prevalence of SLE-PH is largely unknown, with unconfirmed data reporting it from 0.5% to 14% in adults, in whom it is commonly associated with Raynaud's phenomenon [91, 92], and in childhood-onset SLE approximately 4%–8% using TTE assessment [93]. In a study by Prabu et al. [94] in SLE patients assessed by TTE, the prevalence of PH was lower than it usually appears (4.2%), and only 3 of the 12 study patients were found to have high sPAP (>40 mmHg). Although the study sample was very small, these results are worth noting because of the study population, which, in contrast to other studies, had a community nontertiary background and therefore might be considered as vicarious of the general SLE population.

4.4. Rheumatoid Arthritis and Pulmonary Hypertension. Rheumatoid arthritis (RA) is a chronic, systemic autoimmune inflammatory disease, affecting 1% of the general population and over 5% in ages >65 years. Besides its articular manifestations, RA can cause severe disability, with multiple extra-articular insults in over 40% of all RA patients, including the lung, with ILD being the most common manifestation in this organ [95–98].

Incidence of RA-PH is rather unknown, and the largest up-to-date study by Dawson et al. ($n = 146$) reported that 21% of the cohort had mild-to-moderate PH as assessed by TTE, while 19% of all patients enrolled had sPAP values within the 30–35 mmHg range. Major limitation in this study was the low cut-off point selection for sPAP (30 mmHg), which might have resulted in overestimating a considerable number of RA patients that were in the "grey zone" and might have led to precarious results [95].

4.5. Sjögren Syndrome and Pulmonary Hypertension. This is a chronic inflammatory disorder characterized by diminished lacrimal and salivary gland function and associated with lymphocytic infiltration of exocrine glands, especially the lacrimal and salivary glands. Sjögren syndrome (SS) also affects extraglandular systems such as skin, lung, heart, kidney, neural, and hematopoietic system. It can be seen in a sole form as a primary disorder (primary SS) or in the onset of an associated rheumatic disease (RA, SLE, SSc) with a peak among women >50 years of age [99]. The major complaints are skin dryness, xerostomia (mouth dryness), and keratoconjunctivitis sicca (dry eyes). In primary SS, there is a subclinical lung inflammatory process in more than 50% of patients, but interestingly, only 1 in 5 develops clinically significant pulmonary disease. Lung insult can be multiple, with a variety of manifestations such as xerotrachea and bronchial sicca (dryness in the tracheobronchial tree), obstructive small airway disease, ILD, lymphocytic interstitial pneumonitis (LIP), pleural effusions, lung cysts, thromboembolic disease, and PH [100].

Pathogenesis of PH in SS remains a clinical enigma. Drawing on data from a small number of reported cases (45 overall, since 1982; PubMed search June 27, 2012), patients with SS-associated PH (SSPH) have Reynaud's, cutaneous vasculitis, and ILD more frequently, compared to SS patients without PH. In addition, they seem to have quite frequent detectable antinuclear, anti-Ro/SSA, and anti-RNP autoantibodies, as well as positive rheumatoid factor and hypergammaglobulinemia. In summarized data available from 32 out of the 45 overall reported cases, patients' functional status was found to be markedly impaired (NYHA-FC III and IV in most cases), and so were their hemodynamics (mPAP = 44 ± 11 mmHg, CI 2.91 ± 0.72 L/min/m^2) [101]. These findings, although punctuating the data insufficiency in this field, might suggest that systemic vasculopathy, activation of B-cells, and autoimmunity could be factors in the SSPH disease process.

5. Sarcoidosis and Pulmonary Hypertension

Sarcoidosis is a chronic, systemic granulomatous inflammatory disease that can affect any organ [102]. Although there is massive progress during the past decade, the pure pathogenesis of sarcoidosis is still undistinguished.

Sarcoidosis-associated PH (SA-PH) is one of the trickiest to define and lies in group 5.2 (PH with unclear and/or multifactorial mechanisms/systemic disorders) in current Dana Point PH classification, mainly because of its heterogeneity and lack of data, although this specific categorization has been criticized [103]. The main criticism is that sarcoidosis should be included in group 3 (PH owing to lung disease and/or hypoxia), along with pulmonary Langerhans cells histiocytosis (PLCH) and lymphangioleiomyomatosis (LAM), which are currently also classified in group 5.2, based on the fact that PH in such cases mainly occurs due to massive lung involvement and profound hypoxia [104, 105].

Several pathogenic mechanisms are implicated in SA-PH development, with major causal factor the destruction of distal capillaries due to fibrosis that leads to chronic hypoxia,

increased PVR, and pulmonary arterial pressure [106–108]. Vascular involvement is quite established in pulmonary sarcoidosis, with a reported occurrence of 69% to 100% in pathological-histological case studies [109, 110]. However, it is of interest that SA-PH has already been stated as an early complication in the disease course. In addition, there is no reported correlation with the severity of SA-PH and the grade of lung fibrosis. These findings could suggest that other mechanisms might contribute to PH development in such patients, such as "outside" compression by mediastinal and hilar lymphadenopathy on main pulmonary arteries or their large branches [111], vascular granulomatous involvement [112] with the possibility of secondary PVOD development, and pulmonary vasoconstriction induced by vasoactive agents [113]. In certain cases, portal hypertension due to liver sarcoidosis can also cause PH mediated by increased circulating endothelin-1 (ET-1) levels [114].

The exact prevalence of SA-PH is not known, partly because of the population selection in several studies and their different diagnostic protocols. Recently, two separate single-center studies, concerning SA-PH development in consecutive patients suffering from sarcoidosis, reported an incidence of 5% to 15% [115, 116]. In other cohorts enrolling symptomatic-only sarcoidosis patients, the prevalence of SA-PH was higher than 50% [117, 118]. The highest prevalence documented by RHC has been reported in patients listed for lung transplantation (74%), with a concurrent increase in mortality rate, compared to listed patients without PH [111].

6. Idiopathic Pulmonary Fibrosis (IPF) and Pulmonary Hypertension

IPF is an idiopathic, fibrosing, interstitial, chronic lung disease with a characteristic appearance in histological findings currently known as usual interstitial pneumonia (UIP). It involves abnormal collagen deposition in the pulmonary interstitium (alveoli walls) with an associated inflammation. IPF has been linked to cigarette smoking and gastroesophageal reflux disease, but these factors are not present in all IPF patients. Genetic associations with the disease include pulmonary surfactant-associated proteins (SFTPA-1 and SFTPA-2), telomerase reverse transcriptase (TERT), and telomerase RNA component (TERC) [119, 120]. It is of interest that statistically significant association in survival has been reported between IPF patients with and without PH at the time of initial IPF diagnosis [121]; PH in IPF can develop either as consequence of the fibrotic process or disproportionate to the degree of fibrotic lung damage [122]. Although chronic hypoxia and its subsequent pulmonary arterial vasoconstriction are thought to have a major role in secondary IPF-PH, studies that showed the existence of PH in such patients even with arterial pO_2 levels within normal range (normoxic) led the investigators to partly relinquish this concept and redirect to other possible underlying mechanisms [123–125]. However, in one study of 70 IPF patients, there was a significant, but rather loose, correlation between mPAP and both PaO_2 and DLCO ($R = -0.47$, $P < 0.001$ and $R = -0.46$, $P < 0.001$, resp.) [126].

In "out-of-proportion" to the degree of fibrotic lung damage IPF-PH, there is a much more complex mechanism involved. Taking into account the extensive alveolar damage, the growth of connective tissue, and the ongoing inflammatory process in IPF, vascular remodeling of pulmonary arteries might be more important in the development of "out-of-proportion" IPF-PH than hypoxic vasoconstriction. In favor of this perspective, there is an inconsistency in PH severity and pathological findings; reduction in vessel density and vascular ablation in IPF patients have been reported, especially in "honeycombing" areas, along with simultaneous development of new vessels (neoangiogenesis) [127–132].

Furthermore, there is data regarding the role of endothelial cell dysfunction in "out-of-proportion" IPF-PH, also justifying the bad correlation between the severity of lung fibrosis and PH development. A microarray gene study involving a subgroup of IPF-PH patients revealed an unexpected underexpression of genes such as the vascular endothelial growth factor (EGF), the platelet endothelial cell adhesion molecule (PECAM), as well as factors known to regulate vascular tone, such as ACE and ET-1 ($P < 0.05$) [133]. In contrast, an overexpression of the phospholipase A2 gene was noticed, which could be potentially causative in pulmonary vascular remodeling [133].

Interestingly, several mediators that are established in IPAH have been recently incriminated for "out-of-proportion" IPF-PH. Such mediators are tumor necrosis factor alpha (TNF-α), platelet-derived growth factor (PDGF), and fibroblast growth factor [134]. Additionally, studies on the role of eicosanoids both in IPF and PH suggest a potential role of supplementation of PGE2 or prostacyclin in IPF patients, particularly those with PH [134]. The basic postulant in "out-of-proportion" IPF-PH pathogenesis may be ET-1, as suggested by recent data revealing a profibrotic ability of ET-1 in patients with IPF but no clinical evidence of PH [135]. Levels of ET-1 have also been found elevated in airway epithelium, type-2 pneumocytes, and pulmonary vascular endothelial cells [136–138]. In currently published experimental data, PDGF is under investigation as a potential therapeutic target in IPF and it is of interest that it has been found upregulated in PH. Furthermore, tissue growth factor beta (TGF-β), which is a possible pathogenetic cytokine of interstitial fibrosis, showed impaired signaling in patients with IPAH and could be another underlying mediator in pulmonary vascular remodeling in "out-of-proportion" IPF-PH [139].

Epidemiologically, both types of IPF-PH combined (secondary and "out-of-proportion") affect a large number of patients with IPF, especially those who are listed for lung transplantation. The prevalence of PH in all IPF patients shows a wide range, being reported from 14.2% to 84% [124, 140].

This large variation in reported prevalence values might be related, at least in part, to the method of PAP measurement (estimated sPAP in TTE or exact mPAP in RHC), the difference in selected pressure cut-off value, and to the timing of measurement. In recently published data, it was suggested that a key point in such patient cohorts seems to be "how fast" PH progresses in time, and not "how severe"

PH is on a single time point of sPAP estimation by TTE or mPAP measurement by RHC [140–142]. The presence of PH confirmed by RHC in IPF lung transplanted patients preoperatively has a negative effect on survival and notably increases the risk for developing primary graft dysfunction (PGD) in the posttransplantation period; for every increase of 10 mmHg in mPAP, the odds of PGD increase by 1.64 (CI 95%, 1.18–2.26; $P = 0.003$) [141]. One study underlined a PH prevalence of 33% in the initial RHC measurements that jumped to 85% in the pretransplantation assessment. In another study, baseline prevalence was 41% and jumped to 90% in the follow-up RHC measurement [140, 142]. The question of whether the lung fibrotic process and the vascular alterations that lead to PH share common pathophysiologic pathways remains open.

It should be noted that possible treatment options in IPF-PH by means of PAH-specific agents have been tested; disappointingly, 3 large RCTs, where the dual endothelin receptor antagonist (ERA) bosentan and the phosphodiesterase-5 inhibitor sildenafil were used, gave negative results [26, 31, 32].

7. Lymphangioleiomyomatosis (LAM) and Pulmonary Hypertension

It is a multisystemic disease, affecting mostly young women and characterized by abnormal SMC deposition along lymphatics of the thorax and abdomen. As a result, there is a formation of lung cysts and abdominal tumors, predominantly renal angiomyolipomas [143–148]. As far as it concerns the lung, LAM decreases FEV_1 and DLCO, with the latter previously demonstrated as an independent predictor of mortality in patients listed for lung transplantation, and aggravates peak oxygen uptake (VO_2 max) [149, 150].

The pathogenesis of PH in LAM (LAM-PH) is quite complex and not completely clarified. As in other lung diseases, chronic hypoxia resulting from the damaged lung parenchyma (i.e., cyst formation) can cause pulmonary hypoxic vasoconstriction and increase PVR, trigger the vascular remodeling process, and establish PH. However, in LAM patients, there is a low reported observation of RV failure and high PAP at rest, suggestive of different pathway(s) [151]. Taveira-DaSilva et al. evaluated a cohort of LAM patients for PH, estimating resting and exercise PAP with TTE, under cardiopulmonary exercise testing (CPET). Overall, resting TTE-estimated sPAP was found to be 26 ± 0.7 mmHg, while exercise TTE-estimated sPAP was 40.5 ± 1.1 mmHg. Resting LAM-PH was present in less than 10% of the cohort (8 out of 95, sPAP = 43 ± 3 mmHg) [151]. In recently published data extracted from patients with severe disease, listed for lung transplantation and evaluated by RHC, morphological and clinical signs of PH were present in all subjects [152]. Similarly, another recent retrospective multicenter study reported data from RHC evaluations in LAM-PH patients. Severe PH (defined by the investigators as mPAP > 35 mmHg) was present in only 20% of patients. Interestingly, 6 patients received oral PAH specific therapy and improved hemodynamically (mPAP decreased from 33 ± 9 to 24 ± 10 mmHg and PVR from 481 ± 188 to 280 ± 79 dyn/s/cm^{-5}). In this cohort of 20 female patients, the overall 2-year survival was 94% [153]. There is very few available data regarding LAM-PH, and the field needs more large-scale studies to extract more enlightening data regarding pathophysiology and prevalence of disease.

8. Chronic Obstructive Pulmonary Disease and Pulmonary Hypertension

The pathogenesis of "out-of-proportion" PH in COPD (COPD-PH) is quite complex and being continuously elucidated by ongoing research. Pulmonary vascular endothelial dysfunction, as well as the inflammatory effect, is roughly the outline of the disease mechanisms. A major inflammatory factor in COPD is thought to be tobacco smoke inhalation, with established vascular and parenchymal changes in human and experimental animal lungs, and could act additively in COPD-PH as a direct hit to pulmonary vasculature [154, 155]. There is a documented decrease of endothelial NO synthase (eNOS) expression and impaired vasodilation response in asymptomatic smokers, as well as in advanced COPD disease, delineating a potential role of eNOS in the disease [156–160]. Additionally, certain eNOS and ACE polymorphisms have been found to be associated with COPD-PH [161]. Interleukin-6 (IL-6) and the presence of its polymorphism were associated with higher PAP in COPD patients, adumbrating an involvement in COPD-PH pathogenesis [162, 163].

At first, as in other parenchymal lung disease-associated PH subtypes, acute hypoxia-induced vasoconstriction was thought to be the initializing factor in vascular remodeling. In fact, chronic hypoxia induces the neomuscularization of pulmonary arterioles, resulting in intimal thickening by SMC assemblage and extracellular deposition of plenteous collagen and elastin, a phenomenon widely referred as "intimal fibroelastosis." Of great interest is that these changes have also been described in normoxemic (pO_2 within normal range) COPD patients without pulmonary hypertension and also in asymptomatic smokers [159]. In addition, in an experimental animal study, pCO_2 as well as pH was found to have an amplifying effect on acute hypoxia-induced vasoconstriction [164].

Recent data proposes an important role for serotonin (5-HT) and its transporter (5-HTT) in intimal fibroelastosis. The 5-HTT LL genotype, which is linked with greater 5-HTT expression, was found to be associated with considerably high PAP in COPD, compared to other polymorphisms [165]. A pathological examination of postpneumonectomy lungs demonstrated mass attraction of mostly CD8+ lymphocytes infiltrating the vascular adventitia [166].

An adaptive response to hypoxemia is polycythemia (increased total erythrocyte number), which is also incriminated for alterations in pulmonary vasculature. It has been shown experimentally that a sole hematocrit increment in dogs can notably increase PVR by 112% ($P < 0.01$). Moreover, there was a combined augmentation effect of polycythemia and hypoxia, increasing PVR by 308% ($P < 0.005$)

Table 1: Representative randomized control trials and studies on non-PAH pulmonary hypertension related to parenchymal lung diseases.

Treatment	Lung disease	Study/reference	Comments
Sildenafil	Lung fibrosis including an IPF subgroup	Ghofrani et al., 2002, [22]	Improvement in hemodynamics and gas exchange
Sildenafil	IPF	Collard et al., 2007, [23]	Improvement in 6MWD in 57% of patients
Sildenafil	IPF	Jackson et al., 2010, [24]	No improvement in 6MWD
Sildenafil	IPF	Madden et al., 2006, [25]	Only 3 patients treated for 3 months and showed improvement in 6MWD and TTE parameters
Sildenafil	IPF	The IPF Clinical Research Network, 2010, [26]	There was no difference in 6MWD between the two groups, as a primary outcome measure
Sildenafil	COPD	Rietema et al., 2008, [27]	No improvement in stroke volume or exercise capacity
Sildenafil	Sarcoidosis	Barnett et al., 2009, [28]	In 9 patients treated with sildenafil out of 22 total, there was slight improvement in hemodynamics, 6MWD, and NYHA-FC
Sildenafil	Sarcoidosis	Milman et al., 2008, [29]	In 12 patients treated, who were listed for transplantation, there was a significant decrease in mPAP. No improvement found in 6MWD
Sildenafil	COPD	Blanco et al., 2010, [30]	In a RCT of 20 patients with COPD-associated PH, sildenafil improved acute pulmonary hemodynamics at rest and during exercise and deteriorated oxygenation
Bosentan	IPF	BUILD-1 study, King et al., 2008, [31]	Bosentan treatment in patients with IPF did not show superiority over placebo on 6MWD
Bosentan	IPF	BUILD-3 study, King et al., 2011, [32]	No treatment effects were observed on health-related quality of life or dyspnea. The primary objective was not met
Bosentan	COPD	Stolz et al., 2008, [33]	30 patients with COPD were randomly assigned in a 2 : 1 ratio to receive either bosentan or placebo for 12 weeks. Bosentan did not improve 6MWD and deteriorated hypoxemia and functional class
Bosentan	COPD	Valerio et al., 2009, [34]	In a quite small sample size ($n = 16$), there was benefit in PAP, PVR, and 6MWD. No improvement in GOLD IV patients
Riociguat	COPD	Ghofrani et al., 2011, [35]	In a quite small sample size ($n = 22$), there was a trend of improvement in hemodynamics (abstract)
IV epoprostenol	Sarcoidosis	Fisher et al., 2006, [36]	In 5 patients treated with parenteral epoprostenol, there was improvement of NYHA-FC by one or two stages within 29 months
IV prostacyclin	COPD	Archer et al., 1996, [37]	Treatment of 7 mechanically ventilated patients for COPD exacerbation caused worsening of hypoxemia

6MWD: 6-minute walking distance test; COPD: chronic obstructive pulmonary disease; INH: inhaled; IPF: idiopathic pulmonary fibrosis; IV: intravenous; mPAP: mean pulmonary artery pressure; NYHA-FC: New York Heart Association functional class; PAP: pulmonary artery pressure; PVR: pulmonary vascular resistance; TTE: transthoracic tissue Doppler echocardiography.

[167]. Recently, it was demonstrated that the presence of excessive erythrocytosis in mice increased the sPAP *in vivo* [168]. Additive data shows that there is definitely a role of polycythemia in the COPD-PH mechanism, but in humans is yet to be investigated.

The true incidence of clinically significant resting "out-of-proportion" PH is difficult to be estimated in COPD patients, as most data comes from reports that include COPD patients with advanced disease, resulting in a notably wide reported range varying from 5% to 70% [169–171]. This is cofounded by several limitations. Firstly, there are no large-scale studies assessing the true prevalence of COPD-PH by means of RHC. Commonly, the test selected for PH documentation in such patients is TTE. As already emphasized elsewhere in this paper, TTE can only estimate sPAP and mPAP values, and only the invasive RHC can establish the presence of elevated PAP. This must be kept in mind by the clinician when evaluating the reported incidence for COPD-PH, because in many settings PH diagnosis relies only on TTE. There is additive data for this statement, showing TTE inaccuracy in PAP and cardiac output (CO) estimation, when compared to RHC, in several PH subtypes [172]. Secondly, most available studies are of retrospective nature and include mostly patients with severe disease (FEV_1 < 30% predicted). As an example, studies on severe COPD patients report an incidence of 91%, with the majority suffering from mild-to-moderate PH (mPAP = 20–35 mmHg) and 1% to 5% suffering from severe disease (mPAP > 35–40 mmHg) [8, 169, 173]. However, in some COPD patients, the hemodynamic impairment might be more severe than expected from the related progress of parenchymal disease. This group of patients is characterized in anecdotal basis as "PH out-of-proportion to degree of respiratory compromise." This is of significant interest, because such patients have been viewed as potential beneficiaries of PAH-specific therapeutic agents, although, as of now, there is neither consensus on the best candidates for studying such management, nor RCTs running.

It seems that there is a strong negative impact on survival from the occurrence of PH in COPD patients, even though the hemodynamic impairment is rather mild in terms of pressure values *per se*. The 5-year survival regarding severely affected COPD patients with PH (mPAP ≥ 25 mmHg) has been reported as low as 36%, compared to 62% in COPD patients without PH [174]. Although several studies demonstrate high mortality rates in COPD patients with pulmonary hypertension, it is still under discussion if the occurrence of pulmonary hypertension is an independent cause of death or just a sign of disease worsening.

9. Treatment Suggestions for Pulmonary Hypertension in Lung Disease

It should be emphasized that specific treatment for PAH has been approved by regulatory authorities for group 1 (PAH) only [1]. Drug-related information provided herein (text and Table 1) is based on case reports and small case series, provided to roughly inform the reader about current anecdotal use of PAH-specific agents in selected cases. This results in minimum strength of evidence, and the need for large-scale randomized controlled trials is profound.

Patients with underlying parenchymal lung diseases who develop PH are always an intriguing subset regarding their management and treatment, as the occurrence of PH is associated with mortality; whether this association has a causal relation with mortality or simply represents a marker of disease severity is not clear.

There is no clear consensus on how or when to treat severe PH in parenchymal lung diseases. PAH-specific treatment in this setting does not ensure improvement of pulmonary vascular hemodynamics or exercise capacity while on the other hand might worsen ventilation/perfusion (V/Q) mismatch and subsequently lead to shunting and further hypoxia [27, 33, 37].

As of today, the European guidelines regarding "out-of-proportion" PH (PH owing to lung disease and/or hypoxia) recommend performance of TTE for screening (Class of recommendation-Level of evidence, I-C) and RHC for a definite diagnosis of PH due to lung disease (I-C). Again, the use of PAH-specific therapeutic agents is not recommended in this group (III-C). Additionally, optimal treatment of the underlying lung disease and the use of supplemental O_2 are the recommended therapeutic measures in such patients. In PAH associated with CTDs, the recommendation is for the same treatment algorithm as in IPAH (I-A); *terra incognita* remains the group of CTD patients with significant ILD, since such patients have usually been excluded from performed related RCTs. The performance of TTE is strongly recommended in all symptomatic patients with scleroderma for PAH screening (I-C) and RHC is recommended in all patients with the clinical question of starting a PAH-specific treatment (I-C). In nonsymptomatic patients with scleroderma, a screening study (TTE) may be considered (IIb-C) [1].

In conclusion, we emphasize again that the use of PAH-specific therapeutic agents is not approved for patients belonging to groups 3 and 5 by the Dana Point classification [1], which is the case of all the diseases analyzed in this review with the exception of CTDs. Clinical studies and RCTs should be performed in such nongroup 1 patients, in an effort to clearly designate subcategories of subjects that might benefit from specific treatments.

Authors' Contribution

I. Tsangaris and S. E. Orfanos had the main concept idea and critically reviewed and edited the paper, G. Tsaknis wrote, drafted the paper and performed the literature search, and A. Anthi critically reviewed the paper. All authors have read and approved the paper.

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Review Article

Methods for Assessing Expiratory Flow Limitation during Tidal Breathing in COPD Patients

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Patients with severe COPD often exhale along the same flow-volume curve during quite breathing as during forced expiratory vital capacity manoeuvre, and this has been taken as indicating expiratory flow limitation at rest (EFL_T). Therefore, EFL_T, namely, attainment of maximal expiratory flow during tidal expiration, occurs when an increase in transpulmonary pressure causes no increase in expiratory flow. EFL_T leads to small airway injury and promotes dynamic pulmonary hyperinflation with concurrent dyspnoea and exercise limitation. In fact, EFL_T occurs commonly in COPD patients (mainly in GOLD III and IV stage) in whom the latter symptoms are common. The existing up-to-date physiological methods for assessing expiratory flow limitation (EFL_T) are reviewed in the present work. Among the currently available techniques, the negative expiratory pressure (NEP) has been validated in a wide variety of settings and disorders. Consequently, it should be regarded as a simple, non invasive, most practical, and accurate new technique.

1. Introduction

Some experts use the term *chronic airflow limitation* as a synonym for chronic obstructive pulmonary disease (COPD) to indicate the reduction in maximum expiratory flow that occurs in this disease (and indeed in other pulmonary diseases). Patients with severe COPD often exhale along the same flow-volume curve during quite breathing as during forced expiratory vital capacity manoeuvre, and this has been taken as indicating flow limitation at rest (EFL_T). Consequently, the term *tidal expiratory flow limitation* (EFL_T) is used to indicate that maximal expiratory flow is achieved during tidal breathing at rest or during exercise. This is characteristic of intrathoracic flow obstruction. The former term does not imply that EFL_T actually occurs during tidal breathing [1]. The location of expiratory flow limitation is considered to be in the central airways (4th–7th generation) and move to the periphery during forced expiratory manoeuvres. It is located beyond the 7th (i.e., from the 8th onwards) generation during tidal breathing [2–4].

Tidal expiratory flow limitation (EFL_T) [5–8] plays a central role according to a recent hypothesis [5] on the transition from small airways disease (SAD) to overt COPD in smokers. EFL_T implies inhomogeneity of ventilation distribution with concurrent impairment of gas exchange and unevenly distributed stress and strain within the lung, which is amplified by tissue interdependence [6, 7] and may lead to *small airway* injury [5–8]. Initially, the latter is histologically characterized by denuded epithelium, rupture of alveolar-airway attachments, and increased number of polymorphonuclear leucocytes [5–7]. Studies in which heliox (80% He/20% O_2) was administered in COPD patients provided also corroborative evidence that EFL_T was located in the peripheral airways [2–4]. EFL_T promotes dynamic pulmonary hyperinflation and PEEPi with concurrent dyspnoea and exercise limitation [8]. In fact, EFL_T occurs commonly in GOLD III and IV stage patients causing dynamic hyperinflation and severe dyspnoea [9]. It should be noted that the important role of expiratory flow limitation in COPD patients has been studied in a variety of clinical settings (during mechanical ventilation

and exercise, correlation with dyspnoea, orthopnoea, and the other lung function indexes, before and after bronchodilatation, various postures).

2. Clinical Significance of EFL

The important role of EFL_T in chronic dyspnoea and exercise impairment for a surprisingly wide range of clinical circumstances was enlightened by the techniques of detecting it, but mainly by the use of negative expiratory pressure (NEP) technique. EFL_T measured with the NEP technique is a much better predictor of chronic dyspnoea than FEV_1, and FEV_1 is not a specific predictor of EFL_T in COPD patients. These findings suggest that EFL_T measured by the NEP technique may be more useful in the evaluation of dyspnoea in COPD patients than spirometric measurements [10].

The improvement of inspiratory capacity (IC) after bronchodilator administration [11], which is mainly limited to patients with EFL at rest and therefore usually exhibits a reduction of baseline IC, entails reduction in dyspnoea both at rest and during light exercise [12]. The fact that after bronchodilator administration there is a significant reduction of dynamic hyperinflation (DH) only in patients with EFL at rest further supports the usefulness of stratifying COPD patients in subgroups with and without EFL in order to predict an improvement in DH [11]. COPD patients with EFL may experience less breathlessness after a bronchodilator, at least during light exercise, than those without EFL. This beneficial effect, which is closely related to an increase in IC at rest, occurs even in the absence of a significant improvement of FEV_1 [12]. Though, in the past, bronchodilator testing focused on changes of FEV_1, the scrutiny of changes in IC in non-EFL_T and EFL_T COPD patients should provide useful information. In contrast, the detection of EFL_T did not predict the changes of EELV or dyspnoea occurring after bronchodilation [13].

Díaz et al. [14] found that IC was the only spirometric parameter, in which there was almost no overlap between non-EFL_T and EFL_T COPD patients. The non-EFL_T patients had almost all normal IC whilst the EFL_T all had <80% pred in a group of 52 COPD patients. Linear regression analysis performed separately for these EFL_T and non-EFL_T patients showed that in the EFL_T patients the sole predictor of exercise capacity was IC% pred, whilst in the non-EFL_T the ratio FEV_1/FVC% pred was the sole predictor. Díaz et al. [15] also reported that in EFL_T COPD patients, the maximal tidal volume and hence maximal oxygen consumption are closely related to the reduced IC. The EFL_T patients also exhibited a significant increase in $PaCO_2$ and a decrease in PaO_2 during peak exercise. O'Donnell et al. [16] extended the findings of Díaz et al. [14, 15] reporting that since the pathophysiological hallmark of COPD is EFL (occurring during exercise and in the advanced disease even at rest), the latter promoted DH which was correlated best with resting IC. DH curtailed V_T response to exercise. The inability to expand V_T in response to increasing ventilatory demand contributed to exercise intolerance in COPD.

The main finding of these studies was that detection of tidal EFL plays an important role in identifying the factors that limit exercise tolerance because resting EFL clearly separates two populations of patients with significant differences in exercise tolerance. More importantly, their detection provides useful information about the mechanisms limiting exercise tolerance. The detection of EFL during exercise should be carried out also using the NEP technique, as the conventional method for detecting flow limitation based on comparison of tidal with maximal flow-volume curves is not reliable [17]. In the presence of tidal EFL, DH appears to be the main determinant of exercise performance and the magnitude of resting IC, a well-recognized marker of DH, the best clinical predictor [14, 17].

EFL may be absent at rest but can be developed and hence detected during any exercise level by the use of NEP. That explains the fact that COPD patients, who are not hyperinflated at rest, develop DH during exercise [17]. It should be noted here that there are instances when DH (reflected by a reduced IC) can occur in the absence of tidal EFL [18, 19], and the presence of tidal EFL may not necessarily result in DH if the available expiratory flow is sufficient to sustain resting ventilation without the need to increase EELV. This is reflected by the fact that there are patients with EFL_T and normal IC. Thus, measurement of IC and detection of EFL are complimentary ways for assessing bronchodilator and exercise responsiveness in COPD patients.

It was found that almost all COPD patients who require mechanical ventilation are flow-limited over the entire range of tidal expiration and that the supine posture promotes flow limitation [20].

Despite these potentially adverse consequences of EFL, its prevalence has not been extensively studied until recently, probably due to the lack of simple and noninvasive techniques. The aim of this work was to review the existing physiological techniques of assessing tidal expiratory flow limitation (EFL_T).

3. Oesophageal Balloon Techniques

3.1. Fry Method. The definition of EFL implies that a further increase in transpulmonary pressure will cause no further increase in expiratory flow [21]. Therefore, direct assessment of expiratory flow limitation requires determination of isovolume relationships between flow and transpulmonary pressure (*F-P*). Fry et al. [22] were the first who developed such curves in 1950s. The explanation of an isovolumic pressure flow curve lies in understanding its construction. Flow, volume and oesophageal pressure (Poes) are measured simultaneously during the performance of repeated expiratory vital capacity efforts by a subject seated in a volume body plethysmograph, in which gas compression artifact is corrected. The subject is instructed to exhale with varying amounts of effort that are reflected by changes in Poes. From a series of such efforts (~30), it is possible to plot flow against Poes at any given lung volume [21]. The flow reached a plateau at a low positive pleural pressure and that once maximum flow for that volume is reached, it remains constant despite increasing Poes by making expiratory efforts of increasing intensity.

3.2. Mead-Whittenberger's Method. The Mead-Whittenberger method [23] directly relates alveolar pressure to flow. Mead-Whittenberger's graphs can be obtained by plotting the flow measured at the airway opening versus the resistive pressure drop during a single breath. In such a way the phenomenon of flow limitation is documented.

These techniques are technically complex and time consuming. Furthermore, these techniques are invasive because they require the insertion of an oesophageal balloon [22, 23].

3.3. Conventional (Hyatt's) Method. Until recently, the "conventional" method used to detect expiratory flow-limitation during tidal breathing was the one proposed by Hyatt [24] in 1961. It consists in superimposing a flow volume loop of a tidal breath within a maximum flow-volume curve. This analysis and the "concept of EFL" have been the basics for understanding respiratory dynamics. Flow limitation is not present when the patient breaths tidally below the maximal expiratory flow-volume (MEFV) curve. According to this technique, normal subjects do not reach flow limitation even at maximum exercise [1, 25]. In contrast, flow limitation is present when a patient breathes tidally along or higher than the MEFV curve. Patients with severe chronic obstructive pulmonary disease (COPD) may exhibit flow limitation even at rest, as reflected by the fact that they breathe tidally along or above their maximal flow-volume curve [1, 21–25]. However, the conventional method to detect flow limitation based on comparison of maximal to tidal expiratory flow-volume curves suffers from several methodological deficiencies. These include the following.

(a) *Thoracic Gas Compression Artefacts.* Volume should be measured with a body-box, instead of using, as is common practice, a pneumotachograph or a spirometer in order to minimize such errors [26]. Consequently, in practice, flow limitation can be assessed only in seated subjects at rest.

(b) *Incorrect Alignment of Tidal and Maximal Expiratory F-V Curves.* Such alignment is usually made considering the total lung capacity (TLC) as a fixed reference point. This assumption may not always be valid [27, 28].

(c) *Effect of Previous Volume and Time History.* Comparison of tidal and maximal *F-V* curves is incorrect, since the previous volume and time history of a spontaneous tidal breath is necessarily different from that of an FVC manoeuvre. Therefore, it is axiomatic that comparison of tidal with maximal *F-V* curves is problematic. In fact, there is not a single maximal *F-V* curve but rather a family of different curves, which depend on the time course of the inspiration preceding the FVC manoeuvre [29–31].

(d) *Respiratory Mechanics and Time Constant Inequalities.* These are different during the tidal and maximal expiratory efforts again making comparisons of the two *F-V* curves problematic [32–34].

(e) *Exercise.* Exercise may result in bronchodilation or bronchoconstriction and other changes of lung mechanics, which may also affect correct comparisons of the two *F-V* curves [35].

(f) *Patient's Cooperation.* Another important limitation of the conventional method is that it requires patient's cooperation. This is not always feasible [27, 28].

In fact, it has been clearly demonstrated in several studies [11, 17, 36, 37] comparing the NEP with the conventional technique that the latter is not accurate. As a result, the use of the conventional method is no longer recommended.

4. The Negative Expiratory Pressure (NEP) Technique

In order to overcome these technical and conceptual difficulties, the *negative expiratory pressure (NEP) technique* has been introduced [10, 17, 27, 36]. The NEP technique has been first applied and validated in mechanically ventilated ICU patients by concomitant determination of isovolume flow-pressure relationships [38]. This method does not require performance of FVC manoeuvres, collaboration on the part of the patient, or use of a body-box. It can be used during spontaneous breathing in any body position [39], during exercise [17, 40], and ICU settings [20]. With this technique the volume and time history of the control and test expiration are axiomatically the same.

Briefly, a flanged plastic mouthpiece is connected in series to a pneumotachograph and a T-tube (Figure 1). One side of the T-tube is open to the atmosphere, whilst the other side is equipped with a one-way pneumatic valve, which allows for the subject to be rapidly switched to negative pressure generated by a vacuum cleaner or a Venturi device. The pneumatic valve consists of an inflatable balloon connected to a gas cylinder filled with pure helium and a manual pneumatic controller. The latter permits remote-control balloon deflation, which is accomplished quickly (30–60 ms) and quietly, allowing rapid exposure to negative pressure during expiration (NEP). Alternatively, a solenoid rapid valve can be used. The NEP (usually set at about $-5\,\mathrm{cm\,H_2O}$) can be adjusted with a potentiometer on the vacuum cleaner or by controlling the Venturi device. Airflow ($\dot{V}$) is measured with the heated pneumotachograph and pressure at the airway opening (Pao) is simultaneously measured through a side port on the mouthpiece (Figure 1). Volume (V) is obtained by digital integration of the flow signal, and correction of electrical drift is mandatory [36]. While performing the testing, the subjects should be watched closely for leaks at the mouthpiece. Only those tests, in which there is no leak, are valid [41]. Tidal EFL is assessed while seated upright in a comfortable chair or if needed lying supine on a comfortable couch, at least 2 h after eating or taking coffee. Patients are asked to breathe room air through the equipment assembly with the noseclip on (Figure 1). Each subject has an initial 10–15 min trial run, in order to become accustomed to the apparatus and procedure. The flow, volume, and pressure are continuously monitored on the computer screen. When regular breathing is resumed, a series of test breaths are performed with regular breaths in between the test breaths, in which NEP is applied at the beginning of expiration and maintained throughout the ensuing expiration [36].

The NEP technique is based on the principle that in the absence of flow limitation, the increase in pressure gradient between the alveoli and the airway opening caused by NEP should result in increased expiratory flow. By contrast, in flow-limited subjects application of NEP should not

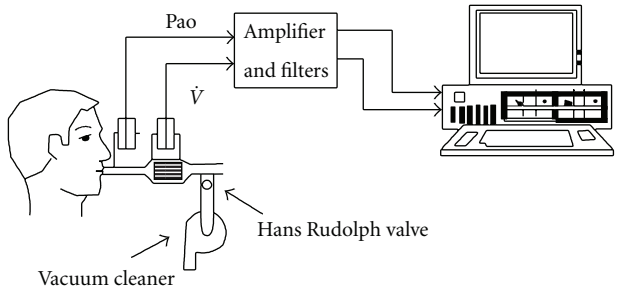

Figure 1: Schematic diagram of equipment setup. Pao: pressure at the airway opening; $\dot{V}$: gas flow (from [36]).

change the expiratory flow. Our analysis essentially consists in comparing the expiratory $\dot{V}$-V curve obtained during a control breath with that obtained during the subsequent expiration in which NEP is applied [36].

Subjects in whom application of NEP does not elicit an increase of flow during part or all of the tidal expiration (Figures 2(b) and 2(c)) are considered flow-limited (EFL). By contrast, subjects in whom flow increases with NEP throughout the control tidal volume range (Figure 2(a)) are considered as non-flow-limited (non-EFL_T). If tidal EFL is present when NEP is applied, there is a transient increase of flow (spike), which mainly reflects sudden reduction in volume of the compliant oral and neck structures. To a lesser extent a small artefact due to common-mode rejection ratio of the system of measuring flow may also contribute to the flow transients [10, 36]. Such spikes are useful markers of EFL.

The degree of flow limitation can be assessed using three different EFL_T indices: (a) as a continuous variable expressed as % V_T in both seated and supine positions (Figure 2) [36], (b) as a discrete variable in the form of three categories classification, that is, non-EFL_T both seated and supine, EFL_T supine but not seated, and EFL_T both seated and supine [36], and (c) as discrete variable in the form of the five-category classification (5-point EFL_T score) [10].

In all studies employing the NEP technique, the latter was not associated with any unpleasant sensation, cough, or other side effects [10, 17, 36]. The finding of O'Donnell et al. [42] that application of $-9.7\,cm\,H_2O/L/s$ of expiratory assistance for 4 min during inspiration and expiration caused unpleasant respiratory sensation can be attributed to negative pressure application differences, that is, NEP, usually at $-5\,cm\,H_2O$ level, is applied only during expiration every 5–10 breaths intervals.

The use of the NEP technique during tidal flow-volume analysis studies has led to realization of the important role of expiratory flow limitation in exertional dyspnoea and ventilatory impairment for a surprisingly wide range of clinical circumstances, for example, before and after bronchodilation, exercise, ICU, and heliox administration at rest and during exercise [8, 43, 44]. Up to date, no study has questioned reliability and accuracy of the NEP technique. Currently, therefore, the NEP technique can be regarded as the new gold standard to detect EFL_T, if one takes into account the pros and cons of each available technique. It is a novel, simple, non-invasive, useful research and clinical lung function tool.

5. Submaximal Expiratory Manoeuvres

Pellegrino and Brusasco [45] proposed an alternative technique to detect expiratory flow limitation. EFL_T was inferred from the impingement of the tidal flow-volume loop on the flow recorded during submaximally forced expiratory manoeuvres initiated from end-tidal inspiration in a body-box. After regular breathing with no volume drift, the subject performs a forced expiration from end-tidal inspiration without breath holding (partial expiratory manoeuvre). Care is taken to coach the subjects not to slow down the inspiration preceding the partial forced manoeuvre, thus minimizing the dependence of forced flows on the time of the preceding inspiration. A deep inspiration to TLC recorded soon after the gentle forced manoeuvre allowed the loops to be superimposed and compared at absolute lung volume. Flow limitation is defined as the condition of tidal expiratory flow impinging on the maximal flow generated during the gentle forced expiratory manoeuvre. Since this method requires a body box measurements cannot be made in different body postures, ICU, or during exercise testing.

6. Squeezing the Abdomen during Expiration

Workers in Brussels have shown that manual compression of the abdomen coinciding with the onset of expiration can be used as a simple way of detecting flow limitation at rest [46] and during exercise [47]. With one hand placed on the lower back of the patient and other applied with the palm at the level of the umbilicus perpendicular to the axis between the xiphoid process and the pubis, the operator first detects a respiratory rhythm by gentle palpation, and then after warning the subject applies a forceful pressure at the onset of expiration. As in the NEP technique, the resulting expiratory flow-volume loop recorded at the mouth is superimposed on the preceding tidal breath. Failure to increase expiratory flow indicates flow limitation. This technique produces clear differences between normal subjects and patients with COPD. The presence of flow limitation during exercise detected during exercise in COPD patients was associated with increases in the end-expiratory lung volume (EELV) [47]. Interestingly, not all subjects with COPD exhibited

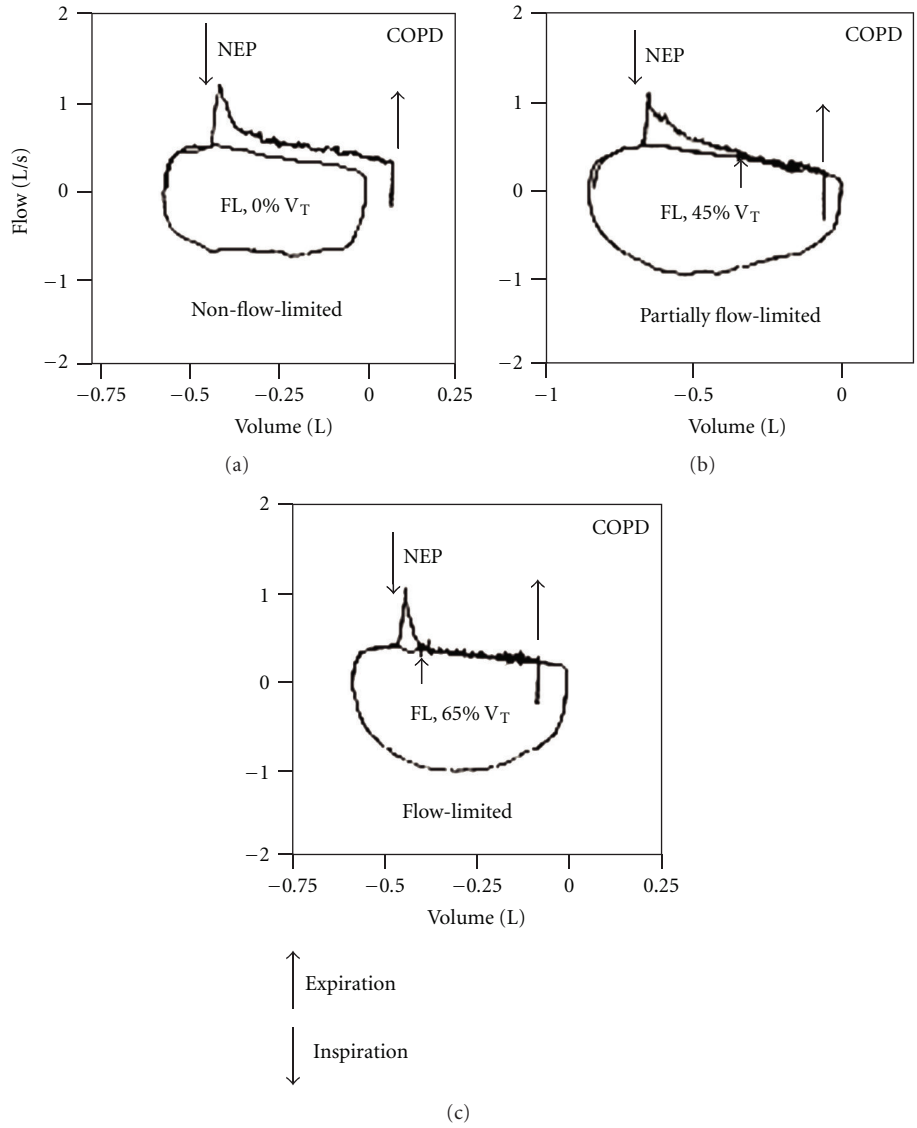

Figure 2: Flow-volume loops of test breaths and preceding control breaths of three representative COPD patients with different degrees of flow-limitation: not flow-limited (NFL) (a), flow-limited (EFL) over less than 50% V_T (b), and flow-limited from peak expiratory flow (EFL) (c). Arrows indicate points at which NEP was applied and removed (modified from [10]).

flow limitation when lung volume changed, a finding which requires confirmation. The method is appealingly simple, not influenced by the upper airway compliance, and like the NEP method, it avoids problems with the preceding volume history of the test breath. Despite initial concerns about the possibility that gas compression in the alveoli would produce false positive results, this does not seem to be a practical problem. However, unlike the NEP method, it is virtually impossible to squeeze at the precise of expiration. Thus far this technique has not been widely applied despite its relative simplicity.

7. Forced Oscillation Technique (FOT)

Another approach for detecting EFL_T has been the forced oscillation technique (FOT) previously applied to look at the frequency dependence of resistance in a range of lung diseases and now available commercially in a modified form using impulse oscillometry [48, 49]. The principle here is that flow limitation will only be present in patients with obstructive pulmonary disease during expiration. Normally oscillatory pressures generated by a loud-speaker system at the mouth are transmitted throughout the respiratory system, and by studying the resulting pressures which are in and out of phase with the signal, both the respiratory system resistance and reactance (a measure of the elastic properties of the system) can be computed. When flow limitation occurs, wave speed theory predicts that a choke point will develop within the airway subtended by that "unit" of the lung. In these circumstances, the oscillatory pressure applied at the mouth will no longer reach the alveoli and the reactance will reflect the mechanical properties of the airway

wall rather than those of the whole respiratory system. As a result, reactance becomes much more negative and there is a clear within breath difference between inspiration and expiration. Dellacá and colleagues [49] used this property to investigate the distribution of changes in intrabreath reactance in normal subjects and COPD patients who were instrumented with balloon catheters. In a recent study Dellacá et al. [50] found a good agreement between NEP and FOT despite the fact that the FOT method may detect regional as well as overall EFL_T. NEP detects the condition in which all possible pathways between airway opening and the alveoli are choked. When this occurs, the total expiratory flow is independent of the expiratory pressure, a condition of "global" expiratory flow limitation. In contrast, FOT assesses the amount of the lung that is choked during expiration only. This measures "regional" flow limitation, and a threshold value may indicate when the regional flow limitation reaches the condition of "global" flow limitation. Therefore, when "global" expiratory flow limitation is reached, the two techniques should produce the same response [50].

It does appear to hold considerable promise, but to date, only a few studies to detect EFL_T with this method have been reported. On the other hand, FOT is very complex, expensive as it requires the special FOT equipment, and time consuming.

8. Technegas Method

Technegas is an aerosol of ^{99m}Tc-labeled carbon molecules with small diameter (<0.01 μm) [19] capable of depositing even in the most peripheral regions of the lung. Pellegrino et al. [19] used the inhalation of Technegas to reveal sites ("hot spots") of EFL_T after induced bronchocontsriction in asthmatic patients. During forced expiration, the flow-limiting segment is known to be located first in the large intrathoracic airways and then to move peripherally. However, the present scintigraphic technique cannot precisely define the anatomical location of the flow-limiting segment during tidal breathing. Therefore, what the "hot spots" represent appears to be uncertain. The authors claim that this technique is useful to detect "regional" EFL_T well before the NEP and submaximal expiratory manoeuvre techniques.

9. Breath-by-Breath Method

The most recent method to detect EFL_T is the one using breath-by-breath quantification of progressive airflow limitation during exercise applied in stable COPD patients [51]. The authors have noted that during heavy exercise in COPD patients, dynamic airways compression leads to a progressive fall in intrabreath flow. This is manifested by an increasing concavity in the spontaneous expiratory flow-volume (SEFV) curve. The new method consists in quantifying the SEFV curve configuration breath-by-breath during incremental exercise utilizing a computerized analysis. For each breath's SEFV curve, points of highest flow and end-expiration were identified to define a rectangle's diagonal. Fractional area within the rectangle below the SEFV curve was defined as the "rectangular area ratio" (RAR). RAR < 0.5 signifies concavity of the SEFV curve. However, this method may be useful only during exercise because inspection of SEFV curve during resting breathing is not a reliable means in detecting EFL_T [41]. Severe COPD patients often exhibit a mechanically active expiration, which is characterized by abdominal activity. This necessarily affects the shape of SEFV curve, making it concave with respect to the volume axis, even in the absence of EFL_T [52].

10. Conclusions

The newer aforementioned techniques represent a substantial advance on traditional approaches which compared tidal and maximal flow-volume loops or even the more robust but time-consuming method of determining partial expiratory flow-volume loops. By freeing both parts, the doctor and the patient, from the limitations of the oesophageal balloon catheters and body plethysmograph, they have opened up a new era in understanding modern physiological principles like the tidal expiratory flow limitation [8, 43, 44]. Among the available physiological techniques to detect EFL_T, the NEP should probably be regarded as the new gold standard. This view is supported by the data obtained from the NEP's application in a wide variety of settings [8, 43, 44]. However, extensive comparisons between these different methods are needed before the best "test" or combination of techniques can be unequivocally recommended to correctly assess EFL_T.

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Research Article

Cigarette and Waterpipe Smoking Decrease Respiratory Quality of Life in Adults: Results from a National Cross-Sectional Study

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Background. Chronic obstructive pulmonary disease (COPD) is gaining an importance over the world, and its effect on quality of life is better grasped. Our objective was to use the Clinical COPD Questionnaire (CCQ) to describe the respiratory quality of life in the Lebanese population, stressing on differences between smokers and nonsmokers. *Methods*. Using data from a cross-sectional national study, we checked the construct validity and reliability of the CCQ. Factors and items correlation with postbronchodilator FEV1/FVC were reported, in addition to factors and scale association with COPD and its severity. We then conducted a multiple regression to find predictors of quality of life. *Results*. The CCQ demonstrated excellent psychometric properties, with adequacy to the sample and high consistency. Smokers had a decreased respiratory quality of life versus nonsmokers, independently of their respiratory disease status and severity. This finding was confirmed in COPD individuals, where several environmental factors, lower education, and cumulative smoking of cigarette and of waterpipe were found to be independent predictors of a lower quality of life, after adjusting for COPD severity. *Conclusions*. Smoking decreases the respiratory quality of life of Lebanese adults; this issue has to be further emphasized during smoking cessation and patients' education.

1. Introduction

Chronic obstructive pulmonary disease is increasing over the world; it is expected to rank third in 2020 as a cause of mortality [1]. In Lebanon, we had demonstrated that the prevalence of respiratory diseases is quite high (COPD and chronic bronchitis in particular) in the population aged 40 and above, paralleling the high prevalence of smoking cigarettes and waterpipes [2]. Although COPD is known to decrease the patients' quality of life [3], a low percentage (20%) of individuals are diagnosed and treated for COPD in Lebanon. The others are still experiencing chronically respiratory symptoms and consequent limitations without seeking help [2]. However, according to the GOLD (Global initiative for obstructive lung disease) guidelines [4] and their updated version [5], the aim of clinical control in patients with COPD includes health-related quality of life goals (improved exercise tolerance and emotional function) added to clinical goals (prevention of disease progression and minimization of symptoms).

Several tools have been developed to evaluate quality of life in patients with chronic respiratory diseases [6, 7], but none of them has been validated for use in the Lebanese population. Moreover, the Saint George Respiratory Questionnaire is long [8], while the American Thoracic Society questionnaire evaluates only symptoms [9]. However, the Chronic COPD Questionnaire (CCQ) seems to have excellent psychometric properties, along with simplicity of application [10]; it is also the first questionnaire that incorporates both clinician and patient guideline goals in the clinical control evaluation of patients with COPD in general clinical practice [11]. It was showed to be the best patient-reported outcome tool to assess functional performance [12]. Although the new recommendations issued by the GOLD steering committee [5] adopted the COPD Assessment Test (CAT) questionnaire as the first one to be used without

neglecting the value of the CCQ, we had conducted the study before the issuing of these recommendations.

Our objective was to describe the respiratory quality of life in the Lebanese population using data from a cross-sectional national study on the prevalence of COPD [2], stressing on differences between smokers and nonsmokers.

2. Methods

2.1. Study Design. Data for this analysis was taken from a cross-sectional study, using a multistage cluster sample all over Lebanon. This study was carried out between October 2009 and September 2010, using a multistage cluster sample ($n = 2201$) across Lebanon. From the list of communities in Lebanon (includes a total of 2782 villages, towns, and cities), one hundred communities were randomly selected with randomization performed on a computerized software. Afterwards, through a representative of local authorities, individuals were randomly chosen to be interviewed, from a provided list of dwelling households aged 40 years and above. All individuals of the household were solicited, if they were eligible.

2.2. Procedure. After an oral informed consent, subjects underwent a baseline spirometry (Micro Lab, Micro Medical Limited, UK), conducted by a trained technician, and answered a standardized questionnaire. Thirty minutes after the inhalation of 2 puffs of ipratropium bromide (18 μg/actuation) and albuterol sulfate (103 μg/actuation) (Combivent) in a pressurised metered-dose aerosol unit, a postbronchodilator spirometry was performed. The best result out of 3 trials was taken into account. Spirometric quality was checked, and FEV6/FVC was $\leq$100% in more than 99.2% of measurements. Additional methodological details are presented in a separate publication [2].

2.3. Questionnaire and Procedure. The standardized questionnaire included sections about sociodemographic characteristics, respiratory diseases and symptoms, and a thorough smoking history evaluation. Moreover, respiratory-related quality of life was measured by the Clinical COPD Questionnaire (CCQ) [10], while the MRC dyspnea scale was used to evaluate dyspnea [13]. The questionnaires were administered in Arabic local language; the translation process was as follows: first, two of the researchers, both bilingual, forward translated the questions into Arabic; instructions were given to them in the approach to translating, emphasizing conceptual rather than literal translations, as well as the need to use natural and acceptable language for the broadest audience. Second, discrepancies were resolved by consensus between them and two other researchers: this panel thus included the original translators, experts in health, as well as experts with experience in instrument development and translation. Third, an independent translator with no knowledge of the questionnaire back translated the questions into English. Translation discrepancies were resolved by consensus between the researchers and the translator. Fourth, the questionnaire was pilot tested on 20 individuals; all questions were deemed clear by these individuals, and no further changes were made to the initial questions.

2.4. Definitions. Chronic Obstructive Pulmonary Disease (COPD) was defined and classified according to GOLD guidelines (FEV1/FVC < 0.70 postbronchodilator) [14], and according to the lower limit of normal (FEV1/FVC post-bronchodilator < 5th percentile of the healthy population having the same age and gender of the individual) [15]. Individuals were finally classified as having COPD if they fulfilled one of the definitions described above. Chronic bronchitis was defined by the declaration of morning cough and expectorations for more than 3 months a year over more than two years in individuals with no COPD [14]. On the other hand, an individual was considered "healthy" from the respiratory point of view if he had no respiratory symptoms and no respiratory disease. Moreover, patients with a partially reversible obstruction (postbronchodilator FEV1/FVC that does not go back to normal) are considered with a mixed disorder of asthma and COPD; they are termed "reversible COPD." Further methodology details are presented in another publication [2].

Cumulative dosing of cigarettes was calculated as the mean number of daily packs multiplied by the duration of smoking (pack$*$years), while that of waterpipe was calculated as the mean number of weekly waterpipes multiplied by the duration of smoking (waterpipe$*$years). Cigarette and waterpipe dependence were defined according to Fagerström Test for Nicotine Dependence (FTND) [16] and Lebanese Waterpipe Dependence Scale (LWDS-11) [17], respectively.

2.5. Statistical Analysis. SPSS version 17.0 was used to enter and analyze data. Weighting was performed according to the numbers published by the Lebanese Central Administration of Statistics in 2007, taking into account gender, age, and dwelling region [18]. Cluster effect was taken into account, according to Rumeau-Rouquette and collaborators [19].

A P value of 0.05 was considered significant. The Chi^2 test was used for cross tabulation of qualitative variables in bivariate analysis, and odds ratios (OR) were calculated. ANOVA and Kruskal-Wallis tests were used to compare between three groups or more, and Pearson correlation coefficient were used to correlate between quantitative variables. Bonferroni adjustment was used for ANOVA post hoc tests of between groups comparison.

To confirm the CCQ construct validity in the Lebanese population, a factorial analysis was launched for CCQ items, using the principal component analysis technique, with a promax rotation since the extracted factors were found to be significantly correlated. The Kaiser-Meyer-Olkin measure of sampling adequacy and Bartlett's test of sphericity were ensured to be adequate. The retained number of factors corresponded to Eigenvalues higher than one. Factors loading of items were recorded. Moreover, Cronbach's alphas were recorded for reliability analysis for the total score and for subscale factors. The total CCQ score represents the sum of the 10 CCQ items divided by 10 (as recommended in the

CCQ manual) [10], while the factors 1 & 2 are the sums of their respective items. Factors and items correlation with postbronchodilator spirometric FEV1/FVC were reported, in addition to factors and scale association with COPD and its severity.

Afterwards, backward linear multiple regression was performed for multivariate analyses, with CCQ score as the dependent variable, and sociodemographic characteristics and other potentially harmful exposures as the independent variables; after ensuring model adequacy to data, relationship linearity, dependent variable normality, and lack of collinearity between covariates. We used this method to find significant predictors of respiratory quality of life in all individuals, in patients with COPD and in nonsmokers. Moreover, partial correlation with CCQ score was presented, taking other covariates into account.

3. Results

3.1. Sample Description. Among 2201 individuals, 978 were considered healthy (44.5%) from the respiratory point of view. Moreover, 233 (10.6%) had COPD, 204 (9.3%) had asthma, 51 (2.3%) had a reversible COPD, 326 (14.8%) had chronic bronchitis, 72 (3.3%) had a restrictive disease, and 336 individuals (15.3%) had miscellaneous respiratory symptoms (MRS). In the following analysis we will exclude patients with asthma, restrictive disease, and miscellaneous respiratory symptoms.

Thus, patients with COPD ($n = 284$), chronic bronchitis ($n = 326$), and healthy individuals ($n = 978$) will only be included. For them, mean postbronchodilators FEV1/FVC significantly differed: 0.62 (SD = 0.09) for COPD patients, 0.83 (SD = 0.05) for chronic bronchitis, and 0.85 (SD = 0.03) for healthy individuals ($P < 0.001$ for all comparisons). Healthy individuals have never been hospitalized for respiratory problems, while COPD and chronic bronchitis patients have both been hospitalized (mean number of hospitalizations is 0.26 for COPD and 0.36 for chronic bronchitis; $P = 0.090$).

3.2. Sociodemographic and Health Characteristics. In Table 1, we present sociodemographic characteristics of different individuals' categories. We note significant differences in percentages of COPD and chronic bronchitis for all categories. Individuals with obstructive diseases were included older ages, more males, less educated, retired, nonmarried, more obese individuals with more cardiac problems, in the regions of Bekaa and South Lebanon ($P < 0.001$ for all). Moreover, 22.2% of patients with COPD and 17.2% of those with chronic bronchitis are getting inhalation therapy.

Smokers had the higher rates of COPD and of chronic bronchitis, compared with never smokers. While mixed smokers had significantly higher prevalences of both diseases versus exclusive smokers, current waterpipe smokers had rates similar to never smokers, while previous waterpipe smokers included more COPD than previous cigarette smokers, with no chronic bronchitis cases (Table 1).

3.3. Clinical COPD Questionnaire (CCQ) Factor Analyses. Although the CCQ questions were part of the cross-sectional study questionnaire, and they were asked to the whole sample, the factorial analysis that was run over the sample of healthy individuals, COPD and chronic bronchitis patients (Total $n = 1588$). CCQ items converged over a solution of two factors that had an Eigenvalue over 1, explaining a total of 67.91% of the variance. A Kaiser-Meyer-Olkin measure of sampling adequacy of 0.876 was found, with a significant Bartlett's test of sphericity ($P < 0.0001$).

The first one, representing "dyspnea and dysfunction", explained 56.30% of the variance; the second factor, representing "chronic bronchitis" explained 11.61% of the variance. Moreover, high Cronbach's alpha were found for factor 1 (0.909), factor 2 (0.859), and the full scale (0.910) (Table 2).

3.4. Quality of Life in Disease Categories. There were significant differences between the means of respiratory quality of life score (Table 3) ($P < 0.001$). Looking at the means, the lowest CCQ quality of life was found for reversible and irreversible COPD patients and chronic bronchitis, compared with healthy individuals. We also compared respiratory CCQ score in COPD grades: there was a significant increase in CCQ along with COPD severity grades ($P < 0.001$). In individuals declaring being treated by inhalation therapy (including short acting and long acting anticholinergics, beta agonists, and steroids), quality of life was significantly lower versus individuals not declaring so ($P < 0.001$). Moreover, we found a significant correlation between the CCQ and the MRC dyspnea scale ($r = 0.763$; $P < 0.001$); individuals with an MRC dyspnea scale higher than zero had significantly worse quality of life (Table 3).

3.5. Quality of Life and Smoking. For previous smoking, we note significantly a higher CCQ score for all types of smoking, including cigarette, waterpipe, and mixed smoking ($P < 0.001$), compared with never smokers; mixed smokers have significantly higher CCQ versus other categories, while cigarette and waterpipe smoking had nonsignificant differences. As for current smoking, no significant difference was found between waterpipe smoking and never smokers; however, cigarette and mixed smokers had significantly higher sores for CCQ (Table 4).

For patients with chronic bronchitis and COPD, any previous smoker had significantly lower CCQ versus never smokers; mixed smokers had significantly higher values than cigarette and never smokers. In current smokers, cigarette and mixed smokers had significantly higher QOL versus waterpipe and never smokers. No significant difference was found between never smokers and waterpipe smokers, and no significant difference was found between cigarette and mixed smokers (Table 4).

On the other hand, there were clear positive dose-effect relationships between different smoking types cumulative doses and quality of life score (the higher the cumulative dose of smoking, the lower the quality of life): correlation coefficients between CCQ and cumulative doses were all

Table 1: Sociodemographic characteristics of the study population.

Characteristic	Healthy ($n = 978$)	COPD (reversible and irreversible) ($n = 284$)	Chronic bronchitis without COPD ($n = 326$)	Total* ($n = 1588$)
Region				
Beirut	57.4%	21.3%	21.3%	277
Mount Lebanon	67.2%	14.8%	17.9%	687
North Lebanon	67.3%	17.1%	15.6%	263
South Lebanon	55.6%	15.3%	29.1%	196
Bekaa plain	43.0%	29.1%	27.9%	165
Gender				
Male	58.9%	20.9%	20.2%	774
Female	64.2%	14.9%	20.9%	812
Age class				
40–44 years	79.4%	6.2%	14.3%	321
45–49 years	78.6%	9.0%	12.4%	266
50–54 years	70.0%	11.5%	18.5%	227
55–59 years	58.8%	16.1%	25.1%	199
60–64 years	48.2%	29.9%	21.8%	197
65 years and more	37.8%	32.5%	29.6%	378
Education				
Illiterate	50.5%	17.6%	31.9%	91
<8 years of school	46.9%	22.1%	31.0%	290
8−12 years of school	54.2%	24.5%	21.4%	323
12.1–15 years of school	61.3%	21.3%	17.4%	432
University studies	79.1%	7.3%	13.6%	441
Work status				
Currently working	71.5%	13.1%	15.4%	846
Retired	42.0%	31.2%	26.8%	231
Not finding a job	66.7%	20.0%	13.3%	15
Do never work	53.6%	19.8%	26.6%	496
Marital status				
Married	62.2%	17.5%	20.3%	1303
Single	64.1%	12.8%	23.1%	156
Widow or divorced	51.2%	28.1%	20.7%	121
Body Mass Index				
No obesity	62.7%	17.8%	19.5%	1261
Obesity	53.8%	20.2%	25.9%	247
Cardiac problem				
No	66.1%	16.2%	17.7%	1331
Yes	38.4%	26.4%	35.3%	258
Inhalation therapy				
No	66.6%	15.0%	18.4%	1477
Yes	0	52.9%	47.1%	111
Current smoking				
Never smokers	84.1%	4.5%	11.4%	552
Cigarette smokers	45.3%	24.6%	30.1%	479
Waterpipe smokers	83.7%	4.8%	11.5%	104
Mixed smokers	50.6%	27.2%	22.2%	81

Table 1: Continued.

Characteristic	Healthy ($n = 978$)	COPD (reversible and irreversible) ($n = 284$)	Chronic bronchitis without COPD ($n = 326$)	Total* ($n = 1588$)
Previous smokers				
Never smokers	84.1%	4.5%	11.4%	552
Cigarette smokers	46.8%	26.9%	26.3%	308
Waterpipe smokers	65.5%	34.5%	0	55
Mixed smokers	30.0%	42.9%	27.1%	70

* All P values were <0.001.

Table 2: Factorial analysis of the Clinical COPD Questionnaire.

Items	Factor loading	Factors correlation*	Correlation with FEV1/FVC*
Factor 1**		Factor 1	−0.436
Had dyspnea at rest	0.480	0.771	−0.356
Had dyspnea on effort	0.607	0.876	−0.422
Was unable to do strenuous effort such as going up stairs	0.701	0.871	−0.451
Was unable to do moderate effort such as walking	0.776	0.896	−0.430
Was anxious about breathing difficulties or getting a cold	0.671	0.786	−0.340
Was depressed because of respiratory problems	0.715	0.733	−0.227
Was unable to socialize (talking, visiting, ...)	0.949	0.767	−0.291
Was unable to do daily activities/dressing ...	0.925	0.819	−0.313
Factor 2**		Factor 2	−0.442
Had sputum production	0.980	0.959	−0.414
Had cough	0.937	0.956	−0.439
Total scale			−0.464

* All correlations were significant ($P < 0.001$); factor 1 correlation with CCQ was 0.980; factor 2 correlation with CCQ was 0.829; **Cronbach's alpha = 0.910 for the full scale, 0.909 for factor 1 and 0.859 for factor 2; factor 1 correlation coefficient with factor 2 was 0.700.

positive ($P < 0.001$); CCQ means differed for previous and current cigarette smoking, for previous and current waterpipe smoking, and for current cigarette and waterpipe dependence classes ($P < 0.001$). Again, similar results are found for COPD and chronic bronchitis patients (Table 5).

3.6. Predictors of Quality of Life. Predictors of respiratory quality of life, measured by CCQ, are presented in Table 6, by decreasing order of importance: cumulative cigarette dose, older age, having at least one smoker in the family, lower education, female gender, any heart disease, heating house by diesel, cumulative waterpipe dose, heating house by hot air, and having at least one smoker at work were significant predictors of a lower respiratory quality of life (higher CCQ score; $P < 0.05$ for all); ever living close to a local power plant (electricity generator) was important but its effect did not reach statistical significance ($P < 0.10$) (Table 6).

In COPD individuals, by decreasing order of importance, CCQ was significantly affected by cumulative cigarette dose, declared inhalation therapy, female gender, lower education, having at least one smoker in the family, older age, cumulative waterpipe dose, having a cardiac problem, not heating home centrally, and COPD severity grading (Table 6).

Finally, we present in a multivariate analysis the predictors of quality of life in never smokers, by decreasing order of importance. We found that lower education, having a cardiac problem, heating home by hot air, older age, heating its house by diesel, ever living close to a heavy traffic road (<100 m), and occupational exposure to toxic fumes were all significantly associated with a lower quality of life; having at least one smoker in the family was important but their effect did not reach statistical significance ($P \leq 0.10$) (Table 6).

In the study sample (healthy, COPD and chronic bronchitis individuals), cumulative dosing of cigarettes ($r = 0.404$; $P < 0.001$) and cumulative dosing of waterpipe ($r = 0.078$; $P < 0.001$) were both significantly correlated with CCQ score. In the COPD and chronic bronchitis subgroup, these values were, respectively: $r = 0.263$ ($P < 0.001$) and $r = 0.103$ ($P = 0.003$).

4. Discussion

In this study, we were able to describe the quality of life of Lebanese residents aged 40 years and more. The CCQ demonstrated excellent psychometric properties, with an excellent adequacy to a cross-sectional sample and high consistency. As expected, the respiratory related quality of life of COPD patients was decreased relative to healthy individuals; in addition, patients with chronic bronchitis without COPD and reversible COPD disorders also demonstrated a lower quality of life versus healthy individuals. These results have already been found by others: Weatherall and collaborators'

Table 3: Respiratory-related quality of life (CCQ[1]) scores.

Categories	Number	Score mean	Score standard deviation
Respiratory diseases			
Healthy	978	0.31	0.60
COPD[2]	233	2.45	1.50
Chronic bronchitis	326	2.12	1.61
Reversible COPD[2]	51	2.06	1.76
Total	1588	1.05	1.44
P value for ANOVA[3]	<0.001		
COPD grades[4]			
Grade 1 (FEV1 $\geq$ 0.8)	37	2.48	1.39
Grade 2 (0.5 $\leq$ FEV1 < 0.8)	124	2.44	1.49
Grade 3 (0.3 $\leq$ FEV1 < 0.5)	43	3.03	1.55
Grade 4 (FEV1 < 0.3)	8	3.63	1.68
P value for ANOVA	<0.001		
Individuals with all COPD[5]			
Taking inhalation therapy	63	3.00	1.48
Not taking inhalation therapy	221	2.21	1.53
P value for ANOVA	<0.001		
Individuals with chronic bronchitis			
Taking inhalation therapy	56	3.42	1.60
Not taking inhalation therapy	270	1.85	1.48
P value for ANOVA	<0.001		
MRC dyspnea scale[6]			
MRC = 0	999	0.33	0.67
MRC > 0	589	2.27	1.57
P value for ANOVA	<0.001		

[1] CCQ: Clinical COPD Questionnaire; [2] COPD: Chronic Obstructive Pulmonary Disease according to GOLD and LLN5% definitions; [3]For CCQ, healthy individuals significantly differed from all disease categories ($P < 0.001$); COPD, chronic bronchitis and reversible COPD disorders did not differ significantly ($P > 0.05$); [4]COPD classification according to GOLD guidelines; [5]Patients with reversible and irreversible COPD; [6] MRC: Medical Research Council scale for dyspnea.

Table 4: Quality of life, obstructive diseases, and smoking types.

Score	Total sample		COPD and Chronic bronchitis subgroup	
Smoking type	Number	Mean (Standard deviation)	Number	Mean (Standard deviation)
Previous smoking				
Never	553	0.45 (0.89)	268	1.33 (1.43)
Cigarette	309	1.56 (1.65)	306	2.15 (1.60)
Waterpipe	55	1.24 (1.41)	33	2.22 (1.40)
Mixed smoking	69	2.21 (1.73)	58	2.95 (1.35)
P value ANOVA/Kruskal-Wallis		<0.001*		<0.001†
Current smoking				
Never	553	0.45 (0.89)	268	1.33 (1.43)
Cigarette	479	1.37 (1.52)	513	1.82 (1.49)
Waterpipe	104	0.44 (1.00)	45	1.18 (1.47)
Mixed smoking	80	1.27 (1.55)	51	1.99 (1.57)
P value ANOVA/Kruskal-Wallis		<0.001**		<0.001**

* No significant difference between cigarette and waterpipe; significant difference between any smoking type and mixed smoking ($P \leq 0.001$); no significant difference between cigarette and waterpipe smokers; **No significant difference between never smokers and waterpipe smokers; no significant difference between cigarette and mixed smokers; † any previous smoker had significantly lower CCQ versus never smokers; mixed smokers had significantly higher values than cigarette and never smokers.

Table 5: Quality of life and smoking doses relationship.

Score/smoking type	Number	All sample	*P* value ANOVA	Number	COPD and chronic bronchitis subgroup	*P* value ANOVA	Correlation coefficient
Previous cigarette smoking							
Never smokers	558	0.45 (0.88)		267	1.33 (1.44)		
1–18 pack-years	94	0.99 (1.39)	<0.001	74	1.65 (1.45)	<0.001¶	0.332‡
18.1–56 pack-years	139	1.42 (1.58)		135	2.06 (1.57)		
>56 pack-years	120	2.71 (1.59)		144	2.84 (1.48)		
Previous waterpipe smoking							
Never smokers	558	0.45 (0.88)		270	1.32 (1.43)		
0.1–29.9 waterpipe-years	42	1.29 (1.54)	<0.001	26	2.44 (1.36)	<0.001¶	0.126‡
30+ waterpipe-years	67	2.36 (1.69)		59	3.02 (1.28)		
Current cigarette smoking							
Never smokers	617	0.51 (0.93)		343	1.30 (1.40)		
1–18 pack-years	139	0.61 (0.92)	<0.001†	92	1.02 (1.08)	<0.001*	0.307‡
18.1–45 pack-years	163	1.28 (1.49)		159	1.88 (1.40)		
45+ pack-years	274	2.18 (1.69)		215	2.42 (1.59)		
Current waterpipe smoking							
Never smokers	574	0.45 (0.88)	<0.001†	281	1.30 (1.42)	0.001*	0.203‡
0.1–20 waterpipe-years	66	0.32 (0.76)		19	0.96 (1.16)		
20+ waterpipe-years	86	1.35 (1.65)		58	2.08 (1.69)		
Current cigarette dependence							
Fagerström 0–5 Low dependence	1259	0.89 (1.35)	<0.001*	833	1.74 (1.56)	<0.001*	0.256‡
Fagerström 6-7 Moderate dependence	116	1.39 (1.48)		128	1.93 (1.39)		
Fagerström 8–10 High dependence	108	2.43 (1.65)		149	2.43 (1.56)		
Current waterpipe dependence							
LWDS-11 0–9 Low dependence	74	0.36 (0.66)	<0.001*	33	0.86 (0.87)	<0.001*	0.435‡
LWDS-11 10–16 Moderate dependence	40	0.63 (1.06)		21	1.64 (1.39)		
LWDS-11 17+ High dependence	59	1.52 (1.76)		35	2.46 (1.75)		

† No significant difference between never and low-level smokers; * no significant difference between low and moderate dependence; ¶ no significant difference between low and moderate smoking level ‡ $P < 0.001$ for correlation coefficients.

work for COPD [20], and Maleki-Yazdi and collaborators' [21] for chronic bronchitis are some examples.

There was also significantly lower quality of life in previous and current smokers in the same disease category versus nonsmokers; one exception is for current smokers of waterpipe. This could be explained with the fact that waterpipe smoking in Lebanon is a relatively new trend, with the majority of waterpipe smokers having a low duration of smoking. However, a dose-effect relationship was clear for the effect of all types of smoking on QOL, with lower quality of life scores in patients with heavier smoking cumulative doses; this result was even found for current waterpipe smokers. Smokers had a decreased respiratory quality of life versus nonsmokers, independently of their respiratory disease. The association of cigarette smoking with lower quality of life has been found by Kotz and collaborators using the CCQ [12], and by Geijer and collaborators, where smoking induced limitations of physical functioning [22]; it was also indirectly shown by Papadopoulos and collaborators, with smoking cessation improving quality of life [23]. For waterpipe, this association seems of lower magnitude; nevertheless, it has been demonstrated by Tavafian and collaborators using the SF-36 [24].

The relationship between other factors and lower quality of life was also confirmed in COPD individuals: besides cumulative smoking of cigarette and of waterpipe that was previously discussed, several indoor and outdoor environmental factors, age, gender, and lower education were found to be independent predictors of a lower quality of life, after adjusting for COPD severity grades. In fact, it has been shown that persons who have similar reductions in forced expiratory volume in 1st second and exercise capacity and similar levels of dyspnea have a wide range of HRQL, suggesting that other variables contributed to quality of life, such as age and gender [25].

In never smokers, older age, lower education, having a cardiac problem, heating its house by hot air or by diesel, occupational exposure to toxic fumes, ever living close to a heavy traffic road, and having at least one smoker in the family were all associated with a lower respiratory quality of life. We had already showed that these factors were

Table 6: Predictors of lower respiratory quality of life (CCQ).

Factor	Beta	*P* value	Standardized beta	Partial correlation
In all individuals (healthy, COPD and chronic bronchitis)*				
Cumulative cigarette smoking (pack∗years)	0.001	<0.001	0.399	0.404
Older age	0.021	<0.001	0.168	0.155
At least one smoker in the family	0.328	<0.001	0.111	0.129
Lower education	0.126	<0.001	0.108	0.117
Female gender	0.273	<0.001	0.095	0.090
Any heart disease	0.301	<0.001	0.077	0.089
Heating house by diesel	0.205	0.003	0.062	0.083
Cumulative waterpipe smoking (waterpipe∗years)	0.002	<0.001	0.064	0.078
Heating house by hot air	0.281	0.008	0.055	0.066
At least one smoker at work	0.166	0.048	0.044	0.051
Ever lived close to a local power plant	0.11	0.094	0.035	0.048
In all COPD individuals¶				
Cumulative cigarette smoking (pack∗years)	0.001	<0.001	0.260	0.263
Inhalation therapy	0.802	<0.001	0.198	0.219
Female gender	0.371	0.002	0.116	0.123
Lower education level	0.165	0.002	0.125	0.123
At least one smoker in the family	0.380	0.003	0.107	0.117
Older age	0.016	0.008	0.115	0.105
Cumulative waterpipe smoking (waterpipe∗years)	0.002	0.003	0.103	0.103
Having a cardiac problem	0.285	0.031	0.08	0.086
Not heating home by central heating	0.315	0.046	0.071	0.080
COPD severity grading	0.097	0.085	0.065	0.069
In nonsmokers†				
Lower educational level	0.256	<0.001	0.318	0.272
Any cardiac problem	0.622	<0.001	0.202	0.217
Heating house by hot air	0.433	0.001	0.111	0.123
Older age	0.010	0.011	0.106	0.094
Heating house by diesel	0.201	0.018	0.08	0.089
Ever lived close to a heavy traffic road (<100 m)	0.215	0.024	0.097	0.084
Occupational exposure to toxic fumes	0.214	0.032	0.072	0.080
At least one smoker in the family	0.106	0.103	0.047	0.059

*$R = 0.590$ and $R^2 = 0.348$ for the model; factors not retained in the model include heating house by butane gas, wood, and central heating, cooking on gas, being occupationally exposed to toxics and ever living close to a heavy traffic road ($P > 0.05$); ¶$R = 0.500$ and $R^2 = 0.250$ for the model; factors not included in the model include ever living close to a heavy traffic road, heating house by hot air, by wood, diesel, being occupationally exposed to toxics, ever living close to a power plant, and at least one smoker at work ($P > 0.05$).†$R = 0.492$ and $R^2 = 0.242$ for the model; factors not included in the model include gender, ever living close to a power plant, at least one smoker at work, heating its house by butane gas, wood, central heating, and cooking on gas ($P > 0.05$).

independently associated with chronic bronchitis [26] and COPD [2]; this may explain their association with lower respiratory quality of life.

One noticeable result is the lower quality of life in individuals declaring being treated with inhalation therapy; one explanation could be the fact that patients who are more symptomatic in general are the ones who go and seek a physician's help. In fact, in our study, patients with COPD and chronic bronchitis who admitted being treated by inhaled therapy also declared having more chronic cough, expectorations, and wheezing than those without therapy; they also had more severe disease staging (results not shown). This issue may further be explained by the delay in diagnosis and treatment of individuals, the noncompliance to treatment of some individuals, and the irreversible nature of the disease. Additional studies are necessary to clarify this point.

Despite excellent results in this epidemiological setting, the value of the CCQ scale to evaluate the respiratory quality of life in the Lebanese population should additionally be tested in clinical settings. Moreover, we suggest a comparison of performance with the CAT scale that was shown to be superior to CCQ as a tool for monitoring the impact of symptom variability on the lives of patients with COPD [5]. Other limitations of our work include a possibility of selection bias, and information bias coupled with the used questionnaire. However, the demonstrated dose-effect relationship and the multivariate analyses are considered strong points of this work. Nevertheless, given this data was collected from a Lebanese population, predictive factors

native to the Mediterranean region such as smoking a waterpipe may not be generalized to the general worldwide population.

5. Conclusions

In conclusion, we were able to describe the respiratory quality of life of Lebanese residents aged 40 years or more, using a valid tool. We found a lower quality of life in smokers versus nonsmokers, even in the same respiratory disease category and severity grade. A dose-effect relationship was also shown with lower quality of life with higher severity of the disease and higher cumulative smoking. This issue should be further emphasized during patients' education and smoking cessation.

Abbreviations

ANOVA: Analysis of variance
CAT: COPD assessment test
CCQ: Clinical COPD Questionnaire
COPD: Chronic obstructive pulmonary disease
GOLD: Global initiative for obstructive lung disease
MRS: Miscellaneous respiratory symptoms
OR: Odds ratio.

Authors' Contribution

S. Joseph has been involved in drafting the paper and data interpretation. K. Georges contributed to conception and interpretation of data. S. Pascale was involved in the study conception and design, data collection, and data analysis. W. Mirna was involved in study conception, manuscript correction and gave the final approval of the version to be published. All authors read and approved the final paper.

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Review Article

Pulmonary Hypertension Secondary to COPD

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The development of pulmonary hypertension in COPD adversely affects survival and exercise capacity and is associated with an increased risk of severe acute exacerbations. Unfortunately not all patients with COPD who meet criteria for long term oxygen therapy benefit from it. Even in those who benefit from long term oxygen therapy, such therapy may reverse the elevated pulmonary artery pressure but cannot normalize it. Moreover, the recent discovery of the key roles of endothelial dysfunction and inflammation in the pathogenesis of PH provides the rationale for considering specific pulmonary vasodilators that also possess antiproliferative properties and statins.

1. Introduction

Pulmonary hypertension (PH) secondary to chronic obstructive pulmonary disease (COPD) is placed in group 3 of the WHO classification of PH, that is, PH associated with lung diseases and/or hypoxemia (Table 1) [1]. PH in COPD has been variably defined as resting mean pulmonary artery pressure (mPAP) > 20–25 mm Hg. PH in COPD adversely affects survival and exercise capacity and is associated with an increased risk of acute exacerbations. Recent studies have shown that endothelial dysfunction and systemic inflammation also play important roles in the pathogenesis of PH. The recent development of specific pulmonary vasodilators with antiproliferative properties has stimulated an immense interest in studying such drugs in PH secondary to COPD.

2. Prevlence of PH in COPD

The prevalence of PH in stable COPD varies from 20 to 91% depending on the definition of PH (mPAP > 20 versus >25 mm Hg), the severity of COPD (forced expiratory volume in the first second: FEV1), and the method of measuring the pulmonary artery pressure (echocardiography versus right heart catheterization) [2–7].

In severe COPD patients with or without resting PH, steady-state exercise may raise pulmonary artery pressure (PAP) to about twice the level of its resting value [8]. In severe COPD activities of daily living such as climbing stairs or walking can induce transient PH.

In patients with severe COPD, oxygen saturation may fall during REM sleep by 20–30% [9, 10] and PAP may rise by as much as 20 mm Hg [11].

During an acute exacerbation of COPD, PAP may rise by as much as 20 mm Hg and return to its baseline after recovery [12, 13].

3. Significance of PH in COPD

In the era before the widespread availability of long-term oxygen therapy (LTOT) it was well known that the presence of PH was associated with poor prognosis in COPD. However, even on LTOT the best prognostic factor is not the FEV1, nor the degree of hypoxemia or hypercapnia, but the level of mPAP. The 5-year survival rate is only 36% in patients with initial mPAP > 25 mm Hg compared to 62% in those with initial mPAP ≤ 25 mm Hg [14]. Moreover, Weitzenblum et al. [15], who followed up hypoxemic COPD patients with PH on LTOT for a period of 6 years, demonstrated a reversal but not normalization of the PAP. Recently, Zieliński et al. [16] also reported similar findings in a larger study.

PH is also an independent predictor of exercise capacity. Sims et al. [17] found that in 362 severe COPD patients

Table 1: Updated clinical classification of pulmonary hypertension (Dana Point, 2008) [1].

(1) Pulmonary arterial hypertension (PAH)
(1.1) Idiopathic PAH
(1.2) Heritable
(1.2.1) BMPR2
(1.2.2) ALK1, endoglin (with or without hereditary hemorrhagic telangiectasia)
(1.2.3) Unknown
(1.3) Drug- and toxin-induced
(1.4) Associated with
(1.4.1) Connective tissue diseases
(1.4.2) HIV infection
(1.4.3) Portal hypertension
(1.4.4) Congenital heart disease
(1.4.5) Schistosomiasis
(1.4.6) Chronic hemolytic anemia
(1.5) Persistent pulmonary hypertension of the newborn
(i) Pulmonary venoocclusive disease (PVOD) and/or pulmonary capillary hemangiomatosis (PCH)
(2) Pulmonary hypertension owing to left-heart disease
(2.1) Systolic dysfunction
(2.2) Diastolic dysfunction
(2.3) Valvular disease
(3) Pulmonary hypertension owing to lung disease and/or hypoxia
(3.1) Chronic obstructive pulmonary disease (COPD)
(3.2) Interstitial lung disease
(3.3) Other pulmonary diseases with mixed restrictive and obstructive pattern
(3.4) Sleep-disordered breathing
(3.5) Alveolar hypoventilation disorders
(3.6) Chronic exposure to high altitude
(3.7) Developmental abnormalities
(4) Chronic thromboembolic pulmonary hypertension (CTEPH)
(5) Pulmonary hypertension with unclear multifactorial mechanisms
(5.1) Hematologic disorders: myeloproliferative disorders, splenectomy
(5.2) Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis
(5.3) Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
(5.4) Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure on dialysis

Simonneau [1].

who underwent right-heart catheterization (RHC) as part of evaluation for lung transplantation, higher pulmonary artery pressures were associated with shorter 6-minute walk distance (6MWD) even after controlling for demographics, anthropomorphics, severity of airflow obstruction, and pulmonary artery wedge pressure (PAWP). They found an 11 m decline in 6MWD for every 5 mm rise in mPAP (95% CI 21, 0.7; $P = 0.04$). In another study Cuttica et al. [7] reviewed the records of 1154 COPD patients listed for lung transplantation and found an association between mPAP and 6MWD independent of lung function and PAWP ($\beta = -1.33$; $P = 0.01$).

Lastly, it has been shown that a mPAP > 18 mm Hg is associated with an increased risk of severe acute exacerbation in patients with moderate to severe COPD [18].

4. Pathophysiology of PH Secondary to COPD

In hemodynamic terms PAP depends upon cardiac output (CO), pulmonary vascular resistance (PVR), and pulmonary artery wedge pressure (PAWP) (Figure 1). Resting PH in COPD results predominantly from an elevated PVR whereas PH during exercise results predominantly from an increase in CO in the face of a relatively "fixed" PVR, that is, there is reduced recruitability and distensibility of pulmonary vessels [19]. Hyperinflation increases PVR [20] as well as PAWP [20, 21] and PAP [20], particularly during exercise.

Traditionally, elevated PVR in COPD has been considered to be the consequence of hypoxic pulmonary vasoconstriction and vascular remodeling, destruction of the pulmonary vascular bed by emphysema, polycythemia, and hyperinflation. Recently, it has been recognized that endothelial dysfunction and systemic inflammation also play key roles in the pathogenesis of PH (Figure 2). In fact it is believed that the initial event in the natural history of PH in COPD could be endothelial dysfunction caused by cigarette smoke [22].

4.1. Pulmonary Vasoconstriction. Hypoxic constriction of the small muscular pulmonary arteries [23] is a protective mechanism to divert blood flow from hypoxic alveoli to

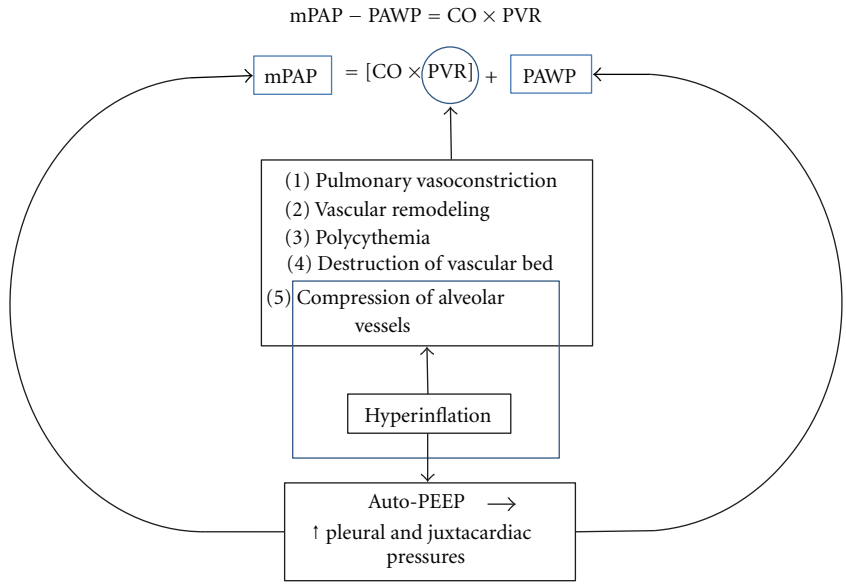

Figure 1: Pathophysiology of PH in COPD. mPAP: mean pulmonary artery pressure, PAWP: pulmonary artery wedge pressure, CO: cardiac output, PVR: pulmonary vascular resistance, PEEP: positive end-expiratory pressure.

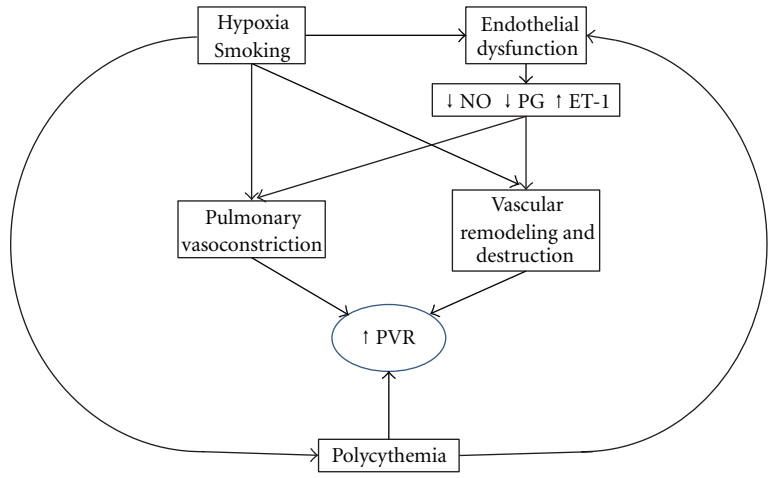

Figure 2: Pathophysiology of elevated PVR in COPD. PVR: pulmonary vascular resistance, NO: nitric oxide, PG: prostaglandin, ET-1: endothelin-1.

better ventilated alveoli and reduce ventilation-perfusion mismatch [24]. However, when alveolar hypoxia is diffuse, such as in severe COPD, it causes generalized pulmonary vasoconstriction and consequently raises the PVR. Persistent hypoxia leads to pulmonary vascular remodeling [25] which contributes to the PVR.

4.2. Pulmonary Vascular Remodeling. Vascular remodeling in COPD patients is seen at all stages of the disease and is characterized by intimal fibrosis and proliferation of longitudinal smooth muscle in the muscular pulmonary arteries and arterioles, and neomuscularization of pulmonary arterioles [26–28]. These pulmonary vascular changes also occur in patients with mild COPD and no hypoxia and in smokers with no airway obstruction. This suggests that mechanisms other than hypoxia also play an important role in the pathogenesis of vascular remodeling [29].

However, pathologic studies in COPD have not shown complex lesions, which are frequently encountered in patients with pulmonary arterial hypertension [30], such as plexiform lesions (irregular mass of endothelial cells) or angiomatoid lesions, characteristic of severe PH.

4.3. Endothelial Dysfunction. The normal endothelium plays an important role in modulating pulmonary vasomotor tone and cellular proliferation. Nitric oxide (NO) produced by endothelial NO synthase (eNOS) has vasodilator and antiproliferative properties. Prostacyclin produced by the activity

of prostacyclin synthase is another vasodilator that also protects against vascular remodeling. Countering vasodilatation is endothelium-derived endothelin-1 (ET-1). Endothelial dysfunction caused by smoking, products of inflammation, hypoxia, and shear stress results in altered production of these mediators of tone and/or proliferation, and consequently pulmonary vasoconstriction and vascular remodeling with the latter perpetuating endothelial dysfunction and creating a vicious cycle. In patients with COPD and PH there is a reduction in the synthesis and/or release of NO from the lung [31]. In COPD there is a reduction in the expression of prostacyclin synthase mRNA [32], and in patients with secondary pulmonary hypertension there is an excessive expression of endothelin-1 (ET-1) [33]. Arterial ET-1 also increases shortly after episodes of nocturnal oxygen desaturation in patients with COPD and remains higher during the day in these subjects [34].

4.4. Inflammation. Cigarette smoking induces a CD8+ T-lymphocyte infiltration of the adventitia of muscular pulmonary arteries, which correlates with both the endothelium-dependent relaxation and the intimal thickness, suggesting the potential involvement of an inflammatory process in the pathogenesis of pulmonary vascular abnormalities in the early stage of COPD [35].

Systemic inflammation is a known component of COPD [36, 37] and inflammation may contribute to the pathogenesis of PH. Chaouat et al. [38] showed that elevated circulating levels of the proinflammatory cytokine interleukin-6 (IL-6) directly correlated with elevations in mPAP ($r = 0.39$; $P < 0.001$). Moreover, C-reactive protein levels have also been shown to correlate with both PAP and levels of ET-1 [39].

4.5. Destruction of the Pulmonary Vascular Bed. Destruction of the pulmonary vascular bed by emphysema reduces the total cross-sectional area of the pulmonary circulation and increases the total PVR when the remaining capacitance vessels are abnormal and unable to accommodate the increased diverted pulmonary blood flow at rest and the increased CO during exercise.

A hypercoagulable state has also been described in patients with COPD [40, 41]. There appears to be an increased frequency of deep venous thrombosis and pulmonary embolism in acute exacerbations of COPD [41–43] and histopathologically thrombotic lesions have been detected in lung tissue from patients with severe emphysema undergoing lung-volume reduction surgery [44]. It is postulated that the inflammatory aspects of the so-called COPD exacerbation may trigger a hypercoagulable state and increase the risk of thrombosis including *in situ* thrombosis.

4.6. Polycythemia. Polycythemia not only increases the viscosity of blood and the resistance to blood flow through the pulmonary circulation [45] but also augments hypoxic pulmonary vasoconstriction by causing a local deficiency of NO which may be related to the excessive removal of NO from the pulmonary circulation by the large amount of hemoglobin [46, 47].

4.7. Genetic Factors. The pulmonary vascular response to hypoxia is genetically determined. Serotonin (5-hydroxytryptamine, 5-HT) and its transporter (5-HTT) play a role in pulmonary artery smooth muscle cell (PASMC) proliferation and vascular remodeling. The severity of PH in hypoxic COPD patients depends upon 5-HTT gene polymorphism. PH is most severe in patients carrying the LL genotype, which is associated with higher levels of 5-HTT expression in PASMCs [48]. ACE is present in very high concentrations in the lungs and its activity is further increased by hypoxia [49]. ACE is a vasoconstrictor and mediator of PASMC proliferation. The ACE DD genotype is associated with increased circulating and tissue concentrations of ACE. Moreover, the ACE DD genotype is associated with exaggerated PH during exercise in COPD patients [50].

4.8. Hyperinflation. Severe emphysema with air-trapping and hyperinflation is associated with intrinsic positive end-expiratory pressure of 5–7.5 cm H_2O [51]. The positive alveolar pressure throughout respiration contributes to the high PVR [20] as well as increases both PAWP [20, 21] and PAP [20]. This mechanism may assume a more important role in development of PH during exercise and in patients with severe emphysema who are not hypoxemic.

5. Right and Left Ventricular Function in PH Secondary to COPD

In response to the increased PVR the right ventricle (RV) gradually undergoes hypertrophy and dilatation-cor pulmonale. This increase in RV end-diastolic volume (RVEDV), that is, preload, to maintain a normal stroke volume (SV) accounts for the reduced RV ejection fraction (EF). RV contractility, as assessed by end systolic pressure-volume relation, is normal in stable COPD patients and the RV operates on an extension of the normal RV function Frank-Starling curve [52].

Changes in RV SV must invariably alter left ventricular (LV) preload, because the two ventricles are serially linked through the pulmonary vasculature. LV preload can also be directly altered by changes in RVEDV by the mechanism of ventricular interdependence. The increased RVEDV in cor pulmonale induces a shift of the interventricular septum into the LV and decreases LV diastolic compliance but this does not adversely affect LV SV because the increased RV systolic pressure in cor pulmonale also pushes the septum into the LV towards its free wall to empty the LV. This "help" from the RV in systole tends to preserve LVEF in emphysematous patients with severe RV hypertrophy [53, 54].

More importantly, hyperinflation, particularly during exercise, has the effect of compressing the two ventricles into each other [55, 56]. This decreases RV preload and results in lower SV and CO. Even in less severe COPD the development of hyperinflation during exercise can similarly lead to a reduction in RV preload and CO.

During an acute exacerbation of COPD, the RV may actually fail, that is, end-diastolic pressure and volume rise and RVEF falls, resulting in peripheral edema and systemic

congestion [57, 58]. However, these changes may not be associated with a rise in PAP suggesting that other factors may be operating to reduce RV contractility [57]. Moreover, an acute exacerbation may be associated with peripheral edema in the absence of RV failure [58].

The pathogenesis of edema formation in COPD is complex. Renal blood flow is reduced, the renin-angiotensin system is activated, renal dopamine output is reduced, and plasma ANP level is elevated leading to increase in proximal renal tubular sodium reabsorption [59, 60]. Sodium retention is enhanced by hypercapnia and ameliorated by long-term oxygen therapy in hypoxemic patients [61]. True right heart failure is characterized by raised jugular venous pressures, congestive hepatomegaly, and peripheral edema.

6. Degree of PH in COPD

Resting PH in stable COPD is usually mild to moderate (mPAP 20–35 mm Hg) and is usually not seen until the disease is advanced (FEV1 < 50%). Severe PH (mPAP > 35–45 mm Hg) is rare (3%–13%) [5–7, 62] and should prompt a search for an additional cause of PH, for example, left heart disease, obstructive sleep apnea (OSA), pulmonary embolism (PE).

6.1. Severe "Disproportionate" PH. Recently a group of patients with severe PH (mPAP > 40 mm Hg) and extremely poor prognosis has been recognized. The 5-year survival is 15% versus 55% in those with less severe PH (mPAP 20–40 mm Hg) [62]. Such patients are characterized by mild to moderate airway obstruction, a very low diffusing capacity, severe hypoxemia, and hypocapnia (Table 2) [62]. Thabut et al. [6] have also described a similar group (mPAP > 45 mm Hg). However, such severe PH in COPD in the absence of an alternative explanation is rare (1–3.7%) [6, 62] and suggests the existence of a "vascular phenotype" or concomitant idiopathic pulmonary arterial hypertension.

7. Diagnosis of PH in COPD

PH secondary to COPD should be suspected in patients with progressive dyspnea on exertion with stable airway obstruction or in patients with mild to moderate airway obstruction with a very low diffusing capacity, severe hypoxemia, and hypocapnia [6, 62].

A diagnosis of PH in COPD (Table 3) should prompt a search for other causes of PH, particularly left heart dysfunction, OSA, and PE before attributing the PH to COPD.

7.1. Clinical Features. The clinical exam lacks sensitivity and specificity. Hyperinflation reduces the yield of cardiac auscultation for the classic signs of PH and right heart failure, that is, loud P2, S3 gallop, the systolic murmur of tricuspid regurgitation. Peripheral edema can be present in the absence of right heart failure in COPD and is not diagnostic of right heart failure.

7.2. CPET. Although cardiopulmonary exercise test (CPET) characteristics show a large overlap in COPD patients with and without PH, the existence of PH in COPD (defined as mPAP > 25 mm Hg) is associated with a significantly reduced ventilatory efficiency during CPET. However, a low SpO_2 at rest and a further decrease during exercise similarly suggest the presence of PH in COPD [63].

7.3. Chest X-Ray. An increase in the diameter of the right descending pulmonary artery to >16 mm on the PA projection, combined with an increase in the diameter of the left descending pulmonary artery of >18 mm on the left lateral projection, has a sensitivity 98% for identifying PH [64].

7.4. ECG. Electrocardiographic criteria for the detection of RV hypertrophy have good specificity, but the sensitivity for RV hypertrophy is only 25 to 40%. The criteria include the following: (a) right axis deviation (>100 degrees without right bundle branch block), (b) R or R′ > S in V1, (c) R < S in V6, (d) R in V1 + S in V5 or V6 = 10 mm, (e) R in V1 = 7 mm, (f) R in V1 = 15 mm with right bundle branch block, and (g) right atrial enlargement [52].

However, ECG may reveal other findings such as left atrial enlargement (LAE), left ventricular hypertrophy (LVH), or myocardial infarction in the past that suggests an alternative cause of PH.

The presence of S1 Q3 T3 (S wave in lead I, Q wave in lead III, and T wave inversion in lead III on ECG—S1, Q3, T3) or right atrial overload pattern (i.e., P wave axis of +90 degrees or more) implies a poor prognosis [65].

7.5. ECHO. Hyperinflation precludes optimal visualization of the heart. In a cohort of lung transplant candidates estimation of systolic PAP (sPAP) was possible in only 38% of the 253 patients with COPD. Hyperinflation with a residual volume >150% lessened the likelihood of sPAP estimation. Sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) of sPAP estimated by ECHO for the diagnosis of PH (defined as sPAP >45 mm Hg estimated by ECHO or measured by RHC) were 76, 65, 93, and 32%, respectively. In the absence of sPAP estimation, figures for RV abnormalities were 84, 56, 96, and 22% respectively. It is important to realize that there was a discordance of >10 mm Hg between estimated and measured sPAP in 52% of patients, and in 28%, the discordance was >20 mm Hg [66]. Although the NPV of ECHO is high enough to exclude PH when the heart is adequately visualized, the presence of a high sPAP or RV abnormalities requires confirmation by RHC unless the ECHO shows left heart disease, for example, low LVEF, high LV filling pressure, LVH, left atrial enlargement, valvular incompetence.

Alternatively, transcutaneous Doppler US can be used to measure jugular vein flow velocity. Matsuyama et al. [67] showed that the ratio of diastolic flow (Df) to systemic flow (Sf) velocity showed a significant correlation with mPAP in COPD patients ($r = 0.844$, $P < 0.0001$). The sensitivity was 71.4%, and the specificity 95.3% (cut-off ratio = 1.0). Jugular venous Doppler US could be performed in all patients while other cardiac echo methods could not be performed in all patients. The specificity of the methods used was higher than other cardiac echo methods [67].

Table 2: Comparison of 2 groups of COPD patients with PH.

	Severe PH Group (mPAP ≥ 40 mm Hg) $N = 11$	Less severe PH (mPAP 20–40 mm Hg) $N = 16$	P value
FEV1 (% predicted)	50 (44–56)	27 (23–34)	<0.01
DLCO (mL/min/mm Hg)	4.6 (4.2–6.7)	10.3 (8.9–12.8)	<0.01
PaO_2 (mm Hg)	46 (41–53)	56 (54–64)	<0.01
$PaCO_2$ (mm Hg)	32 (28–37)	47 (44–49)	<0.01
RAP (mm Hg)	7 (5–9)	3 (1.3–4)	<0.01
mPAP (mm Hg)	48 (46–50)	25 (22–27)	<0.01
PAWP (mm Hg)	6 (4–7)	7 (6.5-7.5)	NS
CI (L/min/m^2)	2.3 (1.8–2.5)	2.8 (2.4–3.1)	<0.01
TPR (Wood units/m^2)	21.3 (17.6–26.6)	9 (7.4–9.9)	<0.01

Table adapted from [63].
PH: pulmonary hypertension, FEV1: forced expiratory volume in the first second, DLCO: diffusing capacity for carbon monoxide, PaO_2: arterial oxygen tension, $PaCO_2$: arterial carbon dioxide tension, RAP: right atrial pressure, mPAP: mean pulmonary artery pressure, CI: cardiac index, TPR: total pulmonary resistance.

Table 3: Various approaches to the diagnosis of PH in COPD.

Modality	Advantages	Disadvantages
ECG	Noninvasive, cheap, and readily available. High specificity for RVH. ECG may reveal other findings such LAE, LVH, or old MI that suggests an alternative cause of PH	Absence of RVH does not rule out PH.
CXR	Non-invasive, cheap, and readily available. An ↑ in the diameter of the right descending pulmonary artery to >16 mm on the PA projection, combined with an ↑ in the diameter of the left descending pulmonary artery of >18 mm on the left lateral projection, has a high sensitivity of 98% for PH	Normal-sized pulmonary artery does not rule out PH.
BNP	Requires only a blood draw, is cheap and readily available.	↑ BNP also correlated with lower PaO_2 suggesting that BNP can also be released in response to hypoxia. More studies are needed.
eNO	Non-invasive.	Expensive, not widely available and has been tested in only one study.
ECHO	High NPV of sPAP or RV abnormalities (93% and 96%, resp.) makes it an excellent screening test. Moreover, it provides additional data for example, LVEF, LV filling pressures, valvular function.	Hyperinflation may preclude optimal visualization of the heart. Although the NPV is high enough to exclude PH, the presence of a high sPAP or RV abnormalities requires confirmation by RHC.
Chest CT	Non-invasive, widely available. High PPV of 95%-96% for PH. LAE could suggest left heart dysfunction.	Expensive. Radiation exposure. Normal sized pulmonary artery does not rule out PH.
Cardiac MRI	Non-invasive, does not involve ionizing radiation, and is not affected by hyperinflation.	Expensive, not widely available and in some cases claustrophobia can be a problem.
RHC	"Gold standard" Confirms diagnosis. Determines severity. Distinguishes occult LV dysfunction from hyperinflation when PAWP is ↑. Measures CO and allows calculation of PVR. Determines responsiveness to O_2.	Invasive. Interpretation of pressures may be difficult when there are large respiratory swings.

PH: pulmonary hypertension, EKG: electrocardiography, RVH: right ventricular hypertrophy, LAE: left atrial enlargement, LVH: left ventricular hypertrophy, MI: myocardial infarction, CXR: chest X-ray, BNP: brain natriuretic peptide, PaO_2: arterial oxygen tension, eNO: exhaled nitric oxide, NPV: negative predictive value, ECHO: echocardiography, sPAP: systolic pulmonary artery pressure, RV: right ventricular, LVEF: left ventricular ejection fraction, LV: left ventricular, RHC: right heart catheterization, CT: computerized axial tomography, PPV: positive predictive value, MRI: magnetic resonance imaging, CO: cardiac output, PVR: pulmonary vascular resistance, PAWP: pulmonary artery wedge pressure, RAP: right atrial pressure, O_2: oxygen.

Table 4: Various approaches to the treatment of PH in COPD.

Counteract hyperinflation	Counteract pulmonary vasoconstriction	Counteract vascular remodeling	Counteract polycythemia
Bronchodilators	O_2	O_2	O_2
O_2	Pulmonary vasodilators	Pulmonary vasodilators	Phlebotomy
Sildenafil		Statins	ARB
LVRS (unless PH severe)			
	Lung transplantation		
	Smoking cessation		

PH: pulmonary hypertension, O_2: oxygen, LVRS: lung volume reduction surgery, ARB: angiotensin receptor blocker.

7.6. BNP. One study of 38 patients with stable COPD, 20 of whom had clinical cor pulmonale, found significant correlation between brain natriuretic peptide (BNP) and ECHO-estimated sPAP ($r = 0.68$, $P = 0.001$) [68]. Elevated BNP also correlated with lower PaO_2 suggesting that BNP can also be released in response to hypoxia.

7.7. Exhaled Nitric Oxide. Clini et al. [69] studied 34 consecutive patients with stable COPD and found that patients with PH (defined as ECHO-estimated sPAP of >35 mm Hg) showed lower values of exhaled nitric oxide compared to those without PH.

7.8. Cardiac MRI. This imaging technique produces excellent images of the RV and RV wall thickness shows a high correlation with the mean PAP ($r = 0.9$; $P < 0.001$) [70]. Moreover, it offers many advantages: it is non-invasive, does not involve radiation, and is not affected by hyperinflation. However, it is expensive, not widely available and in some cases claustrophobia can preclude its use.

7.9. Chest CT Scan. Enlargement of the main pulmonary artery to ≥29 mm in patients with parenchymal lung disease has been shown to have a sensitivity of 84%, specificity of 75%, PPV of 95%, and positive LR of 3.36 for predicting PH (defined as mPAP > 20 mm Hg) [71].

In another study the ratio of the pulmonary artery to aortic diameter >1 was 70% sensitive and 92% specific for PH (defined as mPAP > 20 mm Hg). The PPV was 96% and the NPV was 52% [72].

Moreover, an increased left atrial area on chest CT could suggest left heart dysfunction as a possible cause of PH [73].

7.10. Right Heart Catheterization. RHC remains the "gold standard" for making a diagnosis of PH, accurately determining its severity, and ruling out left heart disease, especially occult LV diastolic dysfunction. An elevated PAWP is not uncommon in severe COPD and does not necessarily imply LV dyfunction [5] as it may be secondary to hyperinflation [21]. Exercise during RHC can help distinguish the cause of an elevated PAWP in COPD. PAWP increases out of proportion to right atrial pressure (RAP) during exercise in comparison to hyperinflation where PAWP and RAP increase proportionately during exercise [74]. Moreover, RHC also measures CO and allows calculation of PVR. Lastly, RHC allows determination of responsiveness to O_2. However, the invasive nature of the procedure precludes its more widespread use.

Table 5: Various pulmonary vasodilators studied for the treatment of PH in COPD.

Inhaled	Systemically delivered	
	Nonspecific	Specific
O_2	CCB: nifedipine, felodipine	PDE5 I: sildenafil
NO	α-1 antagonist: prazosin	ETRA: bosentan
PG: iloprost	ACEI: captopril	

PH: pulmonary hypertension, O_2: oxygen, NO: nitric oxide, PG: prostaglandin, CCB: calcium channel blocker, ACEI: angiotensin converting enzyme inhibitor, PDE5 I: phosphodiesterase 5 inhibitor, ETRA: endothelin receptor antagonist.

8. Natural History of PH in COPD

Kessler et al. [75] studied 131 patients with COPD (mean FEV1 44.6 ± 15.7%) with mild to moderate hypoxemia (PaO_2 > 60 mm Hg) and without resting PH (mPAP < 20 mm Hg). FEV1 was <35% in 28%, 35–49% in 45%, and ≥50% in 26%. Approximately 25% of the patients developed resting PH during a 6-year followup (mean mPAP 26.8 ± 6.6 mm Hg). More importantly, twice as many patients with exercising PH at the onset developed resting PH over time (32% versus 16%). The average change in mPAP was 0.4 mm Hg per year. Patients with accelerated worsening of resting mPAP differed by a significant worsening of exercising mPAP whereas the changes of FEV1 and PaO_2 were rather similar. Moreover, patients who developed resting PH had higher resting and exercising mPAP and significantly lower resting and exercising PaO_2 at baseline [75].

9. Treatment of PH Secondary to COPD

The adverse effect of PH on survival and exercise capacity, and the increased risk of severe acute exacerbations caused by PH provide the rationale for treating PH in COPD. The goals of treatment, therefore, are to improve survival, improve exercise tolerance, reduce exacerbations, and improve quality of life. Various approaches to the treatment of PH in COPD are listed in Table 4. Various pulmonary vasodilators used in the treatment of PH in COPD are listed in Table 5.

10. Oxygen

LTOT improves survival in stable COPD patients with resting hypoxemia ($PaO_2 < 55$ mm Hg) and is associated with a mild improvement in pulmonary hemodynamics [76, 77].

In the Medical Research Council trial ($N = 87$), mortality rate at 5 years was 67% in the no-O_2 group and 45% in the O_2-treated group (15 h/day). In patients alive at 500 days who received repeat RHC, mPAP increased in the no-O_2 group ($n = 21$) at an average rate of 2.7 mm Hg/year and remained unchanged in the O_2-treated group ($n = 21$) [76]. In the Nocturnal Oxygen Therapy (NOT) Trial ($N = 200$), the mortality rate after 1 year was 11.9% in the continuous O_2 therapy group (averaging 17 h/day) and 20.6% in the nocturnal O_2 therapy group (averaging 12 h/day). In patients undergoing hemodynamic measurement at baseline and 6 months after enrollment ($n = 117$), mPAP showed a slight rise in the nocturnal O_2 therapy group and a slight fall (at an average of 3 mm Hg/year) in the continuous O_2 therapy group. PVR decreased by 11.1% in the continuous O_2 therapy group but increased by 6.5% in the nocturnal O_2 therapy group [78].

Unfortunately not all patients with COPD who meet criteria for LTOT benefit from it. Ashutosh et al. [79] showed that patients who exhibited a significant drop in mean PAP of ≥ 5 mm Hg after acute O_2 therapy (28% for 24 h) had an 88% 2-year survival compared to 22% in nonresponders when both groups of patients were subsequently treated with continuous LTOT [79]. Of note, room air VO_2 max provided the same information in that study with 6.5 mL/kg/min being the cut-off that distinguished responders from nonresponders [79].

Similarly, even in the landmark NOT trial O_2 therapy resulted in an improved survival only in patients whose baseline SVI was >30 mL/beat/m^2 (in the continuous O_2 group) or PVR was <400 dyne·s·cm^{-5} (in the nocturnal O_2 group) [78].

Weitzenblum et al. who followed up 16 hypoxemic COPD patients on LTOT for a period of 6 years demonstrated a reversal but not normalization of the PAP [15].

Moreover, supplemental O_2 during exercise decreases PAP and increases exercise tolerance even in COPD patients with mild resting hypoxemia ($PaO_2 > 60$ mm Hg) and moderate-to-severe airflow obstruction [80]. This effect was found to be the result of inhibition of hypoxic pulmonary vasoconstriction and reduction in air trapping (indicated by the difference in slow and forced vital capacity). Others have also shown that supplemental O_2 reduces dynamic hyperinflation and consequently the PAP and PAWP [20, 81]. Supplemental O_2 during exercise also improves RV function [82].

Lastly, O_2 therapy abolishes the nocturnal rise in PAP acutely [83] as well as decreases PAP in the long-term in COPD patients with PH and daytime $PaO_2 > 60$ mm Hg who experience nocturnal desaturation [84].

11. Nonspecific Pulmonary Vasodilators

Various vasodilators: calcium channel blockers, β2-agonists, nitrates, angiotensin converting enzyme inhibitors, and α1-antagonists were studied in the 80s. Most of them caused a modest decrease in mPAP accompanied by an increase in CO and a decrease in PVR but they were also associated with systemic hypotension and worsening of ventilation-perfusion mismatch that in some cases was not offset by the increase in CO [85].

12. Specific Pulmonary Vasodilators

The recent discovery of endothelial dysfunction resulting in the altered production of mediators of tone and/or proliferation, and consequently pulmonary vasoconstriction and vascular remodeling, provides the rationale for considering specific pulmonary vasodilators that also possess antiproliferative properties.

12.1. Inhaled Nitric Oxide. Inhaled nitric oxide (iNO) is a more potent vasodilator than O_2. However, when used alone iNO worsens ventilation-perfusion imbalance. In a randomized controlled trial (RCT) 40 patients with severe COPD (mean FEV1 1.19 ± 0.6 L) and PH (mPAP > 25 mm Hg) who were receiving LTOT were randomized to pulsed iNO (delivered via a novel device NOXXI; Messer, Austria) plus O_2 or O_2 alone for 3 months [86]. There was a significant improvement in mPAP, PVR, and CO. The mPAP decreased from 27.6 to 20.6 mm Hg ($P < 0.001$); PVR decreased from 276.9 to 173 dyne·s·cm^{-5} ($P < 0.001$). Systemic hemodynamics and left heart function remained unchanged. $PaCO_2$ decreased significantly in the treatment group, suggesting improved perfusion of the better ventilated areas. Significant methemoglobinemia was not seen. Although this study shows a promising role for iNO in stable COPD patients with PH, it is important to realize that iNO needs to be delivered in a pulsed manner to limit the formation of nitrogen dioxide and to avoid worsening ventilation-perfusion mismatch, and such delivery requires a more practical device.

12.2. Inhaled Iloprost. In a study by Dernaika et al. [87] 10 males with FEV1 < 65% with Pa O_2 60–75 mm Hg and PH (defined as sPAP > 35 mm Hg plus RV dilatation and/or RV hypertrophy on ECHO) were evaluated before and after inhaling 2 doses of iloprost (2.5 μg). PFT, ABG, 6MWT and ventilatory equivalents for O_2 (VE/VO_2) and CO_2 (VE/VCO_2) were performed at baseline, 30 min following each dose of iloprost, and 2 h after the second dose. Iloprost was associated with improved ventilation-perfusion matching and exercise tolerance. The 6MWD increased by 49.8 ± 35 m ($P = 0.02$).

12.3. Lessons Learnt from the Trials of Inhaled Pulmonary Vasodilators. In patients with severe COPD and resting mPAP > 25 mm Hg inhaled NO and O_2 improve pulmonary hemodynamics and ventilation-perfusion mismatch. The recent development of a lightweight (approximately 4 kg) and portable pulsed delivery system INOpulse DS, that also eliminates the need for calibration or monitoring of NO or NO_2, offers the possibility of using inhaled NO in COPD patients with PH. However, this promising device has not been studied in COPD or PH.

In patients with COPD with FEV1 < 65% and ECHO-estimated resting sPAP > 35 mm Hg iloprost alone improves ventilation-perfusion mismatch and 6MWD. However, its effects last only 2 hours. Another inhaled prostaglandin treprostinil, which is now available and has a longer duration of action, may be a more feasible option. However, it has not been studied in COPD.

12.4. Sildenafil. Alp et al. [88] were the first to report on the acute and long-term effects of sildenafil in COPD. They showed that in 6 patients with COPD with FEV1 < 50% and PH (mPAP 29.5 ± 5.2 mm Hg) sildenafil 50 mg IV, once followed by 50 mg PO BID for 3 months, resulted in significant improvement in both hemodynamics and 6MWD. The mean 6MWD increased by 82 m (from 351 ± 49 to 433 ± 52 m) after 3 months.

However, Holverda et al. [89] failed to show similar results in two studies. They studied the acute effects of a single oral dose of sildenafil 50 mg in 18 patients with GOLD stage II–IV and showed that regardless of the mPAP at rest, sildenafil attenuated the increase in mPAP during submaximal exercise but this was neither accompanied by enhanced SV and CO, nor by improved exercise capacity. However, only 11 patients had PH: 5 at rest (mPAP > 25 mm Hg) and 6 with PH on exercise (mPAP > 30 mm Hg).

The same group went on to study the effects of sildenafil 50 mg PO TID for 3 months in 15 patients with GOLD stage II–IV and reported similar results—neither SV nor exercise capacity improved [90]. However, again, not all patients had PH—only 9 had PH: 5 at rest (mPAP > 25 mm Hg) and 4 on exercise (mPAP > 30 mm Hg).

In a randomized dose comparison trial of sildenafil 20 versus 40 mg in 20 patients with COPD and resting PH (mPAP > 20 mm Hg) both doses improved pulmonary hemodynamics at rest and during exercise but this was accompanied by worsening hypoxemia albeit only at rest [91]. Interestingly, there was also noted to be a slight but statistically significant improvement in FEV1 and forced vital capacity (FVC). Although such a bronchodilatory effect of sildenafil has also been reported in two patients in the literature [92] and is probably mediated through its inhibition of the phosphodiesterase-5 enzyme [93], it has not been evaluated in a controlled manner.

On the other hand, in a double blind RCT of 33 patients with severe COPD and ECHO-estimated sPAP > 40 mm Hg Rao et al. [94] showed that the median 6MWD improved by 191 m and sPAP by 12 mm Hg after sildenafil 20 mg PO TID for 3 months ($P < 0.05$).

12.5. Bosentan. In a double blind RCT of 30 patients with severe to very severe COPD Stolz et al. [95] showed that bosentan 125 mg PO BID for 3 months not only failed to improve exercise capacity but also deteriorated hypoxemia and functional status. It is important to keep in mind that only 14 of 20 patients in the bosentan group and 6 of 10 patients in the placebo group had PH at rest (defined as ECHO-estimated sPAP > 30 mm Hg without adding central venous pressure).

On the contrary, in another RCT, this one of 40 patients with COPD and PH (mPAP > 25 mm Hg and PAWP < 15 mm Hg), Valerio et al. [96] showed that bosentan 125 mg PO BID for 18 months resulted in a significant improvement in hemodynamics, 6MWD and BODE index: mPAP from 37± to 31 ± 6 mm Hg, PVR from 442 ± 192 to 392 ± 180 dyne·s·cm^{-5}, 6MWD from 256 ± 118 to 321 ± 122 m, and BODE index from 6.6 ± 2.8 to 5.5 ± 3 units. Most patients in stage IV, who made up 30% of the study population and were characterized by high BODE index, WHO functional class IV, no reversibility with O2, and higher increases in PAP and PVR during exercise, did not improve but in all such patients the treatment stopped the progressive worsening of hemodynamics.

12.6. Lessons Learnt from the Trials of Oral Specific Pulmonary Vasodilators (Tables 6 and 7). In patients with severe COPD *and* resting mPAP < 25 mm Hg pulmonary vasodilator therapy may improve PAP during exercise but does not improve SV and CO or exercise capacity. This is probably because hyperinflation plays a predominant role in the pathophysiology of reduced SV and CO in such patients (Figure 3). Severe hyperinflation with inspiratory capacity to total lung capacity (IC/TLC) ratio <25% causes a "tamponade" effect on the heart and reduces RV preload [55, 56, 97] whereas any reduction in RV afterload that may result from pulmonary vasodilatation is of no avail and the SV is limited particularly during exercise. Therefore, pulmonary vasodilators should be neither studied nor used in COPD patients with mild resting PH (mPAP < 25 mm Hg or ECHO-estimated sPAP < 40 mm Hg) or in COPD patients with PH only on exercise.

On the other hand, in patients with COPD and resting mPAP > 25 mm Hg or ECHO-estimated sPAP > 50 mm Hg pulmonary vasodilator therapy improves pulmonary hemodynamics and 6MWD. However, more research is needed to recommend the use of pulmonary vasodilators in PH secondary to COPD. Although COPD patients with severe PH (mPAP > 35–45 mm Hg) who probably represent a "vascular phenotype" or have concomitant IPAH will benefit the most from pulmonary vasodilator therapy, it may be worthwhile to try such therapy in COPD patients with less severe PH (mPAP 25–35 mm Hg) especially if hyperinflation is not playing a significant role. Although it has not been evaluated, pulse oximeter plethysmography waveform analysis to identify "pulsus paradoxus" may be a simpler way of identifying patients with severe hyperinflation with IC/TLC ratio <25%.

It is important to keep in mind that even specific pulmonary vasodilators can worsen ventilation-perfusion mismatch and hypoxemia at rest that may or may not be offset by an increase in CO. Lastly, lack of acute responsiveness to pulmonary vasodilators indicates a more altered vasculature that may respond to a longer course of therapy or to statins.

13. Statins

Statins have anti-inflammatory, antioxidant, and antithrombogenic effects and restore endothelial function [98]. Moreover, statins can reduce the synthesis of ET-1 at the transcriptional level [99].

Table 6: Summary of the effects of pulmonary vasodilators in the published studies of such drugs in COPD patients.

First author	Alp et al. [88]	Holverda et al. [89]	Rietema et al. [90]	Stolz et al. [95]	Valerio et al. [96]	Blanco et al. [91]	Rao et al. [94]
Year of publication	2006	2008	2008	2008	2009	2010	2011
Country	Germany	Netherlands	Netherlands	Switzerland	Italy	Spain	India
Drug	Sildenafil	Sildenafil	Sildenafil	Bosentan	Bosentan	Sildenafil	Sildenafil
Dose	50 mg BID	50 mg	50 mg TID	125 mg BID	125 mg BID	20 mg vs 40 mg	20 mg TID
Duration	3 months	Acute effects	3 months	3 months	18 months	Acute effects	3 months
Total *N*	5	18	15	20	20	20	17
N with PH	5	11	9	14	20	12	17
N with resting PH	5	5	5	14	20	12	17
PAP	↓	↓ r + e		No Δ	↓	↓ r + e	↓
CO	NA	No Δ r + e	No Δ r + e	No Δ	No Δ	↑ r + e	
PVR	↓	No Δ r + e		No Δ	↓	↓ r + e	
SpO_2PaO_2		↓ r + e	No Δ r + e	↓ r, No Δ e	No Δ	↓ r, No Δ e	
6MWD (m) at baseline	351 ± 49		385 ± 135	339 ± 81	257 ± 150	396 ± 114	269 ± 140
6MWD (m) after treatment	↑ to 433 ± 52		↑ to 396 ± 116	↑ to 329 ± 94	↑ to 321 ± 122	NA	↑ by 191 ± 127

mg: milligrams, BID: twice a day, TID: three times a day, vs: versus, *N*: total number of patients who received the study drug, *N* with PH: number of patients with pulmonary hypertension, PH: pulmonary hypertension, PAP: pulmonary artery pressure, CO: cardiac output, PVR: pulmonary vascular resistance, SpO_2: oxygen saturation by pulse oximetry, PaO_2: arterial oxygen tension, 6MWD: six-minute walk distance, m: meters, NA: not available or not applicable, r + e: rest and exercise, Δ: change, r: rest, e: exercise.

Table 7: Baseline characteristics of the patients who received pulmonary vasodilators in the published studies of such drugs in COPD.

First author	Alp et al. [88]	Holverda et al. [89]	Rietema et al. [90]	Stolz et al. [95]	Valerio et al. [96]	Blanco et al. [91]	Rao et al. [94]
Year of publication	2006	2008	2008	2008	2009	2010	2011
Drug	Sildenafil	Sildenafil	Sildenafil	Bosentan	Bosentan	Sildenafil	Sildenafil
Dose	50 mg BID	50 mg	50 mg TID	125 mg BID	125 mg BID	20 mg vs 40 mg	20 mg TID
Duration	3 months	Acute effects	3 months	3 months	18 months	Acute effects	3 months
Total *N*	5	18	15	20	20	20	17
N with PH	5	11	9	14[†]	20	12	17
N with resting PH*	5	5	5	14[†]	20	12	17
Age (years)	45–64	66 ± 9	65 ± 2	69.5 ± 8.8	66 ± 9	64 ± 7	60 ± 7
sPAP (mm Hg)				32[‡]			53 ± 12
mPAP (mm Hg)	**29.5 ± 5.2**	23 ± 10	22 ± 9		**37 ± 5**	**27 ± 10**	***33.8 ± 9.2***[§]
CO (L/min)		5.5 ± 1.0	5.4 ± 1.7	2.45 ± 0.4	2.8 ± 0.7	4.9 ± 0.95	
CI (L/min/m^2)						2.7 ± 0.44	
PVR (dynes.s.cm^{-5})	373 ± 118	280 ± 180	259 ± 166	158 ± 30	442 ± 192	339 ± 165	
FEV1 (% predicted)	16–48	52 ± 26	49 ± 24	38 ± 13	37 ± 18	35 ± 11	32.5 ± 11
TLC (% predicted)		126 ± 15	125 ± 16	126 ± 15	132 ± 6	114 ± 19	
DLCO (% predicted)		46 ± 17	48 ± 16	37 ± 18	34 ± 7	44 ± 17	
SpO_2 (%)		93 ± 4	95 ± 2	93 ± 3			
PaO_2 (mm Hg)			74 ± 13		57 ± 10	64 ± 11	
$PaCO_2$ (mm Hg)			39 ± 6		46 ± 8	38.4 ± 4.5	
6MWD (meters)	351 ± 49		385 ± 135	339 ± 81	257 ± 150	396 ± 114	269 ± 140

mg: milligrams, BID: twice a day, TID: three times a day, vs: versus, *N*: total number of patients who received the study drug, *N* with PH: number of patients with pulmonary hypertension, PH: pulmonary hypertension, sPAP: systolic pulmonary artery pressure estimated by echocardiography, mPAP: mean pulmonary artery pressure measured by right heart catheterization, CO: cardiac output, CI: cardiac index, PVR: pulmonary vascular resistance, FEV1: forced expiratory volume in the first second, TLC: total lung capacity, DLCO: diffusing capacity for carbon monoxide, SpO_2: oxygen saturation by pulse oximetry, PaO_2: arterial oxygen tension, $PaCO_2$: arterial carbon dioxide tension, 6MWD: six-minute walk distance.

*resting PH defined as mPAP > 25 mm Hg or ECHO estimated sPAP > 40 mm Hg unless specified otherwise—see below:

[†]PH was defined as estimated sPAP > 30 mm Hg without adding central venous pressure (CVP).

[‡]Estimated sPAP without adding CVP. If CVP is assumed to be 5 mm Hg, this gives a sPAP of 37 mm Hg which amounts to a mPAP of 24 mm Hg based on the prediction equation 0.6 × sPAP + 2 = mPAP [113].

[§]Calculated mPAP based on the prediction equation 0.6 × sPAP + 2 = mPAP [113].

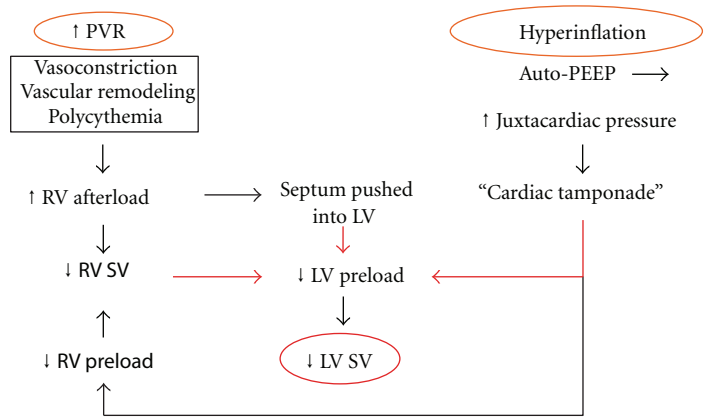

Figure 3: Pathophysiology of reduced SV in COPD. SV: stroke volume, PVR: pulmonary vascular resistance, RV: right ventricular, LV: left ventricular, PEEP: positive end-expiratory pressure.

In a double-blind parallel design study [100], 53 patients with COPD and ECHO-estimated sPAP > 35 mm Hg were randomly assigned to receive either pravastatin 40 mg daily or placebo for 6 months. Exercise time increased significantly 52% from 660 ± 352 to 1006 ± 316 seconds ($P < 0.0001$) in the treatment group. ECHO-estimated sPAP decreased significantly from 47 ± 8 to 40 ± 6 mm Hg. There was also significant improvement in Borg dyspnea score.

In an animal study, Wright et al. [101] studied the effects of simvastatin in guinea pigs exposed to cigarette smoke for 6 months. In half of the animals simvastatin was introduced after 3 months. Cigarette smoke increased the sPAP after approximately 4 weeks. Simvastatin returned the pressure to control levels within 4 weeks of starting treatment, and ameliorated smoke-induced small arterial remodeling as well as emphysema measured both physiologically and morphometrically at 6 months, but did not prevent smoke-induced small airway remodeling either physiologically or morphologically. In precision-cut lung slices simvastatin reversed small arterial endothelial dysfunction and partially reversed smoke-induced loss of vascular NO generation.

Both studies show prospects for the use of statins in COPD and warrant more research.

14. Diuretics

Diuretics reduce right ventricular dilatation and improve its contractility and also reduce extravascular lung water [102]. They should be used cautiously as they can cause intravascular volume depletion that may deprive the RV of adequate preload to maintain a normal SV.

15. Phlebotomy

Phlebotomy is usually indicated in patients with polycythemia not responding to LTOT. In a small study of 7 patients with stable severe COPD (FEV1 33 ± 3% of predicted) and PH, Borst et al. [103] showed that isovolemic phlebotomy resulted in improvement in pulmonary hemodynamics, gas exchange, and exercise tolerance. The patients were phlebotomized 5-6 times over a period of 3 months with substitution of 6% hydroxyethyl starch (molecular weight 40,000). This resulted in a stepwise reduction of the hematocrit from 53.3 ± 2.6 to 45.8 ± 3.1%. Mean PAP decreased from 30 ± 3 to 22 ± 2 mm Hg and PaO_2 increased from 63.2 ± 2.2 to 71.8 ± 3.7 mm Hg at rest. During peak exercise, mPAP decreased from 59 ± 7 to 53 ± 7 mm Hg and PaO_2 increased from 54.0 ± 5.7 to 63.2 ± 2.4 mm Hg after hemodilution. Peak oxygen consumption rose from 573 ± 84 to 750 ± 59 mL/min, corresponding to an increase in CI from 4.25 ± 0.5 to 5.88 ± 0.76 liters/min/m^2. PVR fell from 345 ± 53 to 194 ± 32 dyne·s·cm^{-5}. The patients' peak exercise capacity increased from 9.2 ± 2.0 before to 13.5 ± 3.2 kJ at the end of the study ($P < 0.05$ for all differences).

16. "Bloodless Phlebotomy"

Activation of the renin-angiotensin system may contribute to polycythemia in COPD [104]. Plasma renin and aldosterone levels are increased in such patients when matched with controls for hypoxemia. The mechanism of action is serum-erythropoietin-independent. In a small study, the angiotensin receptor blocker (ARB) losartan was used in weekly escalating doses to a maximum of 100 mg daily for 4 weeks in 9 stable severe COPD patients with polycythemia (hematocrit >52%). The regimen caused a significant reduction in the hematocrit of all patients from 56 ± 0.9% to 46 ± 0.7% ($P < 0.001$). The higher the baseline value, the greater the reduction in hematocrit ($r = 0.7085$; $P < 0.05$) [105]. At 3 months after discontinuation of losartan the hematocrit increased to 50 ± 0.7%. Similarly, in an RCT of 60 patients with severe COPD another ARB irbesartan also induced a significant reduction in hematocrit [106]. Of note, however, neither study evaluated pulmonary hemodynamics, gas exchange or exercise tolerance which makes it difficult to draw any meaningful conclusions.

Although it is tempting to speculate that such a "bloodless" phlebotomy may also result in improvement in pulmonary hemodynamics, gas exchange, and exercise tolerance, it is important to realize that ARBs are also

non-specific vasodilators that can cause a modest decrease in mPAP as well as worsen PaO_2. In fact in a double-blind RCT of COPD patients with transtricuspid pressure gradient (TTPG) >30 mm Hg more patients in the losartan group (50%) than in the placebo group (22%) showed a clinically meaningful reduction in TTPG at any time point during the 12-month period, and these effects seemed more marked in patients with higher baseline TTPG. There were no clear improvements in exercise capacity or symptoms, though [107].

17. Lung Volume Reduction Surgery (LVRS)

Although lung volume reduction surgery (LVRS) is contraindicated in COPD patients with severe PH (mPAP > 35 mm Hg), the reduction in hyperinflation and improvement in gas exchange resulting from such surgery are expected to result in an improvement in PAP in patients with less severe PH. On the other hand excision of some viable pulmonary vascular bed may have the adverse effect of worsening PVR. In fact the few studies of pulmonary hemodynamics before and after LVRS have shown that the mPAP remains unchanged after such surgery [108–111]. Earlier and smaller studies showed that mPAP remains unchanged because CO improves when PVR falls after LVRS [108–110]. In contrast, the most recent and largest study of pulmonary hemodynamics before and after LVRS, which was a cardiac substudy of the national emphysema treatment (NET) trial, did not show any significant change in CO [111]. Reasons for the discrepancy between the results of the earlier studies and the NET trial are not clear, but could be due to differences in patient selection, or surgical methods. Moreover, unlike the other studies, the NET trial did not evaluate pulmonary hemodynamics during exercise.

18. Lung Transplantation

PH secondary to COPD is an indication for lung transplantation. Bjortuft et al. [112] investigated a group of 24 patients, including 19 with COPD, who underwent single lung transplantation. The majority (15 out of 24) of patients had mild-to-moderate PH at the onset and in these patients mPAP significantly decreased from 28 ± 1 to 18 ± 1 mm Hg after transplantation; there was a similar decrease in PVR. These results were maintained after 2 yrs of followup. Therefore, COPD patients with PH normalize pulmonary haemodynamics after single lung transplantation.

19. Conclusion

The pathophysiology of PH in COPD is complex. A diagnosis of PH in COPD should prompt a search for other causes of PH, particularly left heart dysfunction, OSA, and PE before attributing the PH to COPD. PH in COPD adversely affects survival and exercise capacity and is associated with an increased risk of severe acute exacerbations. Unfortunately not all patients with COPD who meet criteria for LTOT benefit from it. Even in those who benefit from LTOT, such therapy may reverse PAP but cannot normalize it. Moreover, the recent discovery of the key roles of endothelial dysfunction and inflammation in the pathogenesis of PH provides the rationale for considering specific pulmonary vasodilators that also possess antiproliferative properties and statins. Studies of pulmonary vasodilators and statins for PH secondary to COPD appear to show a promising role for such therapy in patients with more than mild PH (mPAP > 25 mm Hg) and warrant more research. Success of pulmonary vasodilator therapy appears to depend upon the degree of PH and the severity of hyperinflation. Such therapy is more likely to be successful when PH is moderate to severe (mPAP > 25 mm Hg) and hyperinflation is not playing a significant role, that is, IC/TLC is >25%. Although stable COPD patients with severe PH (mPAP > 35–45 mm Hg) who probably represent a "vascular phenotype" or have concomitant IPAH warrant pulmonary vasodilator therapy, it may be worthwhile to try such therapy in stable COPD patients with less severe PH (mPAP 25–35 mm Hg) especially if hyperinflation is not severe. On the other hand such therapy should be avoided when PH is mild or only during exercise or hyperinflation is playing a significant role, that is, IC/TLC is <25%. Future studies of pharmacotherapy should focus on patients with PH with mPAP > 25 mm Hg and IC/TLC > 25%.

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